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Investigation of common deficiencies observed in scientific assessments and the implementation of a new robust review pathway, the risk-based assessment approach, by the South African Health Regulatory Authority, SAHPRA

by

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DECLARATION

I declare that *Investigation of common deficiencies observed in scientific assessments and the implementation of a new robust review pathway, the risk-based assessment approach, by the South African Health Regulatory Authority, SAHPRA* is my own work, that it has not been submitted for any degree or examination in any other university, and that all sources I have used or quoted have been indicated and acknowledged by complete references.

Full name: Lerato Petunia Moeti Date: 23 November 2022

Signed: 

ABSTRACT

The main objective of this study is to improve patient access to medicines. The research is two-fold, the first component promotes transparency between the South African Health Products Regulatory Authority (SAHPRA), pharmaceutical companies, manufacturers and clinical research organisations by investigating deficiencies in scientific assessments of medicines submitted for approval. The common deficiencies from the regional, Active Pharmaceutical Ingredient (API), Finished Pharmaceutical Product (FPP) and Bioequivalence study sections of dossiers submitted to SAHPRA were qualitatively and quantitatively investigated. The investigation was conducted retrospectively between 2011 to 2017 for non-sterile and sterile generic products finalised by the P&A pre-registration Unit. To strengthen the conclusions, up-to-date data was also collected between 2020-2021 to confirm the consistency of the findings.

In 2011–2017, 3148 products were finalised, 667 of which were sterile. The sample size was calculated with 95% confidence using statistical tables from the literature. Using stratified-systematic sampling, products were selected by their therapeutic category. This resulted in 325 non-sterile and 244 sterile applications. Subsequently, all the deficiencies were collected and categorised according to the regional section and the Common Technical Document (CTD) subsections of the API (3.2.S.) and FPP section (3.2.P). Beyond the 2011-2017 sample, additional investigations were done to corroborate the evaluation standards and identify any changes. The investigations focused on common deficiencies in the following: the restricted part using the sample from 2020 for the API section; regional requirements using applications assessed in 2021; bioequivalence studies using applications assessed in 2020-2021. By comparing the data to the 2011-2017 study, commonalities were observed. The detailed findings identify the sections with the most prevalent deficiencies.

The investigation of common deficiencies in the regional requirements section, Module 1, was conducted using 569 applications and 3042 deficiencies were collected. The labelling section had the majority of deficiencies (52%), followed by the amendment schedule (12%), general deficiencies (11%), foreign registration status (10%), application details (8%) and GMP requirements (7%). Query letters for 62 of the 2021 applications were also obtained, 10 had no Module 1 queries, and 52 reported 373 deficiencies. A similar trend as the 2011-2017 was observed in the 2021 study. In the API section, 1130 deficiencies were found in 325 sampled applications. Most deficiencies were in Modules 3.2.S.3.1 (19.38%) on characterisation, 3.2.S.1.3 (19.11%) on general attributes, 3.2.S.4.1 (10.44%) on specifications, and 3.2.S.4.3 (8.32%) on validation of analytical methods. The study on the restricted parts included the five most common deficiencies that SAHPRA has identified, which are similar to those observed from the 2011–2017 applications. In the FPP section, 3253 deficiencies were identified

in 325 non-sterile applications and 2742 in 244 sterile applications. Specifications (15%), Description and Composition (14%), Manufacturing Process (13%), Stability Data (7.6%), and Container Closure System (7.3%) had the highest FPP deficiencies for non-sterile products. The deficiencies applicable to the sterile products were quantified and the subsection, Validation and/or Evaluation (18%) had the most deficiencies. For the bioequivalence portion, 2458 deficiencies were collected from the sample size for applications with a bioequivalence study submitted between 2011 and 2017. Most deficiencies were *in-vitro* dissolution testing and specifications (18%), study design (17%), test and reference product details (16%), sample analysis (16%), and statistical analysis (10%). In 2020–2021, 103 applications in resubmission windows (RW) 1, 3 and 5 had 492 deficiencies. Recent research from 2020-2021 indicates a similar pattern to 2011-2017 sample, confirming evaluation consistency. The study also compared the deficiencies with those reported by the USFDA, EMA, WHO QTm, and TFDA, highlighting similarities.

The second part of the study was to develop a new regulatory review pathway. This was executed by completing a comprehensive literature review on risk-based scientific evaluations. The investigation's findings on common quality and bioequivalence deficiencies further justified the critical parts identified. A rigorous risk classification template was designed to classify applications as high-risk or low-risk based on the medicinal product's technical characteristics and application of partial reliance, if applicable. The review of the existing end-to-end registration process was also conducted with the root causes of the formation of backlog identified. The developed pathway provides a prototype solution to counteract the influx of drug applications to avoid backlogs. The risk-based assessment (RBA) approach was developed in 2016 and piloted in 2021 to optimise efficiency.

The 2015 RBA project had two phases. The first phase identified the status of 3505 in-process applications, registering 198. The second phase commenced in 2016 on 4397 applications not yet reviewed and the RBA was piloted. The pilot began with 99 master applications received in 2011-2012. A similar pilot study was done in 2021 with 63 master applications to improve efficiency. The 2016 pilot resulted in a median finalisation time of 90 calendar days and a median approval time of 109 calendar days from the date of the initial allocation. The RBA pilot study had a median finalisation time of 68 calendar days compared to 501 days for the current process. A reduced finalisation time is also observed in the 2021 pilot study compared to 2016 due to optimisation of efficiency. The 2016 and 2021 investigations reported 6-7 hours for a low-risk quality assessment, 9-10 hours for a high-risk quality assessment, 7-8 hours for a bioequivalence assessment and 2-3 hours for a biowaiver and initial response assessment. In the 2022 Phase 2 pilot project, the quality assessment timelines for high-risk products are reported as a median of 14 hours and 10 hours for low-risk products. The lengthier timeline compared to the initial phase is attributed to the evaluator having to authenticate the evaluation template pre-populated by the applicant.

SAHPRA's 2011-2022 registration processes were studied to identify the root cause of the backlog. The three processes and timelines at each stage of the process are extensively discussed and compared. The 2011-2017 generic products had a median approval time of 2092 days. The median approval time of 591 days for the Backlog clearance project (BCP) process was lowered to 511 days by implementing the RBA procedure. The finalisation timeline which entails the time taken from application allocation to finalisation by the P&A pre-registration Unit, which conducts the bulk of the evaluation, is used as a tool for the direct comparison of the processes. The 2011-2017 finalisation time is a median value of 1470 days while BCP is 501 days, and the RBA process is 68 days. This shows a substantial reduction in finalisation time and demonstrates the effectiveness and efficiency of the RBA process.

The study executed its objectives by identifying the common deficiencies witnessed in scientific assessments. In addition, it promoted transparency by publishing these deficiencies with the relevant stakeholders for submission of quality dossiers to the authority. For improving the registration turnaround time of the authorities, a new review pathway was developed for generic applications that do not qualify for application of a reliance strategy and require full review. The RBA approach reduced the approval times for medicinal products without compromise on quality, safety and efficacy of the medicinal products. The results reported show that the robust RBA process can be utilised by other regulatory authorities worldwide to alleviate a backlog and to promote efficiencies in the existing process.

PUBLICATIONS AND MANUSCRIPTS

Lerato Moeti (LM), Madira Litedu (ML), Jacques Joubert (JJ)

1. **Moeti L, Litedu M, Joubert J. Common Deficiencies Found in the Active Pharmaceutical Ingredient (API) Section of Non-sterile Generic Products Submitted for Registration by SAHPRA. Ther Innov Regul Sci, 2022:56;276–290. https://doi.org/10.1007/s43441-021-00359-9.**

2. **Moeti L, Litedu M, Joubert J. Common deficiencies found in Generic Finished Pharmaceutical Products (FPPs) submitted for registration by the South African Health Products Regulatory Authority (SAHPRA). J Pharm Pol Pract. 2022;15:1- 21.**

3. **Moeti L., Litedu M, Joubert J. Bioequivalence Common Deficiencies in Generic Products Submitted for Registration to the South African Health Products Regulatory Authority (SAHPRA). Ther Innov Regul Sci. 2022:56;822–838. https://doi.org/10.1007/s43441-022-00429-6.**

4. **Moeti L, Litedu M, Joubert J. The implementation of a risk-based assessment approach by the South African Health Products Authority (SAHPRA), Pharm Med. 2023;37:71-91. https://doi.org/10.1007/s40290-022-00452-w**

5. **Moeti L, Litedu M, Joubert J. Regulatory registration timelines of generic medicines in South Africa: Assessment of the performance of SAHPRA between 2011-2022. J Pharm Pol Pract. 2023;16(34):1-13. https://doi.org/10.1186/s40545-023-00537-0**

6. **Moeti L, Litedu M, Joubert J. Common Deficiencies witnessed in the regional section, Module 1, on applications submitted to the South African Health Products Regulatory Authority (SAHPRA).** Manuscript submitted to the South African Pharmaceutical Journal.

AUTHOR CONTRIBUTIONS

For all manuscripts and publications

Lerato Moeti (LM), Madira Litedu (ML), Jacques Joubert (JJ)

LM: developed the study design, collected and analysed the data, interpreted the results and wrote the first draft of the manuscripts. ML: Developed the study design, assisted in collecting and analysing the data, provided guidance for the data collection and analysis, interpreted the results and reviewed the manuscripts. JJ: Developed the study design, provided guidance on the data analysis, interpretation and relevance of the results and reviewed the manuscripts.

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KEYWORDS

South African Health Products Regulatory Authority (SAHPRA)

Common Deficiencies

Active Pharmaceutical Ingredient Master File (APIMF)

Drug Master File (DMF)

Common Technical Document (CTD)

Active Pharmaceutical Ingredient (API)

Bioequivalence

Bioavailability

Biostudies

Generic products

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CHAPTER 1

Introduction

1.1 Drug discovery and Medicine research

Through scientific research and drug development, medicine has created reliable methods for protecting and extending the lifespan of humans (Edington et. al., 2016). The discovery of numerous Active Pharmaceutical Ingredients (APIs) such as tenofovir disoproxil fumerate (Clercq E, 2012), paclitaxel (Wani MC and Horwitz S, 2014), linezolid (Durrant C, 2001), and metformin hydrochloride (Bailey C, 2017), has enabled the saving of lives across the globe. As a result, the pharmaceutical industry devotes substantial resources to scientific research for new cures and treatment options to combat the multitude of illnesses and diseases affecting the global community today (Durrant C, 2001). With the advancement of scientific research comes the obligation to ensure that these discoveries are safe for human and animal use. Consequently, each country should have a medicines regulatory authority to protect the public.

1.2 History of regulation

Regulatory authorities are tasked with ensuring the safety and efficacy of pharmaceutical products through rigorous scientific evaluation of dossiers submitted to the authority on all aspects of the medicinal product. They ensure that animal and human studies adhere to Good Laboratory Practice (GLP), that clinical trials adhere to Good Clinical Practice (GCP), and that drugs are manufactured under current Good Manufacturing Practice (cGMP) standards (Rago L and Santoso B, 2008).

Pharmaceutical companies use all the data accumulated during discovery and development stages to register and thus market the medicinal product. Throughout the development stages, they are required to abide to an array of strict rules and guidelines in an effort to ensure quality, safety and efficacy of the drug in humans (Rago and Santoso, 2008; WHO, 2022; Ndomondo-Sigonda M et al., 2017). Each country has its own regulatory authority, which is responsible for enforcing the rules and regulations and issuing the guidelines to regulate the drug development process, licensing, registration, manufacturing, marketing, labelling, and product life cycle (WHO, 2003).

The strict regulatory laws come after a pharmaceutical manufacturer S. E. Massengill Company, produced an elixir of sulfanilamide using diethylene glycol as a solvent, causing the death of more than 100 people in the United States in 1937 (Ballentine, 1981). In 1956, another tragedy over thalidomide occurred, which was introduced in 46 different countries worldwide resulting in an estimated 10,000 babies being born with phocomelia and other deformities (Rago and Santoso, 2008; Enochson, 2014; Rehman et al., 2011). This

catastrophe majorly triggered the development of modern regulatory controls on drug development and supply.

Over the years the pharmaceutical industry has seen immense growth as people around the world are taking medications more than at any time in history for many reasons, such as increased population numbers and ages, the prevalence of chronic diseases, infectious diseases, lifestyles and the discovery of new diseases (Al-Worafi WM, 2020). The global pharmaceutical market was worth $ 1.42 trillion by the end of 2021 which is a significant increase from 2001 when the market was valued at just 390 billion (Mikulic M, 2022). This illustrates the increased commitment to innovation and future advances in the industry. The pharmaceutical market in Africa has been growing at a rapid pace and was valued at $ 45 billion in fiscal year 2021 (African Health Economics and Policy Association (AFHEA), 2021). It is rated as the second fastest growing pharmaceutical market in the world which makes it one of the most attractive markets for pharmaceutical companies (Juhi R, *et al*, 2018). This comes as a consequence of the African population being plagued by several communicable and non-communicable diseases resulting in high demand for medicines (Juhi et al., 2018). The African continent has the highest prevalence (18.7%) of substandard and counterfeit (Ozawa S, et. al., 2018). Regulatory Authorities face difficulties with low staff turnover and lack of competent regulatory professionals, as well as poor regulatory infrastructure and ineffective regional collaborations (Dansie LS et al., 2019; Calder A, 2016; Glover B, 2018; Ndomondo-Sigonda, M et al., 2018). Except for the Sahrawi Republic, all African nations have regulatory authorities or administrative units performing some or all of the expected medicines regulatory functions (Ndomondo-Sigonda M et al., 2017). Nonetheless, the level of regulatory oversight on the continent varies widely, with some countries having robust and functional regulatory authorities and others having virtually non-existent regulatory systems (Dansie LS et. al., 2019; Mwangi LM, 2016; Ndomondo-Sigonda M et al., 2017). These factors tend to have a negative impact on the overall performance of regulatory authorities, resulting in longer approval times and growing application backlogs.

1.3 The South African regulatory authority, SAHPRA

Approval times serve as key indicators to assess the performance of a regulatory authority (Bujar M et al., 2015). The Centre for Innovation in Regulatory Science (CIRS) conducted a study on the approval times of 18 regulatory authorities. Figure 1 depicts the median approval times (CIRSa, 2019). The approval times had a median value of 500 calendar days with a minimum of 244 and a maximum of 2900 calendar days.

The South African Authority, South African Health Products Regulatory Authority (SAHPRA) stands out with the highest approval time of up to 2900 days with a median of approximately 1600 days for New Chemical Entities (NCEs) (CIRSa, 2019). The authority receives more than 90% of applications that are generic medicines, and a median approval time of 1810 calendar days was reported between 2015-2017 (Keyter A, 2020). Increasing availability of generic medicines in a country creates fair competition, which

thereby lowers prices allowing for access to affordable essential medicines (The Science Based Medicine, 2019; Patel A et al, 2012). Due to poor infrastructure, processes and limited resources, the entire review process in South Africa is delayed (Matthew I, 2019). Adding to the delay, are the large number of applications that are received on a daily basis. Therefore, despite the advances in science and innovation that have occurred over the years, patient access to medicines is hindered by the regulatory authority's lengthy approval procedures. This inevitably led to 16 000 applications backlogged by SAHPRA in 2018 of both pre-registration and post-registration applications (Low, 2018).

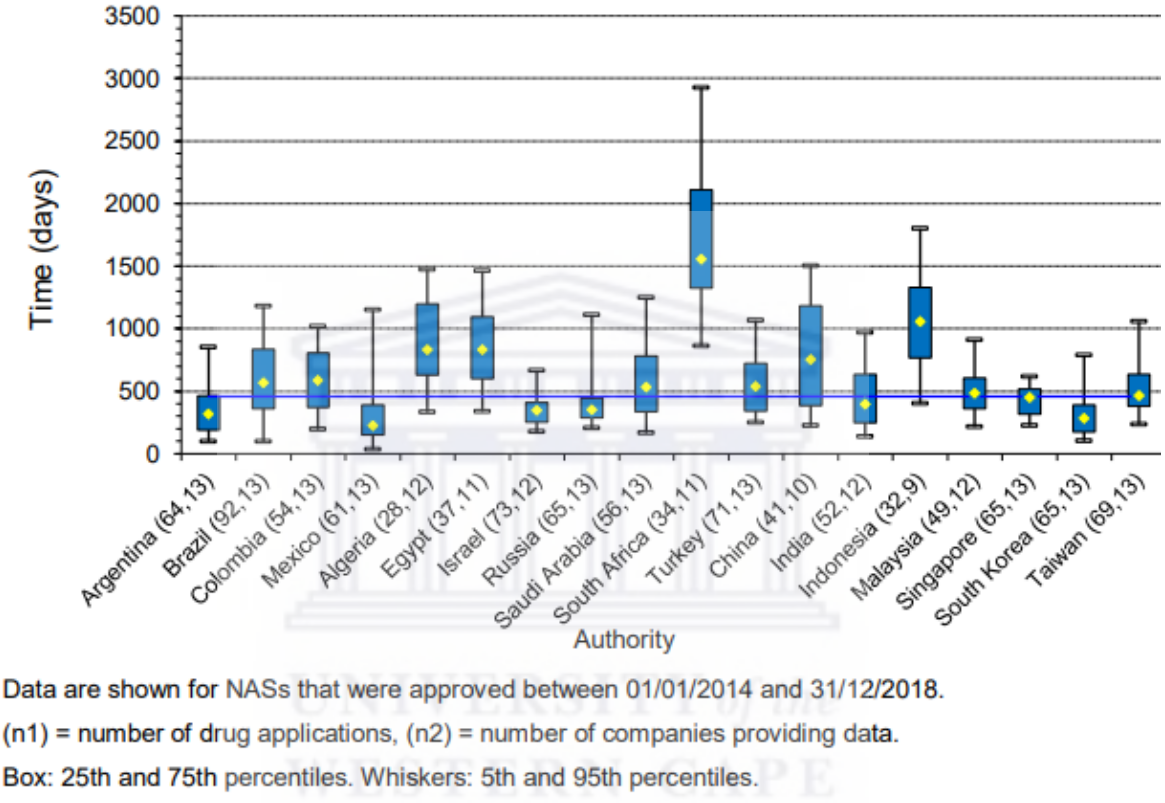

Figure 1: Approval times between 2014 - 2018 for NCEs from emerging markets. *Adopted from CIRS, 2019a*

The authority assessed the regulatory procedure in South Africa in 2018 and recognised the need for change and therefore made the commitment to diminish this backlog within two years (SAHPRA, 2019; Matthew I, 2019). The backlog clearance project (BCP) was then initiated in 2019 to clear the applications (SAHPRA, 2019). By June 2021 the authority requested an extension of a further year to execute the project (SAHPRA, 2021). To date, 09 November 2022, the backlog has not been cleared and a new backlog has been created within SAHPRA in the business-as-usual (BAU) section. A dramatic improvement in strategy is therefore required to drastically improve the current review processes which is what this study aims to investigate and address. Interventions were developed and implemented in 2021 to promote an improved system that could accelerate access to medicines.

1.4 Pathways to accelerate access to medicines

Measures have been taken by regulatory authorities to reduce the approval times which include the publication of guidelines, guidance documents on specific topics, pharmacopoeial monographs (The USP, 2022; The Ph. Eur, 2022), seminars with industry, and creation of databases e.g. database on dissolution methods by the United States Food and Drug Administration (USFDA) (USFDA, 2022). These are strides taken to promote transparency between the regulator and the pharmaceutical industry with hopes of reducing the back-and-forth communication during the review process.

Regulatory authorities also employ reliance models with the aim to avoid duplication of scientific assessments of dossiers by different authorities. The European Medicines Agency (EMA) through the European Directorate for the Quality of Medicines & HealthCare (EDQM) has developed a Certificate of Suitability (CEP) database (EDQM, 2021). Upon completion of the evaluation, a CEP is allocated to the Active Pharmaceutical Ingredient (API) manufacturer which is accepted by other regulatory authorities. This results in reduced assessment times, which thereby results in reduced approval times. The World Health Organisation Pre-Qualification Team (WHO PQTm) has also developed a pre-qualification procedure (WHO, 2022) similar to the CEP by the EDQM, which can be used by other regulatory authorities resulting in reduced assessment times. Authorities also employ reliance models such as abridged review, verification review and mutual recognition with countries they are aligned with (Matthew I, 2019; Keyter et al., 2021; Haqaish W, 2017). The introduction of additional review pathways, along with target review timelines, supports the assumption that the review of dossiers will result in faster approvals.

In 2019, SAHPRA introduced new review pathways which applies the reliance approach (Keyter et al., 2021). It was assumed that the introduction of accelerated review pathways such as the reliance approach will decrease review timelines. The approach was reported to reduce approval times, however, 70-80% of applications still required full review since un-redacted reports from other authorities were not easily acquired (Keyter A et al., 2021). At a workshop convened by the CIRS, on the Risk-Based Evaluation of Medicines, held in Sao Paulo, Brazil in 2017, many regulatory authorities expressed an interest in applying risk-based evaluation approaches as a strategy to be explored that can introduce a new review pathway for authorities to use (Keyter A et al., 2020).

Publication of common regulatory deficiencies identified by regulatory authorities have been another aspect that improves transparency and alerts pharmaceutical companies and manufacturers enabling the submission of better-quality dossiers. The United States Food and Drug Agency (USFDA) (Srinivasan A et al., 2010a; Srinivasan A et al., 2010b; Srinivasan A et al., 2011a; Srinivasan A et al., 2011), European Medicines Agency (EMA) (Borg JJ et al., 2009), Taiwan Food and Drug Agency (TFDA) (Sun CI et al., 2014) and World Health Organisation Pre-Qualification Team (WHO-PQTm) (Stahl M et al., 2012; Stahl M et al., 2014) have reported on the common deficiencies witnessed in the submissions received and noted how this has improved the quality of submissions. These are detailed further in the chapters to follow.

1.5 Aims and Objectives

The purpose of the study is to promote transparency between the South African regulatory authority, SAHPRA, and pharmaceutical companies by publishing work conducted in the Pharmaceutical Evaluations and Management (PEM) Programme, P&A pre-registration Unit. The objective of the study is three-fold. Firstly, is to report on common deficiencies witnessed in applications submitted to the authority in order to improve the turnaround approval times. Secondly, the study details the development and implementation of a new review pathway, the risk-based assessment approach aimed to reduce the approval times and allow accelerated access to medicines to patients. Lastly, the study seeks to investigate and review the end-to-end approval/registration process employed by SAHPRA between 2011-2022 in order to monitor and improve the process with the intent to promote accelerated access to medicines.

The sections to follow comprehensively details the following:

- Chapter 2 illustrates the common deficiencies observed during the assessment of the regional section, Module 1, by the PEM pre-registration Unit.
- Chapter 3 reports on the common deficiencies observed during scientific assessments in the API section of dossiers submitted to the regulatory Authority, SAHPRA.
- Chapter 4 highlights the common deficiencies observed during scientific assessments in the FPP section of dossiers submitted to the regulatory Authority, SAHPRA.
- Chapter 5 illustrates the common deficiencies observed during scientific assessments in the bioequivalence section of dossiers submitted to the regulatory Authority, SAHPRA,
- Chapter 6 details the development and implementation of a risk-based assessment approach which provides a prototype solution to counteract the influx of medicinal product applications received.
- Chapter 7 assesses the performance of the authority by in-depth analysis of the end-to-end registration process employed. Median finalisation and approval timelines are calculated and reported for the processes employed between 2011-2022.
- Chapter 8 provides overall summaries and conclusions of the study and developed tools which regulatory authorities can utilise to alleviate backlogs.

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CHAPTER 2

Common deficiencies witnessed in Module 1 assessed by the Pharmaceutical Evaluation and Management (PEM) pre-registration Unit within the South African Health Products Regulatory Authority (SAHPRA)

This chapter has been submitted to the South African Pharmaceutical Journal.

Abstract

Background: Well-functioning health systems need effective medicine regulation. The regulatory authorities are governed by basic principles such as transparency, accountability and science, to facilitate access to medicines. The South African authority has had a backlog for 10 years, delaying patient access to medicines. To increase transparency, a series of articles on common deficiencies were published. The sharing of deficiencies would assist applicants to improve their submissions in the regional, Active Pharmaceutical Ingredient (API), finished pharmaceutical product (FPP) and bioequivalence sections. The current study focuses on the authority's common deficiencies in the regional section.

Methods: Module 1 deficiencies from sections evaluated by the Pharmaceutical Evaluation and Management pre-registration Unit were collected from 2011-2017 applications. From 3148 finalised applications, 325 non-sterile and 244 sterile were selected. A further analysis of 62 applications was evaluated between January and May 2021 to confirm the consistency of assessments and requirements.

Results: For the 2011-2017 study, 3042 deficiencies were collected. Labelling sections accounted for 52% of the deficiencies, followed by amendment schedule (12%), general deficiencies (11%), foreign registration status section (10%), application details (8%) and GMP standards (7%). Labelling, had the highest deficiencies (57%) in the 2021 study, followed by foreign regulatory status (15%) as well as GMP documentation and application details (10%). These deficiencies were found in 52 query letters, as 10 did not consist of any queries from Module 1.

Conclusions: The qualitative and quantitative data provided herein is intended to assist applicants in building quality submissions in order to convey acceptable regional requirements during submission and reduce the authority's overall registration turnaround time.

2.1 Introduction

The mandate of a medicine regulatory authority is to ensure the quality, safety and efficacy of medicines, and the accuracy of the product information submitted.[1] Most regulatory authorities in third-world countries are confronted with a convergence of obstacles against a backdrop of limited resources similar to small states.[2] In general, these authorities should be able to design regulatory systems based on the demands of their respective health systems, while guaranteeing proper oversight and regulation.[2] In order to achieve improved regulation and monitoring of national medicines markets, regulatory authorities must do more with less, making it imperative to adopt efficiencies, leverage the work of others, and collaborate across regulatory authorities and institutions.[3] Due to the challenges as highlighted above, by 2018, the South African Health Products Regulatory Authority (SAHPRA) inherited a backlog of 16 000 applications which resulted in significant delays in the access of medicines to patients.[4] For improved regulation that is tailored to suit the need of South African patients, SAHPRA developed a new regulatory pathway called the risk-based assessment approach which resulted in significant improvements to the registration turnaround times.[5] One other fundamental concept they utilised is transparency, which has been lacking in the South African regulation for the past decade. According to reports, the publication of common deficiencies by the regulatory authorities results in sufficient and correct information provided to authorities thereby reducing scientific evaluation times.[6] In an effort to be more transparent and to assist applicants and manufacturers in incorporating quality into their registration submissions, a series of articles were published. The articles focused on deficiencies commonly identified in the Active Pharmaceutical Ingredient (API)[7], Finished Pharmaceutical Product (FPP)[8], and bioequivalence sections of SAHPRA[9] submissions. The current study focuses mostly on the common deficiencies found by SAHPRA in specific sections of Module 1 of the regional section as assessed by the PEM Pre-registration Unit.

From its inception in 1964 until the year 2002, South African authority (previously known as the Medicines Control Council (MCC)) required the dossiers to be submitted in the *Medisynebeheerraad* (MBR) format.[10] In 2003, the format was changed to the Medicine Registration Form (MRF) which is similar to the CTD except for the specific granularity in order to facilitate harmonisation with other international authorities.[11]

Seven years later, in June of 2010, MCC implemented the use of the CTD format and published the General & Module 1 Guideline.[11] Module 1 and Module 3.2.R are regional information sections that are country-specific, therefore, based on the required information, it is up to the regulatory authority to decide how the design will be. According to the International Council for Harmonisation (ICH) M4 R4, Organisation of CTD for the Registration of Pharmaceuticals for Human Use, Module 1 should contain region-specific documents such as application forms, proposed labelling aspects, inspection certificates and foreign regulatory status of the application.[12]

SAHPRA adopted the format used by the Australian agency, Therapeutic Goods Agency (TGA) for Module 1[13] with the inclusion of Module 1.7, which is critical for the inspectorate Unit consisting of all the GMP

documentation required. Module 1.5.2.1 was also added which details any amendments to be implemented in the dossier as depicted in Table 1. This was effective in the response phase to facilitate the review of any changes in the dossier. Module 1 as detailed in Table 1 consists of sections 1.1 to 1.11. The granulation entails the application form (Module 1.2.1), annexures to the application form (1.2.2) which are proof of payment, letter of authorisation for communication on behalf of the applicant, dossier product batch information, curriculum vitae of the qualified person for pharmacovigilance, etc. The documentation forms part of requirements for submission of Module 1. Module 1.4 includes information about the quality, clinical and non-clinical experts while Module 1.10 details information regarding foreign regulatory status of the application.

Table 1: Granulation of the SAHPRA Module 1 section of the dossier.[14]

Module 1		
1.0	Letter of Application	
1.1	Comprehensive table of contents	
1.2	1.2.1 Application form	
	1.2.2 Annexes to the Application form	1.2.2.1 Proof of payment
		1.2.2.2 Letter of authorisation for communication on behalf of the applicant
		1.2.2.3 Dossier product batch information
		1.2.2.4 Electronic copy declaration
		1.2.2.5 Curriculum vitae of the qualified person for pharmacovigilance
		1.2.2.6 API change control
		1.2.2.7 EMA certificate for a Vaccine Antigen Master File (VAMF)
		1.2.2.8 EMA certificate for a Plasma Master File (PMF)
1.3	1.3.1 South African Professional Information	1.3.1.1 Professional Information (PI)
		1.3.1.2 Standard references
	1.3.2 Patient Information Leaflet (PIL)	
	1.3.3 Labels	
	1.3.4 Braille	
1.4	1.4.1 Information about the Expert - Quality	
	1.4.2 Information about the Expert - Non-clinical	
	1.4.3 Information about the Expert - Clinical	
1.5	1.5.1 Literature based submissions	
	1.5.2 Amendments / Variations	1.5.2.1 Tabulated schedule of amendments
		1.5.2.2 Medicines Register Details
		1.5.2.3 Affidavit by Responsible Pharmacist
	1.5.3 Proprietary name applications and changes	
	1.5.4 Genetically modified organisms (GMO)	
	1.5.5 Package Insert and Patient Information Leaflet amendments /updates	
1.6	Environmental risk assessment	
1.7	1.7.1 Registration certificates or marketing authorisation	
	1.7.2 Inspection reports or equivalent document	

	1.7.3 Latest Good Manufacturing Practice (GMP) certificate or a copy of the appropriate license	
	1.7.4 Release	1.7.4.1 Active Pharmaceutical Ingredient (API)
		1.7.4.2 Inactive Pharmaceutical Ingredients (IPIs)
		1.7.4.3 Finished Product Release Control (FPRC) tests
		1.7.4.4 Finished Product Release Responsibility (FPRR) criteria
	1.7.5 Confirmation of contract	
	1.7.6 CPP (WHO certification scheme) if applicable	
	1.7.7 South African Pharmacy Council (SAPC) registration	
	1.7.8 Registration with the Registrar of Companies	
	1.7.9 Other documents relating to the Applicant	
	1.7.10 Sample and Documents	1.7.10.1 Confirmation of submission of the sample
		1.7.10.2 Batch Manufacturing Record (BMR) of the sample (or refer to 3.2.R.8, or confirm if available for inspection)
		1.7.10.3 Certificate of Analysis (CoA) of sample (final product and API used)
	1.7.11 Certified copy of permit to manufacture S5, S6, S7 and S8 substances	
	1.7.12 Inspection flow diagram	
	1.7.13 Organogram	
1.8	1.8.1 Details of compliance with screening outcomes	
	1.8.2 Details of any additional data submitted	
1.9	1.9.1 Individual patient data - statement of availability	
1.10	1.10.1 List of countries in which an application for the same product as being applied for has been submitted	
	1.10.2 Registration certificates or marketing authorisation	
	1.10.3 Foreign prescribing and patient information	
	1.10.4 Data set similarities	
1.11	1.11.1 Bioequivalence trial information	

A new design for Module 3.2.R was also implemented which was required for generic products, as there were some sections that were not designated in the CTD format. The additional sections included:

- Information and documentation for bioequivalence summaries (3.2.R.1).
- The location for a CEP/CPQ to be placed when it has been submitted (3.2.R.3).
- A comparative study report for when more than one API manufacturer is used (3.2.R.4).[15]

The format is different from other authorities. For instance, the United States Food and Drug Administration (USFDA), has Module 1 sections that start from Module 1.0 to 1.20 which are considered requirements for the region.[16] The additional sections include sections such as meetings in Module 1.6 since the authority does

pre-submission consultations with the applicants. Other sections included a special protocol assessment request in Module 1.8, promotional material in Module 1.15 and post-marketing studies in Module 1.17.[16]

The general regulations made in terms of the medicines and related substances act, 1965 (act no. 101 of 1965), as amended, consist of instructions on the regulation of the Professional Information (PI), Patient Information Leaflet (PIL) and Labelling of South African Medicines.[17] Therefore, Module 1.3 is evaluated according to the regulation. With the recent harmonisation with the European Medicines Agency (EMA) in 2019, SAHPRA has adopted the latest PI and PIL format from the EMA summary of product characteristics (SmPC) with a few additions for local requirements.[18, 19] The harmonisation of the labelling also reduces the workload for pharmaceutical companies in designing different packaging inserts for different regions.

The regional administrative information is evaluated by the Clinical Evaluations Management (CEM) pre-registration Unit, Inspectorate Unit and Pharmaceutical Evaluations Management (PEM) pre-registration Unit. The CEM pre-registration Unit confirms that the labelling located in Module 1.3.1 and 1.3.2 of the generic products, is in accordance with the registered innovator products, while the Inspectorate evaluates Module 1.7 and utilises the details for conducting inspections. The PEM pre-registration Unit evaluates specific sections in Module 1 which relate to the quality of the product as well as validation of the remaining sections to confirm that the required documentation has been provided and concurs with the respective modules in the CTD. Therefore, this study aimed to investigate the common deficiencies identified in the assessments conducted by the PEM pre-registration Unit for applications finalised between 2011-2017. An additional study is conducted on applications assessed in 2021 to confirm consistency of the requirements over the years. This information will allow pharmaceutical companies to submit dossiers of acceptable quality, reduce registration turnaround times and accelerate access to medicines for South African patients.

2.2 Methods

The common deficiencies observed in specific sections of Module 1, as assessed by the PEM pre-registration Unit, were collected from applications finalised between 2011-2017. The method used for obtaining the data is comprehensively detailed in the publications for common deficiencies in the Active Pharmaceutical Ingredient section[7] and the Finished Pharmaceutical Product section[8] of the CTD. A sample size of 325 applications for the non-sterile products and a sample size of 244 for the sterile applications were selected and used for the investigation of the common deficiencies. Thus, an overall sample of 569 applications was used to investigate the deficiencies in the regional section, Module 1. A further investigation of common deficiencies found in Module 1 was undertaken using 62 applications evaluated between January and May 2021 in order to confirm the consistency of the assessments and requirements. The SAHPRA electronic document system, which houses all records pertaining to the applications, was where the query letters were located. The data collection involved extraction of the specific query from the letter and collating according

to the section or sub-section in Microsoft Excel ® 2016 Worksheets. The results on the common deficiencies observed are detailed below.

2.3 Results

From a sample of 569 applications, 3042 deficiencies were collected as recorded in Table 2 which includes the quantity of deficiencies calculated as a percentage value, per section in Module 1. Figure 1 provides an illustration of the most common deficiencies identified for each section for applications finalised between 2011-2017.

For an example:

- Labelling sections covered 52% of the deficiencies,
- The amendment schedule section covered 12%,
- General deficiencies 11%,
- Foreign registration status 10%,
- Application details 8%
- GMP requirements 7%.

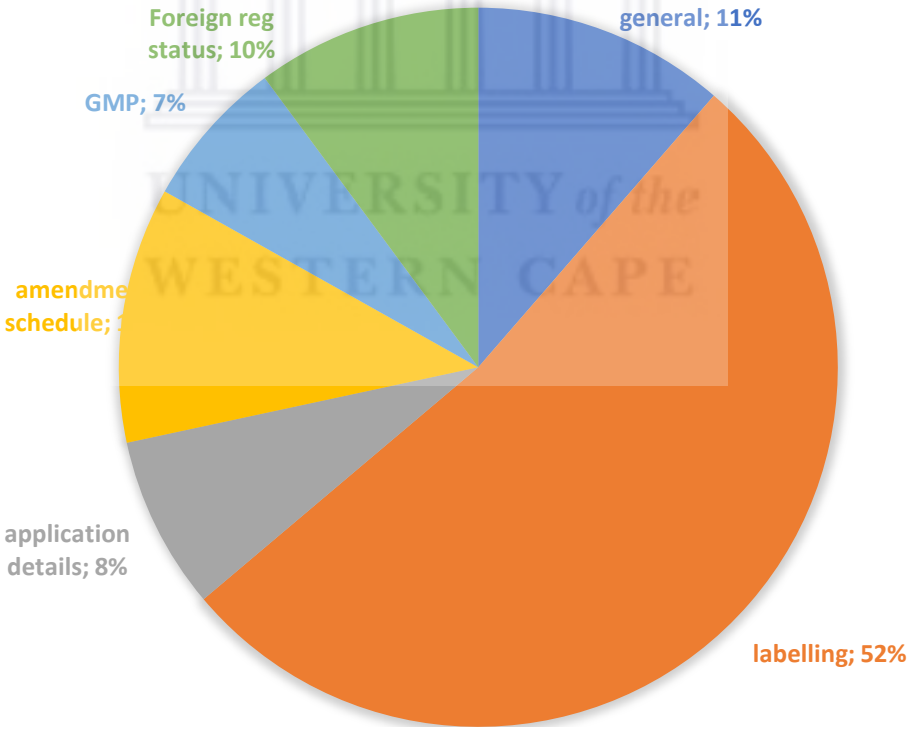

Figure 1: Graphical illustration of the common deficiencies observed by SAHPRA during assessments of Module 1 for applications finalised between 2011-2017.

For the applications evaluated in 2021, the following data was discerned:

- Query letters for 62 applications were retrieved, and as the remaining 10 applicants had no queries relevant to Module 1, 373 deficiencies were gathered from 52 applications.
- Out of the 62 applications found, 21 were sterile while the remaining 41 were non-sterile.

In Table 2, each deficiency observed is listed and quantified in the 2021 column. It is also worth noting that there were no new deficiencies identified that are different to those collected in the 2011-2017 sample, as the requirements of Module 1 requirements remained the same between the two study periods. The labelling section contained the most deficiencies (57%), as shown by the graphical representation of the distribution of the deficiencies in Figure 2. This observation is also witnessed in the sample from 2011 to 2017. The section on foreign regulatory status-comes in second with 15%, and the third largest sections with 10% are on GMP documentation and application details. The last two sections with the least number of deficiencies are on the amendment schedule section (6%) and the general queries section (2%).

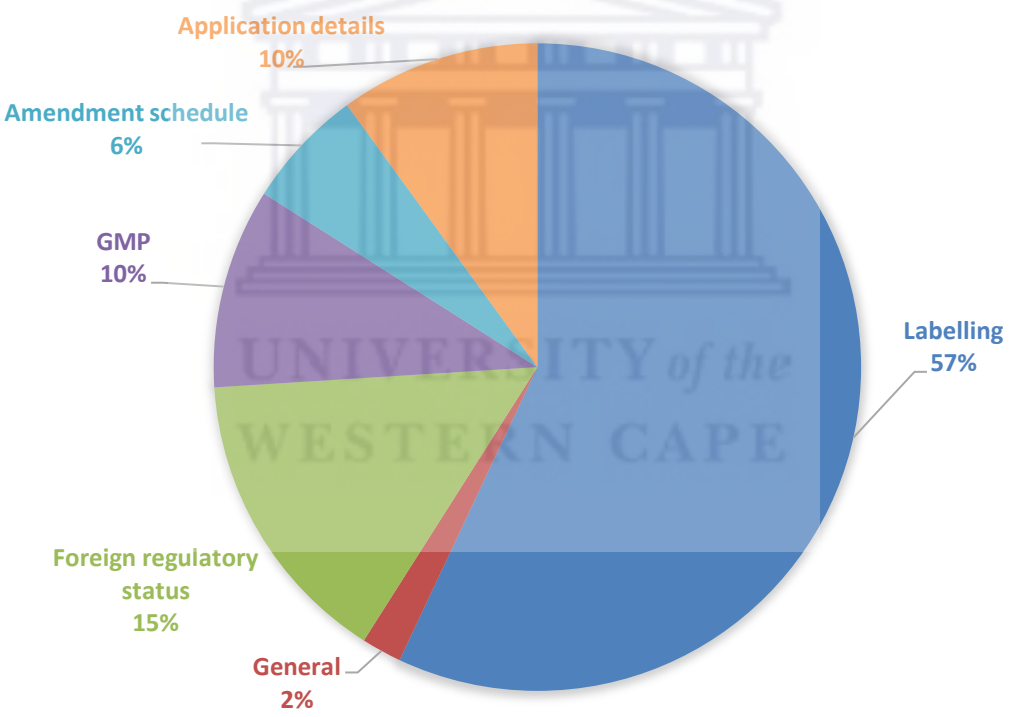

Figure 2: common deficiencies observed by SAHPRA during assessments of Module 1 for applications assessed in 2021.

Table 2: Quantification of the deficiencies observed in Module 1 of dossiers submitted to SAHPRA assessed by the PEM pre-registration Unit.

DEFICIENCY	No of deficiencies (2011-2017)	% of deficiencies per section (2011-2017)	No of deficiencies (2021)	% of deficiencies per section (2021)
General				
Provide double-sided copies in future.	34	10		
Do not use shading as legibility is generally compromised.	33	9.5		
Provide a comprehensive table of contents in accordance with the general guidelines.	58	17		
Consistently comply with metrication on the regional information especially Module 1.3	89	26	5	63
Include tabs and dividers for various sections of the dossier (based on previous paper submissions)	25	7.2		
Questions/queries not being adhered to resulting in the recommendation being sent out again.	66	19		
The general quality of the dossier is not up to the required standard, and the general information guideline was not complied with.	29	8.4	3	37
Correct the inconsistencies with regard to the name of the manufacturers between different sections of the dossier.	12	3.5		
	346		**8**	
Details of the Application and Annexes (Module 1.2)				
The letter from the Chief Executive Officer (CEO) authorising communication with the authority on behalf of the applicant should be submitted. This delegation cannot be by the responsible pharmacist, it should be signed by the CEO of the company authorising the delegation.	55	27	8	22
Include a signed application form with an application number included, submission date, whether application is registered in the country of origin and the correct dosage form and strength.	38	19	6	16
State the strength per dosage unit of the product.	63	31		
In the API change control section submit a confirmation or declaration that the API for which the CEP was granted is identical in all aspects to the API in the original application.	10	4.9	8	22
API change control must be submitted by the API manufacturer. This should include that communication will be made to the authority should any significant changes occur.	35	17.1	15	40
Others	4	2.0		
	205		**37**	
South African Labelling and Packaging (Module 1.3.1, 1.3.2 and 1.3.3)				
State the approved name with the specified quantity in mg units of the API per tablet.	61	3.8		
Describe the outer container and state the pack sizes if greater than the number 10 per blister pack	49	3.1		

Describe the components of the blister pack.	57	3.6	5	2.3
Include the constituents of colourant e.g. Opadry yellow under excipients in the PI and PIL.	19	1.2	15	7.0
The quantity of the alcohol contained in the medicine should be indicated on the label, if such quantity exceeds two percent by volume.	24	1.5	7	3.3
List all the excipients in the product in the PI and PIL under composition and "What the product contains" respectively.	24	1.5		
Indicate the size of the vials used as the container closure system for the product.	32	2.0	3	1.4
Correct the description under presentation in the PI & PIL by including the size, type and colour of the ampoules used.	16	1.0	5	2.3
Expand the identification and Presentation by including the Type of glass vial used (Type I/II) and the type of rubber closures.	56	3.5	12	5.6
Remove the amount of salt under composition in the PI, PIL and labels and correct the sentence to read for instance, "each vial contains esomeprazole sodium equivalent to 40 mg esomeprazole".	12	0.8	8	3.6
Correct the statement on the stability of the reconstituted solutions under storage in the PI to read: "Although chemical and physical stability of reconstituted/diluted solutions has been demonstrated for 24 hours at 2 - 8 °C (depending on data submitted), from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions".	110	6.9	18	8.5
Expand the description of the screw cap and tamper-evident ring to include the chemical nature, density and opacity of the material under Presentation in the PI and PIL	24	1.5	10	5.0
Compatibility with the recommended IV solutions must be proven in 3.2.P.2 and 3.2.P.8.	15	0.9	15	7.0
The label on the immediate container must be corrected to comply with all the requirements of regulation 8.2 for containers larger than 5 ml (see regulations to act 101 of 1965).	34	2.1	13	6.1
Correct the heading of PI to reflect the correct API as well as the type of dosage form, chewable, slow-release, film-coated tablet etc.	33	2.1	2	0.9
Under composition in the PI and PIL include all excipients present and omit those that are not or may alarm the patient in the product and in the coating material.	61	3.8	26	12.2
Include the colour and the clarity of the HDPE container or blister packs used.	40	2.5	3	1.4
Include the presence of sugar or the statement that it is sugar-free, as well as the quantity of the sugar.	155	9.7	25	12
The label has to be in two of the official languages and correct spelling on the official languages.	21	1.3		
Indicate that the primary container closure system should be kept in the carton until required for use.	66	4.1	2	0.9

Amend the PI, PIL and Label to read the correct storage conditions and as per Module 3.2.P.8.	38	2.6	10	5.0
Amend the PI, PIL and Label to include the correct container closure system as per Module 3.2.P.7.	20	1.0		
Expand the description of the presentation in the PI and PIL to include the use of the outer carton.	68	4.3		
Include the tablet sizes in the description to facilitate distinguishing between the different strengths.	39	2.4	5	2.3
Under the storage instructions, add protect from light, heat and moisture since the studies show that the product is sensitive to these.	46	2.9	5	2.3
Include the instruction “do not freeze” in the PI, PIL and label.	6	0.4		
Under storage instructions include at or below (the temperature) and keep well closed.	159	10	3	1.4
Expand the description of the blister packs in the PI and PIL to include type of blister and colour.	73	4.6		
Include the presence of an antioxidant and/or preservative as well as the correct measuring units.	9	0.6	3	1.4
State the instruction "keep out of reach of children" clearly on the PI, PIL and Label.	21	1.3	1	0.5
Include the instruction, “discard any unused portions”.	5	0.3	10	5.0
Indicate that the product is “for single use only”.	56	3.5	5	2.3
Provide justification of the score line under 3.2.P.2.	20	1.3		
Indicate the colour of the ink used for imprinting on the tablet or capsule.	16	1.0	1	0.5
Remove the content of the salt or ester under composition.	33	2.1		
Ensure that the correct and same scheduling status is used between the PI, PIL and the label.	10	0.6	2	0.9
Under dosage and direction include whether it should be taken with or without food with a glass of water and should not be chewed or crushed or for powder indicate that a heaped or level spoon should be used.	2	0.1		
For the reconstituted suspensions include the statement "shake well before use".	26	1.6	4	1.8
Under composition in the PI and PIL of the tablet delete the inclusion of purified water as an excipient.	5	0.3		
Include aluminium lidding foil in the packaging material description under Presentation.	25	1.6		
Others	10	0.6		
	1596		**213**	
Tabulated amendment schedule (Module 1.5.1.2)				
Comply with the requirements of the completion of the Amendment schedule.	91	38	15	68
Information is only included in the amendment schedule and not in the actual dossier.	146	62	7	32
	237		22	
Good Manufacturing Practice (Module 1.7)				
Include an inspection flow diagram indicating sites of manufacture.	23	6.6		

The submitted inspection flow diagram is incorrect or insufficiently detailed, submit the correct flow diagram detailing all Units and manufacturers involved.	11	3.1		
Evidence of recent registration with SAPC by the responsible pharmacist and person authorised to communicate with SAHPRA should be submitted.	68	19.4	10	27
List each of the FPRC laboratories responsible for identification and Assay of the FPP after importation.	54	15.4		
Include the facility responsible for the final product release.	68	19.4	5	13
Indicate that the active ingredients will at least be re-assayed and identified and a commitment should be made for full testing at least once a year, in addition, include the address of FPRC.	30	8.6	11	30
Indicate that the inactive ingredients will at least be re-assayed and identified and a commitment should be made for full testing at least once a year as well, in addition, include the address of the FPRR.	30	8.6	11	30
The submitted organogram is incomplete and does not cover the complete regulatory arm of the organisation, provide the complete organogram.	48	13.7		
Others	18	5.1		
	350		**37**	
Foreign regulatory status (Module 1.10)				
Explain why the product is not registered in the country of origin.	83	26.0	18	32
Define the abbreviations of the names of the countries in which the products have been registered in Module 1.10.1.	55	17.4	2	3.0
Submit a report on the progress made in the registration of the product. Any negative decisions should be reported without delay to the authority.	156	49.2	30	54
Provide a valid GMP Certificate and market authorisations where the product is registered. (this is however assessed and verified by the inspectorate Unit)	14	4.4	6	11
Others	9	3.0		
	317		56	

Within the labelling section, there are three subsections that contain the following documents:

- Module 1.3.1 – Professional Information (PI)
- Module 1.3.2 – Patient Information leaflet (PIL)
- Module 1.3.3 – label.

For the 2011-2017 study, the five most common deficiencies in the labelling section as recorded in Table 2. They are highlighted in Figure 3 as follows:

i. the temperature used in the labelling for the storage condition = 159 (10%),

ii. the request to include the presence of sugar and its quantity = 155 (9.7%),

iii. the storage of the reconstituted solution = 110 (6.9%),

iv. type, nature and colour of the primary packaging material = 73 (4.6%),

v. the fifth highest deficiency in the section was on the use of the outer secondary packaging material 68 (4.3%) to protect sensitive products.

For the 2021 study the following trend was observed:

i. the highest deficiencies are the inclusion of excipients and omission of those that may alarm the patient such as hydrochloric acid and potassium hydroxide as pH adjusters = 26 (12.2%),

ii. the presence and quantity of sugar present = 25 (12%),

iii. the third highest is the stability and storage instructions of the reconstituted solution = 18 (8.5%).

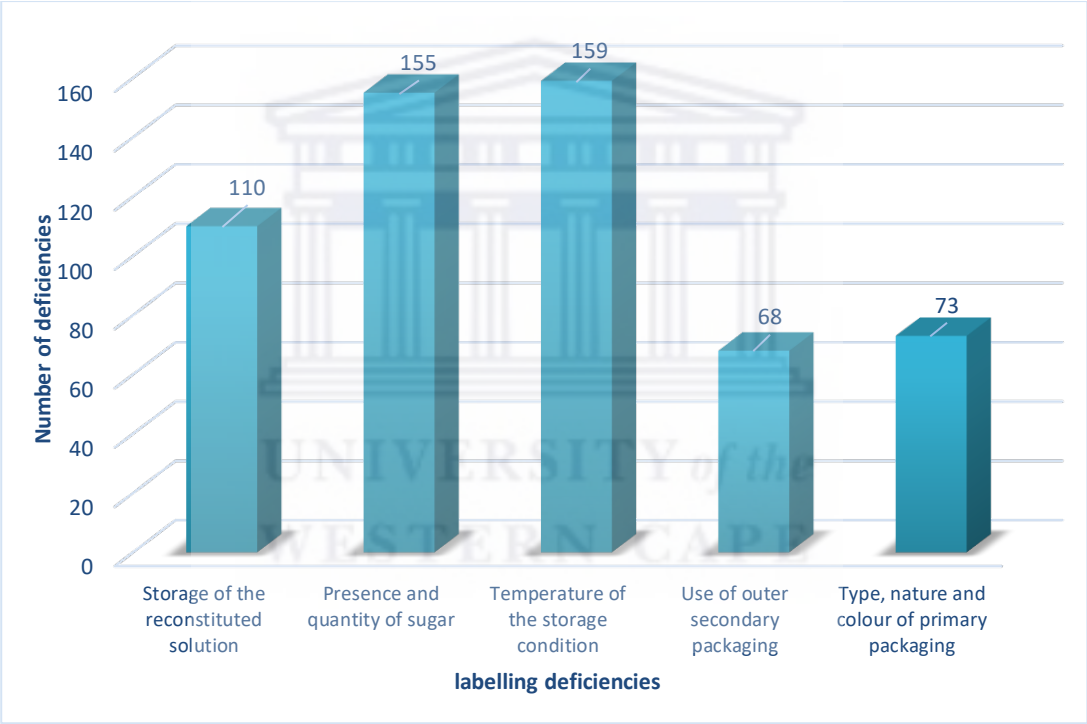

Figure 3: The top five highest deficiencies in the labelling section of Module 1.

2.4 Discussion

The deficiencies in the regional and administration section are discussed below in accordance with the identified categories. Reports of common deficiencies from other authorities were not available for Module 1, as these are country-specific and vary in granularity between countries.

2.4.1 Labelling

The highest prevalent deficiency across the 2011–2017 study, the temperature for the storage condition, is crucial and should be correctly stated for the end-user in accordance with the stability data submitted. If not clearly stated, the product might be at risk of being stored at temperature conditions that are not favourable for the product, resulting in the degradation impurities which may be toxic for consumption. The second highest deficiency, the request to include the presence and quantity of sugar is based on Regulation 8 (1) (h) (i) of the Medicines and Related Substances Act of 1965 (Act 101 of 1965),[17] for administration by the oral or parenteral route for all medicines intended for human use. In 2013, MCC developed a guideline for labelling for sugar containing medicines.[20] Even with the publication of the guideline, applicants continue not to include the instruction as required. The guideline is intended to provide guidance to applicants on how to label medicines containing "sugar" to alert prescribers and users to be cognisant to the presence of any sugar in the medicine and to take the necessary steps or decisions. For instance, patients with rare hereditary conditions such as fructose intolerance, lactose intolerance, glucose-galactose mal-absorption or sucrose or isomaltase insufficiency should not take these sugars. The storage instruction of reconstituted solutions is also important, and this would normally be supported by stability data to store the solution in aseptic conditions at 2-8 °C. To minimise contamination of the sterile medicine, from a microbiological point of view the instruction is included to advise the end user to use the medicine immediately after preparation. The last two highest deficiencies in the top five are based on the container closure system used. Inclusion of the type, nature and colour of the primary packaging and the secondary packaging material serves two-fold, to facilitate visual identification of counterfeit medicines and additional protection for light-sensitive products. This similar trend is observed in the 2021 study and the above reasoning also applies.

2.4.2 Amendment Schedule

Module 1.5.1.2, which is the amendment schedule, accounted for 12% of the deficiencies observed in Module 1 for the 2011-2017 study and only 6% in the 2021 study as depicted in Figures 1 and 2 respectively. The amendment schedule is a template used in the response phase by the applicants to outline the query raised, the response by the applicant, changes made, the section where the change is made and the reason for the

change. This information can be cross-referenced with the information in the dossier to facilitate review and reduce the evaluation times for responses. The deficiencies where the applicant did not comply with the requirements in the completion of the amendment schedule were quantified as 38% and 68% in the 2011-2017 and 2021 studies respectively. The other 62% and 32% respectively for both studies were on applicants indicating that the information has been included in the amendment schedule. However, the documentation as stated in the amendment schedule could not be located in the dossier upon evaluation. This prompted another round of queries, which ultimately caused the product's finalisation to be further delayed.

2.4.3 General

This section contains deficiencies frequently recorded relating to the paper-based submissions used until 2019. These are not applicable since SAHPRA is currently receiving submissions in electronic format using eCTD and eSubmission, hence these are not recorded for the 2021 study. The predominant general recommendations in both studies were on the use of the Metrication Act on regional sections denoting SI units, commas etc. which accounted for 26% of deficiencies in the section for the 2011-2017 study and 63% for the 2021 study. The second highest deficiency was on applicants not addressing the queries (19%), which leads to the recommendations being sent out again leading to further delays in finalisation.

2.4.4 Foreign regulatory status

The report on the progress made in the registration of the product accounted for 49% of the deficiencies in this section for the 2011-2017 study and 54% for the 2021 study. The status of approval by other authorities provides a level of confidence on the product since it was reviewed by another authority, which means the risk is low. In the case where the product is registered by the authority SAHPRA aligns itself with, a registration certificate should also be submitted to confirm this and 4.4% of applications did not include this certificate. With the reliance approach adopted by SAHPRA since 2019, no assessments are necessary; only verification with reports from the other regulatory bodies that SAHPRA is aligned with is required to establish that the dossiers/products are the same. This defines the aspect of reliance, which is the act whereby one regulatory authority may consider and give significant weight to totally or partially rely upon scientific assessments or inspection reports performed by another authority or trusted institution in reaching its own decision.[4] SAHPRA designed a template which enables verification of similarity of the dossier submitted to the other regulatory authority, once this is confirmed, the product can be registered.

2.4.5 Good Manufacturing Practice (GMP)

The highest deficiency under the GMP section for the 2011-2017 study, entails the request for confirmation of registration with the South African Pharmacy Council of the responsible pharmacist and the pharmacist responsible for communication with the authority. The second deficiency with the same quantity was on the inclusion of the facility responsible for final product release (19.4%), to ensure that the product is within the acceptance limits before it is distributed. This section is largely evaluated by the Inspectorate Unit and the PEM pre-registration Unit assess the specific sections relevant to the quality of the product such as 1.7.4 and 1.7.10.3 as depicted in Table 1. From the deficiencies identified, it is evident that the PEM pre-registration Unit used to evaluate the whole section resulting in duplication of efforts. Therefore, the Units are encouraged to communicate and clearly outline the sections they cover to avoid such duplication in future. This was implemented for the risk-based assessments approach which entailed elimination of duplication.[5]

2.5 Conclusion

The two studies outline the common deficiencies observed in the regional section, Module 1, assessed by the PEM, pre-registration Unit within SAHPRA between 2011-2017 and in 2021. The five most common deficiencies are extensively discussed with the labelling section as the highest by a 52% margin for the 2011-2017 study and 57% for the 2021 study. The other deficiencies that were identified from Module 1 are on the amendment schedule, GMP, general information and foreign regulatory status. A similar trend was observed in the identified deficiencies in both studies which confirms the consistency of deficiencies over the years since Module 1 requirements did not change over the two study periods. This research, therefore, provides transparency to the South African pharmaceutical companies on Module 1 deficiencies to address before dossier submissions. These findings will guide pharmaceutical companies in submitting quality dossiers, which will reduce the registration turnaround time and thereby accelerate access to medicine for patients.

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CHAPTER 3

Common deficiencies found in the Active Pharmaceutical Ingredient (API) section of non-sterile generic products submitted for registration by SAHPRA

Abstract

Purpose. This research study aims to determine the qualitative and quantitative common deficiencies included in the API section of dossiers submitted to SAHPRA. The study was conducted retrospectively over a 7-year period (2011-2017) for non-sterile generic products that were finalised by the Pharmaceutical and Analytical pre-registration Unit. In this period, the restricted part of the CTD was evaluated when needed therefore this was not conducted on all applications. The requirement to evaluate the restricted part for all applications was initiated in January 2020, thus, a separate study has been conducted to identify the common deficiencies in the restricted part. **Methods.** There were 2089 applications finalised between 2011-2017 and in order to attain a representative sample for the study, the multi-stage statistical sampling called the 'stratified systematic sampling' was selected as the method of choice. Sample size was obtained using the statistical tables found in the literature and confirmed by a sample size calculation with a 95% confidence level, resulting in the selection of 325 applications. Subsequently, all the deficiencies were collected and categorised according to CTD subsections. For the restricted part study, all new applications evaluated between January to May 2020 were used. **Results**. A total of 1130 deficiencies were collected from 325 applications sampled. The majority of the identified deficiencies were from Module 3.2.S.3.1 (19.38%) on characterisation, Module 3.2.S.1.3 (19.11%) on general properties, Module 3.2.S.4.1 (10.44%) on specifications and Module 3.2.S.4.3 (8.32%) on validation of analytical methods. The study on the restricted parts included the five most common deficiencies that SAHPRA has identified, which are similar to those observed from the 2011-2017 applications. This confirms that the quality of the evaluations has been maintained over the years. Comparison of the deficiencies with those reported by other agencies such as the USFDA, EMA, WHOPQTm and TFDA are discussed with similarities clearly outlined. **Conclusions**. The most common deficiencies observed by SAHPRA were extensively discussed. These findings could serve as a guidance for API manufacturers to submit better quality APIMFs which will improve turnaround times for registration and accelerate access to medicines for patients.

3.1 Introduction

The South African government established a medicines regulatory authority in 1965 shortly after the implementation of the Medicines and Related Substances Act (Act 101 of 1965). [1] The quality and efficacy aspects of finished pharmaceutical products (FPP) are evaluated by the Department, Pharmaceutical Evaluations and Management (PEM) pre-registration Unit within SAHPRA. The pre-registration Unit utilised 15-20 external experts as evaluators. The experts formed part of the Pharmaceutical and Analytical (P&A) Committee, which provided the necessary support to the Unit and the Committee meetings served as a quality assurance measure for all applications. Committee members provided technical and scientific advice for evaluations in the pre-registration Unit. This meant that each report on the assessment of the information provided in the dossier was discussed in the meeting before communication with the applicant. The applications are submitted in the form of a dossier in the Common Technical Document (CTD) format to the Health Products Authorisation (HPA) and distributed to different Units within SAHPRA for evaluation. A CTD is an internationally agreed format for the preparation of new product applications for submission to regional regulatory authorities. The CTD format is divided into five modules as illustrated in Figure 1 [2].

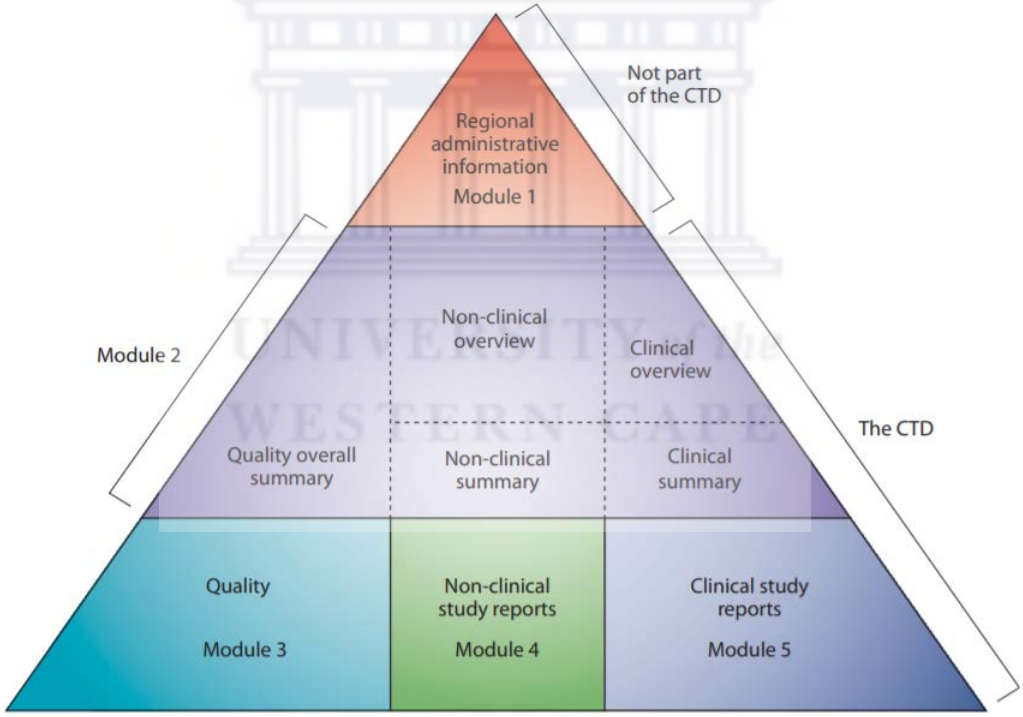

Figure 1: The organisation of the CTD into five modules. Module 1 is intended to be region specific while the rest of the modules are common for all regions. [2]

The quality part of the dossier is divided into two main sections namely, information on the active pharmaceutical ingredient (API) and information on the finished pharmaceutical product (FPP). A list of deficiencies referred to as recommendations are then produced from the evaluation process and

communicated to the applicant. The applicants are given three months to respond and update the dossiers with the requested information necessary to verify the quality of the product. There were no specified rounds of communication given between the applicant and the agency. Once all the requirements have been met by all the Units and the quality of the drug product is considered safe and efficacious as required by the agency, the FPP is finalised and is recommended for registration.

SAHPRA received the API part in the form of a DMF/APIMF (applicant part), or requirements supported by a Certificate of Suitability (CEP) or a Certificate of pre-qualification (CPQ). The CEP and CPQ are certificates allocated for APIs where DMFs have been approved by EDQM [3] and WHO-PQTm [4] respectively. Authorities such as EMA, [3] USFDA, [5] TFDA [6] and Health Canada [7, 8] have implemented the APIMF/DMF procedure. In this procedure, the complete data is assessed including confidential information from manufacturers. This procedure has not been adopted by many authorities due to insufficient resources and capacity, therefore, only the applicant part of the DMF is submitted and assessed. International medicines regulators worldwide such as TFDA [6], USFDA [9, 10] and EMA [11-15] as well as WHO-PQTm [16, 17] have published several articles on various regulatory aspects in order to promote transparency between the authority and the manufacturers. Those publications are intended to assist applicants to improve the quality of their submitted dossiers, in order to facilitate and accelerate the approval process. The study therefore aims to highlight the common deficiencies observed from the API section submitted by APIMF holders to the health authority, SAHPRA. This is aimed at guiding the manufacturers in submitting better quality APIMFs which will decrease turnaround times for registration and accelerate access to medicines for patients.

3.2 Methods

Over the 7-year period (2011 – 2017), 2089 applications were finalised by SAHPRA. These applications were used to study the trends observed by the authority in order to refine the current processes and inform industry of the current requirements from a scientific viewpoint. Thus, due to the large number of applications received, a statistical sampling method became a requirement for this research. Sample selection in this study should provide a true representation of the population enabling the results to be generalised to the population as a whole. In statistics, stratified sampling is a method of sampling from a heterogeneous population which can be partitioned into subpopulations. [18] It involves dividing the entire population into homogeneous groups called strata. [18] The sampling method ensures that each subgroup is adequately represented within the whole sample of a research study. Sampling of medicinal products from a large population would require stratified sampling due to the different critical variables involved such as the applicant, the dosage form, the API used, the therapeutic category and finalisation time of the drug product. Thus, stratified sampling would be suitable for the population in this research study. In addition, systematic sampling is preferred as opposed to random sampling in order to ensure that proportional number of units are selected accordingly at the

respective strata. [19-22] The multi-stage sampling technique used is therefore called stratified systematic sampling.

Sample size determination can be obtained using various methods such as a census for small populations, a sample of a similar study, published tables or statistical formulae. [23-25] For sample size calculation, the formula reported by Israel G. D, (1992) [24] contains three variables which are a requirement when determining a sample size (see Supplementary material for equations and calculations, page 272). The variables are; level of precision, level of confidence and the degree of variability. [24, 25] The level of precision used is often expressed in percentage points and described as the percentage error which is selected as ± 5%. [24] In this regard, the level of confidence is therefore 95%. Cohran W. G. (1963) [22] developed an equation to yield a representative sample for proportions of large samples where the confidence level corresponds to a Z-score which is calculated as 1.96 for the selected confidence level as per the developed equation. The degree of variability (p) refers to the distribution of attributes in the population and a 50% variability is ideal for a heterogeneous population as it gives higher variability. [21, 22] thus a proportion of 50% (0.5) was selected. This equation was used in calculating the sample size for this research study. The calculated sample size obtained was 325 from a population of 2023. Comparison of the calculated sample size with the table reported by F.B. Mahammad [27] for a given population size showed a similar reported value for a population of 2000 of 322 with the same confidence interval and level of precision. There are many other tables reported [24, 25, 27] with sample size ranging between 322 to 333. The k^{th} term serves as a constant value used for systematic sampling and is aimed at ensuring that adequate representative units are selected in each strata. This was calculated as six, which means selection was conducted at each 6^{th} value in order to attain the representative sample size.

The full history of all products finalised between the 7-year period (2011-2017) were collected. The history comprises of all communication between the authority and applicants until finalisation. The documents include the recommendations sent to the applicant and the responses received, as well as the evaluation reports of responses. These paper documents were obtained from the P&A Committee meeting minutes and the registry files where all documents relating to the product are kept. The investigation process involved obtaining the type and extent of the deficiencies raised in the first deficiency letter following the initial evaluation process, thereafter, extracting all the responses and feedback during multiple follow-up rounds of communication.

For the investigation of common deficiencies in restricted parts of the dossier, initial query letters sent between January to May 2020 were obtained and the recommendations recorded. The investigation is initiated in order to alert pharmaceutical companies of the common deficiencies identified by SAHPRA in the restricted parts, allowing them to submit dossiers with the required information from the onset. These were obtained from SAHPRA's electronic dossier folder and recorded.

Information for 2018 and 2019 is not included in this study due to the disruptions caused by the protesting action in 2018 and the move to the new premises in 2019 which halted production. During the transition of the authority from MCC to SAHPRA, SAHPRA staff continued to be housed in Civitas building in Pretoria with the NDoH employees. From April 2018, the department employees working in the Civitas building embarked on a protest action because of concerns about working conditions in the building. SAHPRA as a Section 3A public entity, moved into new premises at the end of 2018. Flow of submissions regained momentum by the middle of 2019.

3.3 Results

Stratified systematic sampling ensures that sampling is not random and biased and that all critical variables are considered. Aspects such as the applicant, the dosage form, the API used, the therapeutic category and finalisation time of the drug product were considered as important variables. Out of the above five mentioned variables, the most critical and of importance is the therapeutic category since we are dealing with pharmaceutical products.

Regulation 25 of Act 101 classifies and categorise medicines in South Africa as follows:

- Category A for Medicines which are intended for use in humans and are without manipulation, ready for administration;
- Category B for Medicines which cannot be administered without further manipulation; and
- Category C for Medicines intended for veterinary use, which are without further manipulation, ready for administration. [28]

Table 1: The different strata (pharmacological classifications) generated with respective population and sample sizes.

Pharmacological/therapeutic classifications	Population (*N**)	%	Sample (n∗)
1.1 Central analeptics 1.2 Psychoanaleptics (antidepressants) 1.4 Respiratory stimulants	103	4.9	17
2.1 Anaesthetics 2.2 Sedatives, hypnotics 2.5 Anticonvulsants, including anti-epileptics	149	7.1	25
2.6 Tranquillisers 2.6.5 Miscellaneous structures	191	9.1	32
2.7 Antipyretics or antipyretic and anti-inflammatory analgesics 2.8 Analgesic combinations 2.9 Other analgesics 2.10 Centrally acting muscle relaxants and	51	2.4	9
3.1 Antirheumatics (anti-inflammatory agents) 3.2 Non-hormonal preparations 3.3 Anti-gout preparations	51	2.4	9
4.0 Local anaesthetics	5	0.2	1

5.2 5.3	Adrenolytics (sympatholytics) Cholinomimetics (cholinergics)	69	3.3	11
5.4.1	Anti-Parkinsonism preparations	68	3.3	11
5.6	Histamine	10	0.5	2
5.7.1	Antihistaminics	29	1.4	5
7.1	Vasodilators, hypotensive medicines	51	2.4	9
7.1.3	Other hypotensives	328	15.7	55
7.1.5	Vasodilators - peripheral	48	2.3	8
7.3	Migraine preparations	25	1.2	4
7.4 7.5	Lipotropic agents Serum-cholesterol reducers	92	4.4	15
8. 8.2 8.4	Medicines acting on blood and haemopoietic system Anticoagulants Plasma expanders	13	0.6	2
10 10.2 10.2.1	Medicines acting on respiratory system Bronchodilators Inhalants	88	4.2	14
11. 11.1 11.4.3 11.5 11.9.2 11.10	Medicines acting on gastro-intestinal tract Digestants Other Laxatives Special combinations and Others	72	3.4	12
13.4.1 13.4.2 13.9 13.11 13.12 14. 14.2	Corticosteroids with or without anti-infective agents Emollients and protectives Radiation protectants Acne preparations Others Preparations for treatment of wounds Wound dressings	15	0.7	3
5.8 16.1 16.3 16.4	Preparations for the common cold including nasal decongestants Nasal decongestants Surface anaesthetics Naso-pharyngeal and bucco-pharyngeal antiseptics	24	1.1	4
18.1 18.2 18.3 18.8	Diuretics Antidiuretics Ion-exchange preparations Ovulation controlling agents	24	1.1	4
20.1.1 20.1.2 20.1.6	Broad and medium spectrum antibiotics Penicillins Topical antibiotics	125	5.9	21
20.2	Antimicrobials, Other than antibiotics	13	0.6	2
20.2.2 20.2.3 20.2.6	Fungicides Tuberculostatics Medicines against protozoa	34	1.6	5
20.2.8	Antiviral agents	213	10.2	36
21.1 21.2	Insulin preparations Oral hypoglycaemics	37	1.8	6
21.3	Thyroid preparations	12	0.6	2
21.5.1	Corticosteroids and analogues	8	0.4	1
21.8.2	Progesterones with or without oestrogens	10	0.5	2
21.12	Hormone inhibitors	43	2.1	7
26	Cytostatic agents	31	1.5	5
32	Other substances or agents	10	0.5	2

34 Others	47	2.2	8
TOTAL	**2089**	**100**	**349**

All medicines in the population are category A. This category is subdivided into 34 pharmacological classifications, some of which are subdivided further. Each therapeutic category is considered a stratum. These are grouped into 33 categories. The sample size in each stratum as illustrated in Table 1 varies according to the relative importance of the stratum in the population, i.e. percentage contribution. For example, if 16% of the population are antiviral agents, then 16% of the sample should contain products in that group.

The sample sizes of all strata were combined to attain a representative sample size of 349 products. The rounding down of the k^{th} term resulted in slightly more samples (349) being selected. However, the acceptable range is 322-333 as indicated above. There were 330 samples selected, five of these were omitted from the study as they undertook a different registration process called the ZaZiBoNa collaborative assessment process which SAHPRA joined in June 2016 [29] Therefore, the samples used in the study were 325 as per calculations (see Supplementary material for equations and calculations, page 272).

The deficiencies were collected and information populated in the respective Microsoft Excel® Worksheets and quantified using the complete history of finalised products. This research focuses on the API, 3.2.S part of the CTD. The 3.2.S. part of the quality section of the CTD consists of sections stipulated in Table 2 regarding the API used in the product. It contains seven sections in which five have subsections.

Table 2: The CTD sections and subsections for Module 3.2.S regarding the API.

CTD sections and subsections	Content
3.2.S.1	**General information**
3.2.S.1.1	Nomenclature
3.2.S.1.2	Structure
3.2.S.1.3	General properties
3.2.S.2	**Manufacture**
3.2.S.2.1	Manufacturer
3.2.S.2.2	Description of manufacturing process and process control
3.2.S.2.3	Control of Materials (Restricted part)
3.2.S.2.4	Control of critical steps and intermediates (Restricted part)
3.2.S.2.5	Process Validation and/or Evaluation (Restricted part)
3.2.S.2.6	Manufacturing process development (Restricted part)
3.2.S.3	**Characterisation**
3.2.S.3.1	Elucidation of Structure and other Characteristics
3.2.S.3.2	Impurities
3.2.S.4	**Control of active pharmaceutical ingredient**

3.2.S.4.1	Specifications
3.2.S.4.2	Analytical procedures
3.2.S.4.3	Validation of analytical procedures
3.2.S.4.4	Batch analyses
3.2.S.4.5	Justification of specifications
3.2.S.5	**Reference standard or materials**
3.2.S.6	**Container closure system**
3.2.S.7	**Stability**
3.2.S.7.1	Stability summary and conclusions
3.2.S.7.2	Post approval stability protocol and stability commitment
3.2.S.7.3	Stability Data

A total of 1130 API deficiencies were collected from 325 letters from products that were finalised in 2011-2017. The deficiencies observed were all collected as indicated in Table 3. The table outlines all the deficiencies recorded from 325 letters in the API section. These were categorised per subsection and quantified. The quantities per subsection were recorded as the number of times they were observed in the recommendation letters, then as the percentage of a subsection in a CTD section and lastly as a percentage in the whole 3.2.S CTD section. Figure 2 summarises the results of the common deficiencies per subsection in percentages thereby showing the frequent deficiencies.

Table 3: List of API common deficiencies recommended by SAHPRA in the products finalised by the pre-registration unit between 2011 – 2017.

Subsection	**Deficiency**	**Quantity**	**% subsection**	**% overall**
3.2.S.1	The documentation must comply with the SA Guide to GMP Chapter 4, Requirements for Documentation, including at least a unique identification, version and date. In addition, a declaration that it is current must be included.	55	17.57	4.9
3.2.S.1 (3.2.R.4)*	Include a comparison of the method of synthesis, specifications and batch analysis data to confirm similarity or outline differences between the different API manufacturers.	18	5.75	1.6
3.2.S.1 (3.2.R.3)*	Submit an updated CEP as observed from the EDQM website or ensure that the declaration of access to give the applicant access is signed by the CEP holder.	24	7.67	2.1
3.2.S.1.3	State the polymorphic form of the API used.	14	4.47	1.2
3.2.S.1.3	Provide evidence of occurrence of isomers and chirality where applicable. The absence should also be confirmed.	11	3.51	1.0
3.2.S.1.3	The solubility of each API should be stated in terms of a unit part of the substance per number of parts of the solvent, or in unit mass of substance in a given volume of solvent, at a specific temperature. The investigation should include water and the solvent(s) relevant to the product formulation.	157	50.16	14

3.2.S.1.3	Include information on the hygroscopicity of the API under physical properties.	26	8.31	2.3
3.2.S.1.3	The physical and chemical properties of the API, including e.g. solubility, particle size, hygroscopicity should be included when a CEP has been submitted	8	2.56	0.7
		313		
3.2.S.2.1	The name, business and physical address of each manufacturer of the API being applied for (including any intermediate manufacturer) should be stated.	3	3.1	0.3
3.2.S.2.2	A short description of the synthesis and a flow chart which includes the structures and stereochemistry of starting materials and intermediates; reagents, catalysts, solvents, isolation and purification; and any other relevant aspects were not included. This should be submitted.	58	59.2	5.1
3.2.S.2.2/3	The starting material proposed is considered complex. Include the tests and specifications as well as the method of synthesis of the starting material or a Certificate of analysis (CoA) to confirm that the starting material is adequately controlled.	13	13.3	1.2
3.2.S.2.3	Include the complete name and address of the manufacturer of the starting materials.	10	10.2	0.9
3.2.S.2.3	Provide information with respect to control of critical steps and intermediates in the manufacturing process description.	7	7.2	0.6
3.2.S.2.3	Briefly describe if there were recovery of materials or solvents (if any) in the method of synthesis and how they were conducted.	3	3.1	0.3
3.2.S.2.4	Provide the controls of the critical steps and isolated intermediates used in the manufacturing process of the API.	4	4.1	0.4
		98		
3.2.S.3.1	Provide interpretation of spectra, graphs and figures regarding the elucidation of the structure of the API.	94	35.1	8.3
3.2.S.3.1	Legible spectra, graphs and figures regarding the elucidation of the structure should be submitted.	99	34.0	8.8
3.2.S.3.1	Provide proof of correctness of structure. Spectra, graphs and figures were not submitted to support the correctness of structure.	4	1.5	0.4
3.2.S.3.1	Two polymorphic forms have been reported. It should be demonstrated that the one polymorphic form remains unchanged during storage. This is regardless of the fact that the synthetic route yields only one form. State if the identity test can discriminate between the different polymorphs.	17	6.3	1.5
3.2.S.3.2	Provide a description of impurities, indicating the possible source of impurities and a clear distinction between actual and possible impurities.	17	6.3	1.5
3.2.S.3.2	Provide a description of possible degradation products.	32	11.9	2.8
3.2.S.3.1	In the case of enantiomers an additional test is required to confirm the identity of the enantiomer and should be controlled in the final API specifications.	5	1.9	0.4
		268		
3.2.S.4.1	Include particle size during stability for micronised API to ensure that the API has a well-defined dissolution behaviour.	16	6.9	1.4
3.2.S.4.1	Tighten the specifications for individual impurities and total impurities in accordance to ICH guidelines and submitted batch analysis data.	10	4.3	0.9
3.2.S.4.1	Include a genotoxic impurity in the final API specifications or provide a justification for its omission.	2	0.9	0.2

3.2.S.4.1	The API specifications must be expanded to include a limit for residual solvents including benzene and the relevant validated control procedure must be described.	18	7.7	1.6
3.2.S.4.1	Include a specification for the test for polymorphism to ensure that the correct polymorph is consistently formed.	10	4.3	0.9
3.2.S.4.1	Include a test for microbial purity/content.	6	2.6	0.5
3.2.S.4.1	Include enantiomeric purity in the final specifications to ensure that the enantiomer is consistently controlled.	23	9.9	2.0
3.2.S.4.1	Tighten the assay release and stability specification to 95 - 105% in accordance with the SAHPRA guidelines and include this as a percentage label claim or in mg.	7	3.0	0.6
3.2.S.4.1	Include signed and dated specifications by authorised personnel and confirm that they are the same as the FPP's API specifications.	9	3.9	0.8
3.2.S.4.1	Bring the API specifications in line with those indicated in a recognised pharmacopoeial monograph and if a CEP is submitted the specifications must be in line with the European Pharmacopoeial monograph.	12	5.2	1.1
3.2.S.4.1	Include the specifications for particle size in the FPP manufacturer's API specifications, if applicable.	5	2.1	0.4
3.2.S.4.3	Provide details of the reference standards used for validation of related substances.	3	1.3	0.3
3.2.S.4.3	Submit validation data for the assay method of the API, residual solvents and related substances including the respective supporting chromatograms.	32	13.8	2.8
3.2.S.4.3	The FPP manufacturer must include partial validation or verification for APIs that are pharmacopoeial.	13	5.6	1.2
3.2.S.4.3	Include a more stability indicating method than Thin Layer Chromatography (TLC) as the pharmacopoeia includes the use of one, such as High-Performance Liquid Chromatography (HPLC).	5	2.1	0.4
3.2.S.4.3	Indicate the stability of the reference standard solution and the sample solutions.	5	2.1	0.4
3.2.S.4.3	Inconsistencies observed in the validation data submitted and clarification required.	36	15.6	3.2
3.2.S.4.4	Provide numeric values for the data, "complies should be avoided".	5	2.1	0.4
3.2.S.4.5	Provide justification of the limits set for final API specifications.	8	3.5	0.7
3.2.S.4.5	Provide supporting data to prove the justification of the exclusion of certain residual solvents from final specification testing with results tested on six consecutive batches.	8	3.5	0.7
		233		
3.2.S.5	Provide comparative overlaid IR spectra of the in-house reference standard with the pharmacopoeail reference standard/ qualification of the working standard with the reference standard.	26	42.0	2.3
3.2.S.5	Provide the purification method for the in-house reference standard.	3	4.8	0.3
3.2.S.5	Provide the CoA of the pharmacopoeial reference standard and/or the in-house reference standard as well as the source of the reference standard.	33	53.2	2.9
		62		
3.2.S.6	Provide a description of the container closure system(s) used.	52	76.5	4.6
3.2.S.6	Identity of materials of construction of each primary packaging material as well as the identification test used.	10	12.3	0.9

3.2.S.6	Submit control procedures, specifications and CoAs of the primary packaging material.	9	11.1	0.8
		71		
3.2.S.7.3	Provide additional stability data for the consideration of the requested retest period.	42	56.0	3.7
3.2.S.7.3	The out of specification results and justification provided are not accepted and therefore the requested re-test period not granted.	2	2.7	0.2
3.2.S.7.3	Indicate the type of batch e.g. pilot/production/experimental as well as the batch size used.	12	16.0	1.1
3.2.S.7	Include full stability data for a consideration of the retest of an API. This section should be submitted in compliance with the SAHPRA guidelines	29	25.3	2.6
		85		

(3.2.R.3)* This is a section relating to 3.2.S but has been placed under the regional section 3.2.R.3 on the submission of a CEP.
(3.2.R.4)* This a section relating to 3.2.S in cases where more than one API source has been applied for, this is placed under the regional section 3.2.R.4 on multiple API manufacturers.
Modules: 3.2.S.1 general properties of the API, 3.2.S.2 manufacture, 3.2.S.3 characterisation, 3.2.S.4 control of the API, 3.2.S.5 reference materials, 3.2.S.2.2 description of manufacturing process and process controls, 3.2.S.2.3 control of materials, 3.2.S.2.4 controls of critical steps and intermediates, 3.2.S.3.1 elucidation of structure, 3.2.S.3.2 impurities, 3.2.S.4.1 specifications, 3.2.S.4.2 analytical procedures 3.2.S.4.3 validation of analytical procedures, 3.2.S.4.4 batch analysis 3.2.S.7 stability, (see Table 2 for further descriptions)

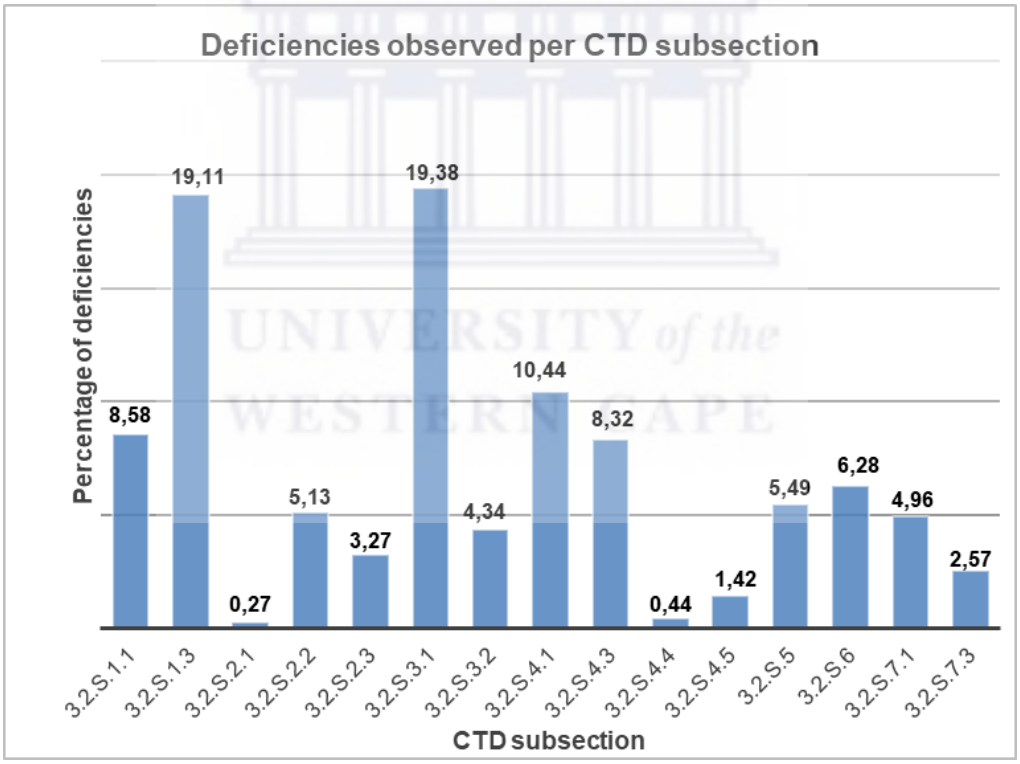

Figure 2: Distribution of deficiencies per API CTD subsection.

In 2020, SAHPRA updated the requirements and introduced the request of the restricted part of generic products. A study was conducted which seeks to provide common deficiencies observed from the restricted part. This was conducted on applications evaluated between January – May 2020 by the PEM pre-registration

Unit (business-as-usual, BAU section). The deficiencies collected from the 20 initial letters are stipulated in Table 4. Overall, 275 deficiencies were observed from the letters communicated to applicants.

Table 4: The common deficiencies observed from 20 initial query letters from 31 APIMFs in the restricted part**.**

Subsection	Deficiency	Quantity	% subsection	Request rate (%)
3.2.S.2.3	The API starting materials proposed are complex and form a large part of the backbone of the final API, therefore these require to be well characterised and adequately controlled during the synthesis of this starting material. This therefore requires further redefinition of the starting materials in accordance to the ICH Q7 and ICH Q11 guidelines. In addition, submit the specifications of the starting material to confirm that it is adequately controlled.	31	11.3	100
3.2.S.2.3	State the scale of manufacture, the typical batch size, and the maximum batch size (the range) for which the process is described as well as quantities (mass or molar equivalents) of the starting materials and yield ranges for each step of the synthesis.	31	11.3	100
3.2.S.2.3	Confirm that no alternative processes are applied during the proposed manufacturing process.	30	10.9	96.8
3.2.S.2.3	State if reprocessing or reworking of the API or reaction intermediate occurs. If so, describe this in detail.	30	10.9	96.8
3.2.S.2.3	Briefly describe the recovery of materials or solvents (if any), including how the materials or solvents are recovered.	31	11.3	100
3.2.S.2.3	Where particle size is considered a critical attribute of the API, the milling/micronisation equipment, process parameters and procedures should be described.	23	8.4	74.2
3.2.S.2.3	Provide equipment used during each step of the manufacturing process and operating conditions (e.g. temperature, pressure, pH, time)	27	9.8	87.1
3.2.S.2.3	Confirm that no blending of the final batches is allowed. Should allowance be made for blending then clearly indicate which criteria/tests is/are used to ensure that the individual batch incorporated into the blend meet specifications set for the final product prior to blending.	21	7.6	67.8
3.2.S.2.4	Provide the controls of the critical steps and isolated intermediates, including the reaction conditions, completion of individual reaction steps and the identity and purity of the isolated intermediates.	25	9.1	80.6
3.2.S.2.6	Indicate any significant changes made throughout the various development stages: these can be changes to the manufacturing process and/ or site of the API since production of earliest batches including non-clinical, clinical batches (e.g. bio-batch supplied to the FPP manufacturer) in	16	5.8	51.6

	comparison to scaled-up pilot and production batches (if applicable).			
	Other	10	3.6	32.2
		275	**100**	

3.4 Discussion

3.4.1 Common deficiencies observed by SAHPRA in the submitted DMF/APIMFs.

3.4.1.1 Highest common deficiencies

Subsection 3.2.S.3.1 had the highest deficiencies of 19.38% in the 3.2.S section. It is a requirement that proof of correctness of the structure be submitted if no official standard is available in which case sufficient evidence, such as Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR), Infrared (IR), Mass Spectroscopy (MS), elemental analysis etc., (with interpretation) should be provided in support of the structure and stereochemistry. These were either not submitted (1.5%), submitted with no interpretation (34.1%) or legible copies (35.1%) were not submitted and were therefore requested. The other 6.0% of the deficiencies were due to the characterisation of the polymorphic form. In instances where the API exists in more than one polymorphic form, the applicant is required to submit data on consecutive batches confirming that during the manufacturing process only one form is consistently produced. Studies should be performed comparing other polymorphic forms found in literature to the required polymorphic form. This is normally done by comparing their powder X-ray diffraction- (pXRD), differential scanning calorimetry- (DSC) or Fourier transform infrared (FTIR) spectra. Polymorphism is when the same molecule crystallizes into more than one type of crystal. The crystals, or polymorphs, are made of the same atoms but in different crystalline arrangements. The solubility and hence the bioavailability may be very different in the two different arrangements. [30] One API could have different polymorphic forms which differ in internal solid-state structure and may, therefore, possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. [31-32] The unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences, therefore, control is crucial.

A classic example which showcases the importance of polymorphism is ritonavir which was originally dispensed as an ordinary capsule, with a polymorphic form of form I.[33] During development in 1996, only the polymorph now called form I was found, but in 1998, a lower free energy, more stable polymorph (form II) appeared. [33] This more stable and less soluble crystal form compromised the oral bioavailability of the drug. This led to the removal of the oral capsule formulation from the market.

3.4.1.2 Second highest common deficiencies

Figure 2 shows that subsection 3.2.S.1.3 had the second highest number of deficiencies. The recommendations were based on physico-chemical properties of the API. Aspects such as polymorphism, chirality, isomerism, solubility and hygroscopicity of the API were not addressed by the API manufacturer and were therefore requested. Close to 50% of these recommendations were requesting the solubility of the API at physiological pH (1.2 - 6.8) with several buffered solutions and with solvents relevant to the product formulation and the temperature at which the solubility studies were conducted, to be included. This is critical information that assist in determining the Biopharmaceutics Classification System (BCS) class of the API and hence establish its behaviour during dissolution and bioequivalence studies. Solubility is critical to determine the formulation, the process and the performance of a product, therefore a study is normally required to investigate the solubility of each API. Hygroscopicity on the other hand with 3.0% of the deficiencies will provide insight into the stability of the API and establish whether the API or formulation may be sensitive to moisture. Chirality and stereochemistry (1.7%) of the API are important aspects to be detailed in the structure of the API since other isomers are required to be controlled in the final API specifications if not in the intermediate specifications. The product can have several isomers which may be harmful to the patient even though the structures are similar, therefore isomers serve as impurities and should be controlled as such.

3.4.1.3 Third highest common deficiencies

The third largest number of deficiencies in the subsections were from tightening specifications in view of the results submitted from batch analysis and stability data of the API. Sixty percent of the responses from applicants stated that the results were within the ICH guideline limits (ICH Q3A (R2)) [34] which was correct, while in other instances the applicant's limits would exceed the ICH limits and they would not provide a sufficient justification for this. ICH Q3A has the following impurity thresholds: identification threshold (IT), reporting threshold (RT) and qualification threshold (QT). Impurities present that are higher than the IT needs to be identified and impurities higher than QT needs to be qualified for safety. The P&A Committee accepted this justification for reporting, identification and qualification thresholds as SAHPRA is an ICH observer. The second deficiency (1.6%) which led to the back-and-forth communication was applicants who would omit the test of a specific residual solvent, especially benzene which is a class I solvent, without providing supporting data of consecutive production batches to confirm that the solvent is not present in the final API and results being less than 30% of the ICH limit of 2 ppm. The presence of the following solvents in the manufacturing process result in this query being requested since they are known to be potential carriers of benzene; acetone, Toluene, Xylene, Hexanes and Isopropyl alcohol. Depending on where these are used in the manufacturing process, applicants are requested to control benzene in the final API or in the specific solvent specifications.

3.4.1.4 Fourth highest common deficiencies

The fourth highest deficiencies were from subsection 3.2.S.1. The general information referred to here, is regarding the DMF/APIMF number if a DMF/APIMF is submitted, the CEP validity, if a CEP is submitted and comparison of manufacturing methods if more than one DMF is submitted. These are deficiencies which relate to the API section but do not have a specific location in the CTD and have been placed under regional information but will be discussed in this subsection. The DMF documentation must comply with the SA Guide to GMP Chapter 4 Requirements [35] for Documentation including at least unique identification, version and date. A declaration that it is current should be included. There was 17% of the deficiencies in the subsection relating to the DMF not being submitted as per the above requirements. This is crucial since different FPP manufacturers would source the same API manufacturer who would continually update the DMF/APIMF, therefore it is important for the authority to be informed of the latest version in order to generate a database and avoid duplication of evaluation in cases where the same API source is used by different FPP manufacturers. Also, DMF/APIMFs can be sent to multiple authorities resulting in frequent updates.

Information about the CEP is placed in the regional information section 3.2.R.3 but will be discussed in this section since it relates to the API. Applicants are requested to submit the latest version of the CEP (2.4% of the 3.2.S section). The EDQM generally updates the status of each CEP therefore it is easy to find out if the submitted CEP is valid or not through the Certificate of Suitability database [3].

The section on multiple API manufacturers is also placed under regional information in section 3.2.R.4. In cases where more than one API source is used it is required that the applicant provides a comparison of the method of synthesis, specifications and batch analysis to confirm similarity or outline differences between the API manufacturers which should be conducted by an independent laboratory. Although this may be obtained in the individual DMFs the summary provided assists in the evaluation and makes it easy for the evaluator to notice discrepancies, if any. Only 5.8% of the deficiencies in the subsection were as a result of this.

3.4.1.5 Fifth highest common deficiencies

The fifth highest CTD subsection is 3.2.S.4.3. Almost 14% of the deficiencies in the section were due to applicants not submitting the required validation data of the analytical procedures used in specification tests. Other deficiencies were of discrepancies witnessed in the submitted validation data (15.6%) and partial validation data which should be submitted by the FPP manufacturer if they are using the same analytical procedures as the API manufacturer (5.6%).

3.4.1.6 Sixth highest common deficiencies

Stability deficiencies (Modules 3.2.S.7.1 & 3.2.S.7.3) were the sixth most frequent deficiencies. In most cases, the deficiency was due to inadequate stability data being submitted for the consideration of a full retest period (56% of the requests in the subsection). Another common deficiency in this section was applicants submitting data which shows results that are out of specification with no valid justification for the results, these were only 2.7% of the subsection. For this reason, the retest period would not be allocated and a justification is requested. From the responses it was confirmed that the justifications provided differed per application, some stated that it was due to inaccurate results, others used stability results to insist on a widened specification limit, these were treated on a case-by-case basis depending on the specification. This also led to back-and-forth communication between the agency and applicants resulting in delayed finalisation.

3.4.1.7 Deficiencies from the restricted part

A comparison of the 2020 results was made with those reported on products finalised between 2011 - 2017. Table 3, subsection 3.2.S.2.2 – 3.2.S.2.4 shows similarity of the common deficiencies with those obtained in Table 4. For example, on the aspect of the complex starting material being submitted in Module 3.2.S.2.3, either the complete method of synthesis of starting material to simpler molecules as well as specifications or the CoA to confirm adequate control of the impurities was requested. This request is similar to that reported in Table 4 for the redefinition of starting material amongst others. Another similarity amongst others was regarding the confirmation and description of residual solvent recovery. This investigation confirms that the quality of the evaluations has been maintained since critical aspects from the restricted part have always been requested by SAHPRA.

3.4.2 Comparison of API common deficiencies with that of other authorities.

3.4.2.1 Comparison of API deficiencies, SAHPRA vs USFDA

The USFDA reported on how effective the DMF procedure is since it aims to avoid duplication of assessments by the authority. [10, 36] A DMF database was created and updated annually once all the requirements have been addressed. [10, 36] The authority does not quantify the deficiencies per subsection in the reports that have been made thus far.

The first deficiencies outlined under general information by FDA were aspects such as solubility, stereochemistry, hygroscopicity and polymorphism. These were also observed from the deficiencies received in SAHPRA applications which were the most frequent (19.1%) and discussed in detail above. The USFDA also included API characterisation as one of the common deficiencies observed with the applicant not submitting legible copies and analysis to confirm the polymorphic form. These are similar to the frequent recommendations sent to applicants by SAHPRA, making the section 3.2.S.3.1, the highest of common deficiencies.

Another critical deficiency discussed by the USFDA which was the third highest for SAHPRA was the control of impurities (3.2.S.4.1). As discussed in the above section, all impurities in an API which are present

at greater than the identification threshold (IT) as described in the ICH Q3A guidance need to be identified, in addition, impurities at levels greater than the qualification threshold (QT) need to be qualified for safety. [34] Thus, setting limits for unknown impurities higher than the IT will invariably lead to a deficiency. Similarly, not providing qualification information for the known impurities set higher than the QT will also not be acceptable. These were the frequent deficiencies observed regarding the individual impurities. This was followed by the request to tighten the total impurities' specifications based on the submitted stability results. Table 5 provides a comparison of the top five deficiencies from all the agencies.

Table 5: Comparison of the top five common deficiencies from the six regulatory bodies listed below.

	USFDA	**WHOPQTm**	**EDQM**	**TFDA**	**SAHPRA**
1	3.2.S.1	3.2.S.2.3	3.2.S.2.3	3.2.S.2.2	3.2.S.3.1
2	3.2.S.2	3.2.S.2.2	3.2.S.3.2	3.2.S.2.3	3.2.S.1. & 3
3	3.2.S.3	3.2.S.7	3.2.S.2.2	3.2.S.4.1	3.2.S.4.1&3
4	3.2.S.4	3.2.S.3.2	3.2.S.2.4	3.2.S.4.3	3.2.S.7.1 & 3
5	3.2.S.5	3.2.S.4.1 & 5	3.2.S.4.4	3.2.S.7	3.2.S.2.2

Modules: 3.2.S.1 general properties of the API, 3.2.S.2 manufacture, 3.2.S.3 characterisation, 3.2.S.4 control of the API, 3.2.S.5 reference materials, 3.2.S.2.2 description of manufacturing process and process controls, 3.2.S.2.3 control of materials, 3.2.S.2.4 controls of critical steps and intermediates, 3.2.S.3.2 impurities, 3.2.S.4.1 specifications, 3.2.S.4.4 batch analysis 3.2.S.7 stability, (see Table 2 for further descriptions)

3.4.2.2 Comparison of API deficiencies, SAHPRA vs EDQM

The reported results on the top 10 deficiencies of new applications submitted to the EDQM are not quantitative and does not provide a thorough comparison. The EDQM reported the deficiencies annually from 2007 – 2016. [11-14] The top five deficiencies are modules; 3.2.S.2.3, redefinition of the starting materials required, 3.2.S.3.2, absence of the discussion of potential mutagenic and genotoxic impurities, 3.2.S.2.3, absence of discussion on the carry-over of impurities and by products from key materials in the process, 3.2.S.2.2, lack of details and poor description of the manufacturing process of the starting materials and 3.2.S.2.3 inadequate or poorly justified specifications to control the quality of starting materials. [11-14] From the above, it is witnessed that most deficiencies are from Module 3.2.S.2 and 3.2.S.3. This information is found in the restricted part of the dossier and SAHPRA only required the information when needed due to the sensitivity of information. Hence, the limited amount of API deficiencies for that section. It was recorded that 98 of the deficiencies (8.2% of the total deficiencies) were from the 3.2.S.2 section with 59% of them due to an insufficient flow diagram detailing the required information and 24% due to the redefinition of the starting materials and request of their specifications. With the introduction of the APIMF procedure, the study on the restricted part queries show that the redefinition of the starting material and other critical aspects of the restricted part are now requested for all applications by SAHPRA.

3.4.2.3 Comparison of API deficiencies, SAHPRA vs WHO PQTm

WHO PQTm reported on the common deficiencies witnessed from the 159 products assessed in the period January 2007 - December 2012. [17] The qualitative and quantitative information provided allows for comparison of the deficiencies to those observed by SAHPRA. The most frequent subsection was found to be module 3.2.S.2.3 with 69.5% of deficiencies in the 3.2.S.2 section. This is a large difference to SAHPRAs 8.2% observed in the same subsection. The deficiencies included insufficient information provided on the starting material such as the manufacturer of the starting material, specifications of the starting material were either not provided or were unsatisfactory and the request for redefinition of the starting material. [17] API manufacturers have found it cheaper to buy intermediates instead of manufacturing them, hence the frequency of the deficiencies. Redefinition of the starting material is thus not provided or if provided, does not comply with the definition of ICH Q7 [37] and Q11 [38], which makes it difficult for regulatory authorities to assess potential impurities that may arise during preparation. [17] SAHPRA proposed the request of specifications and the CoA of the complex starting material instead of the redefined synthesis method. This gives assurance that the impurities are controlled and removed.

3.4.2.4 Comparison of API deficiencies, SAHPRA vs TFDA

A total of 471 DMF applications were filed between October 2009 and December 2011 by the TFDA and evaluated for common deficiencies. [6] The primary deficiencies observed in the initial assessments were in categories of the manufacturing process (31%) these were data for critical parameters, in-process controls and intermediates being incomplete. These were followed by API specification deficiencies (17%) where proposed limits were not in line with the pharmacopeia, then starting material deficiencies (16%), as redefinition of the starting material does not comply with the definition of ICH Q7 and Q11. [6] Lastly, analytical method validation (11%) where process validation was not included for the purification and sterilisation steps and validation was not conducted on consecutive batches. [6] It was clear that the analysis from the study may assist manufacturers in improving their submission quality and facilitates granting of DMF certificates. The difference and similarity of these with that reported by SAHPRA are highlighted in Table 5.

3.5 Conclusion

The study includes a list of common deficiencies observed over a seven-year period and highlighted the top six most common deficiencies identified by SAHPRA. In addition, with the implementation of the APIMF procedure in 2020, the common deficiencies requested from the restricted part were also highlighted. A list of all deficiencies observed was outlined. This study therefore provides transparency to pharmaceutical companies on deficiencies pertaining to Module 3.2.S. to address before dossier submissions are made to SAHPRA, this in turn will reduce turnaround timelines for product registration. Comparisons with other

regulatory authorities showed that the evaluation standards employed by SAHPRA are similar to other international regulatory agencies. These findings will guide the API manufacturers and pharmaceutical companies in submitting quality DMFs/APIMFs in future, which will thereby accelerate access to medicine for patients.

3.6 References

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CHAPTER 4

Common deficiencies found in generic Finished Pharmaceutical Products (FPPs) applications submitted for registration by the South African Health Products Regulatory Authority (SAHPRA)

ABSTRACT

Background. The aim of the study was to investigate the common deficiencies observed in the finished pharmaceutical product (FPP) of generic product applications submitted to SAHPRA. The study was conducted retrospectively over a 7-year period (2011-2017) for products that were finalised by the Pharmaceutical and Analytical pre-registration Unit. **Methods.** There were 3148 finalised products in 2011-2017, 667 of which were sterile while 2089 were non-sterile. In order to attain a representative sample for the study, statistical sampling was conducted. Sample size was obtained using the statistical tables found in literature and confirmed by a sample size calculation with a 95% confidence level. The selection of the products were according to the therapeutic category using the multi-stage sampling method called stratified-systematic sampling. This resulted in the selection of 325 applications for non-sterile products and 244 applications for sterile products. Subsequently, all the deficiencies were collected and categorised according to Common Technical Document (CTD) subsections of the FPP section (3.2.P). **Results**. A total of 3253 deficiencies were collected from 325 non-sterile applications while 2742 deficiencies were collected from 244 sterile applications. The most common deficiencies on the FPP section of non-sterile products were on the following sections: specifications (15%), description and composition (14%), description of the manufacturing process (13%), stability data (7.6%) and the container closure system (7.3%). The deficiencies applicable to the sterile products were quantified and the sub-section, validation and/or evaluation (18%) has the most deficiencies. Comparison of the deficiencies with those reported by other agencies such as the USFDA, EMA, TFDA and WHOPQTm are discussed with similarities clearly outlined. **Conclusions**. The overall top five most common deficiencies observed by SAHPRA were extensively discussed for the generic products. The findings provide an overview on the submissions and regulatory considerations for generic applications in South Africa, which is useful for FPP manufacturers in the compilation of their dossiers and will assist in accelerating the registration process.

4.1 INTRODUCTION

Pharmaceutical companies use data accumulated during discovery and development stages of a pharmaceutical product in order to register and thus market the medicine. Throughout the development stages, they are required to abide by an array of strict rules and guidelines in order to ensure safety, quality and efficacy of the Finished Pharmaceutical Product (FPP) in humans [1]. Inspection of manufacturing plants and laboratory quality control analysis only do not guarantee product quality and safety [2]. All processes involved in the manufacture of the active pharmaceutical ingredients (APIs) and the FPP need to be controlled [2]. Therefore, assessment of the product dossier prior to its acceptance is paramount [2]. Countries possess their own regulatory authority, which is responsible for enforcing the rules and regulations and issue the guidelines to regulate FPP development process, licensing, registration, manufacturing, marketing, labelling and the product life cycle of the FPP. In this highly regulated environment, regulatory affairs play a critical role as the leading department to provide strategic advice on extremely difficult decisions through the life of the FPP [1]. Even with the strict rules and guidelines, very few pharmaceutical companies submit quality dossiers which do not require any additional amendment or additions at initial review. Dossiers possessing a large number of deficiencies will necessitate more interaction between the authority and the manufacturer during the assessment process, thus increasing the turnaround times for registration of medicines [3]. Subsequently delaying patient access to urgently needed medication.

Over the years, a number of regulatory authorities have witnessed and reported on recurring deficiencies observed from the submitted dossiers. Authorities such as United States Food and Drug Administration (USFDA), European Medicines Agency (EMA) and Taiwan Food and Drug Administration (TFDA) have noted how the implementation of publication of common deficiencies has resulted in the submission of improved quality dossiers from pharmaceutical companies. The USFDA published a 4-part series citing the common deficiencies observed from the Abbreviated New Drug Applications (ANDA) on the quality aspects of the dossier. Part 1 of the series, dealt with the deficiencies cited in the API section [4]. Part 2-4 of the series was on common deficiencies observed from the FPP part of the dossier [5-7]. The 4-part series was however only qualitative and not quantitative. The TFDA also reported on common deficiencies witnessed in the FPP for applications submitted from June 2011 to the end of May 2012 [8], while EMA's study focused on applications finalised during the Committee for Medicinal Products for Human Use (CHMP), during 12 consecutive plenary meetings held in 2007 and 2008 [9]. World Health Organisation Pre-Qualification Team (WHOPQTm) reported on the deficiencies observed in the API and FPP sections for products submitted between April 2007 and December 2010 [3]. A guidance document was also published by WHOPQTm in 2018 to alert manufacturers of the FPP deficiencies witnessed [10]. The studies conducted were aimed at collecting and analysing the quality review issues, which will serve as a reference and a communication

medium for applicants to understand the regulatory requirements in the respective countries, which could be useful for compilation of the dossier and to facilitate the approval process.

South African Health Products Regulatory Authority (SAHPRA) has not implemented this transparency since the inception of the authority in 1965. The registration process by SAHPRA involves a scientific evaluation of the dossier submitted by the applicant in the form of a Common Technical Document (CTD). During this evaluation, a list of recommendations is generated related to the quality, safety and efficacy, which are forwarded to the applicant once discussed at the Pharmaceutical and Analytical (P&A) Committee meetings, to be addressed and resolved prior approval. The P&A Committee managed to conclude and finalise on the scientific assessments of 3148 applications between 2011-2017. With SAHPRA receiving approximately 1200 applications annually, by 2016, a backlog of 7902 applications was accumulated. Within the period 2010-2015 only 3779 application were registered or rejected. From the backlog of applications, 4397 applications had not yet been allocated for evaluation while 3505 were in-process in the pre-registration phase. This shows the urgent need to employ measures such as collecting and analysing the quality review issues, which will serve as a reference and a communication medium for applicants to understand the regulatory requirements, thereby accelerating approval process by the authority.

In order to identify general trends in the quality deficiencies for SAHPRA, we analysed all deficiencies from products finalised during the P&A Committee meetings over a 7-year period (2011-2017). The 3148 applications finalised during this period were considered a large sample to use for the study therefore a statistical sampling approach was employed to obtain a representative sample.

The manufacturing of the FPP is governed by precise requirements and guidelines such as good manufacturing practises and International Conference of Harmonisation guideline, ICH 3QB. [11] This is to ensure that the medicinal products are fit for their intended use and do not pose risk to the patients as a result of inadequate safety, quality or efficacy [12, 13]. In the assessment of the medicines for registration by regulatory authorities, deficiencies are frequently observed in the applications, thus a proactive approach is intended in order to promote transparency between SAHPRA and the FPP manufacturers. The investigation undertaken is therefore aimed at identifying common deficiencies in the FPP section of applications submitted to SAHPRA. Publication of these will assist in the submission of quality dossiers which will accelerate the registration process and promote access to medicines for patients.

4.2 METHODS

There was an overall of 3148 applications finalised in the 7-year period, of which 2089 were non-sterile products while 667 were sterile products. Veterinary (68), Biologicals (86), Medical Devices (5) and New Chemical Entities (NCEs) (233) were also finalised by the P&A Committee in the period as shown in Figure

1 but was not included as part of this study. The NCEs were not included because they involve a more extensive evaluation, which required the compulsory submission of the restricted part of the Active Pharmaceutical Ingredient Master File (APIMF). As a result, a set of additional recommendations which are not observed in the generic applications will be communicated to the applicant. Biologicals were not included due to the same reasons as the NCE as well as due to differences in the nature and preparation of the APIs used, this will necessitate a separate study as per the work published by EMA on Biosimilars [14]. Veterinary products were not included since the P&A Committee was only providing support to the Veterinary Unit and each application requires the submission of Clinical trials data assessed by the Veterinary Clinical Committee, therefore it would be out of the scope of the research study. Lastly, the Medical devices were not included since the sample was too small to render the deficiencies as common. One of the main reasons for exclusively conducting a study for generics is that the generic applications constitutes majority of the applications received by SAHPRA annually and the lessons learnt for the generics can also be employed for non-generic applications.

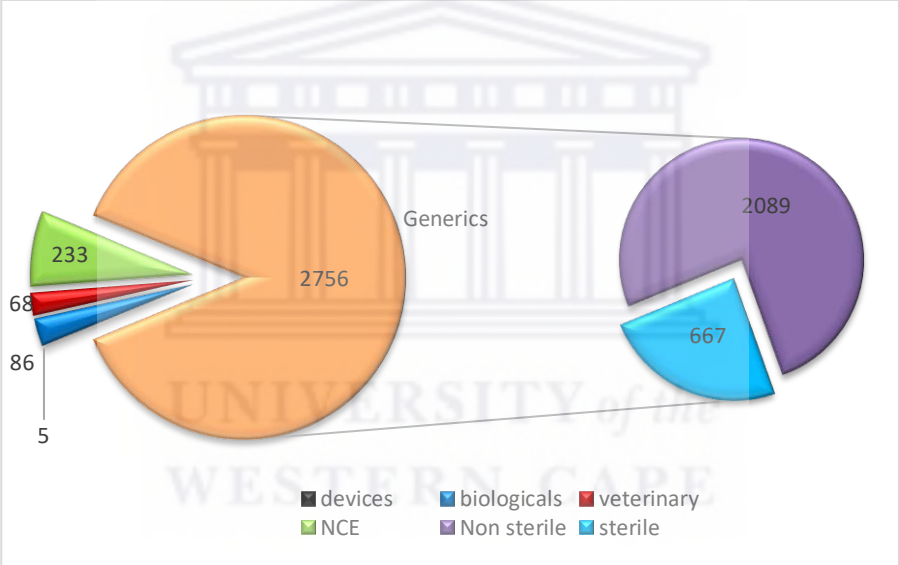


Figure 1: The distribution and grouping of the finalised products between 2011-2017 by the SAHPRA P&A Committee, pre-registration Unit.

Given the large size of the submitted applications, a statistical method was applied to yield a representative sample adequate to use for the study. The calculated sample size obtained was 325 for the non-sterile products and 244 for the sterile products using the equations reported by Israel G. D, (1992) [15] and Kadam P. *et.al.* (2010) [16] as equations 1 and 2.

$$n_{0.} = \frac{Z^2 pq}{e^2} \ldots\ldots Equation\ (1)$$

$$n = \frac{n.}{1+\frac{n.-1}{N}} \ldots\ldots Equation\ (2)$$

The equations consist of the following parameters:

z = The confidence level corresponds to a Z-score, for a 95% confidence level z is 1.96

p = The degree of variability,

q = Relates to degree of variability above, indicated as 1-p depending on the variability of the population,

e = Level of precision which is ± 5% for the selected confidence level of 95%,

n_0 = Sample size,

n = adjusted Sample size for population sizes that are less than 3000,

N = Population size [15, 16].

Calculation for the sterile products is stipulated below with a population of 667. The same was applied for non-sterile products with a population of 2089 where the sample size of 325 was obtained.

$$n_{0.} = \frac{Z^2 pq}{e^2} \ldots\ldots \textit{Equation (1)}$$

$$= \frac{1{,}96^2 0{,}5^2}{0{,}05^2}$$

$$= 384.16$$

$$n = \frac{n.}{1+\frac{n.-1}{N}} \quad \ldots \textit{Equation (2)}$$

$$= \frac{384.16}{1+\frac{384.16-1}{667}}$$

$$\underline{n = 244}$$

Comparison of the calculated sample size with the table reported by F.B. Mahammad [17] for a given population size showed similarity in that the reported value for a population of 650 is 242 with the same confidence interval and level of precision. There are many other tables reported [17-19] with sample size ranging between 240 – 255.

A multi-stage called stratified systematic sampling method was employed. In this method, the entire population is divided into a number of homogeneous groups usually known as “strata” and thereafter units are systematically sampled from each of these stratums [19, 20].

It is pivotal to ensure that the selection is not random and biased. Stratified systematic sampling allows for this as it ensures that all critical variables are considered. Aspects such as the applicant, the dosage form, the API used, the therapeutic category and finalisation time of the drug product were considered as important variables to be considered when sampling is conducted. Out of the above five variables, the most critical is the therapeutic category since we are dealing with pharmaceutical products. The best way to categorise the products is through their therapeutic indications i.e. function and pharmacological classification of the drug.

Regulation 25 of Act 101 classifies and categorise medicines in South Africa as follows:

- Category A for Medicines which are intended for use in humans and which are, without manipulation, ready for administration, including packaged preparations where only a vehicle is added to the effective medicine;
- Category B for Medicines which cannot be administered without further manipulation; and
- Category C for Medicines intended for veterinary use, which are without further manipulation, ready for administration including packaged preparations where only vehicle is added to the effective medicine [21].

All medicines in the population are category A. This category is subdivided into 34 pharmacological classifications some of which are subdivided further. Each therapeutic category is considered a stratum. These are grouped into 19 categories as depicted in Table 1. The sample size in each stratum varies according to the relative importance of the stratum in the population, i.e. percentage contribution. For example, if 16% of the population are antiviral agents, then 16% of the sample should contain drug products in that group. From Table 1, each stratum is now treated as a population with a specific sample size. The strata are arranged in terms of therapeutic category of the applications. Thus, the numbers in the first column Table 1 are the number of finalised applications within that therapeutic category for sterile products. For example, there were 138 applications finalised with a pharmacological classification, Central nervous system depressants.

The k^{th} term serves as a constant value used for systematic sampling and is calculated as illustrated in Equation 4 with ***N**** as the population size and ***n**** as the calculated sample size [15]. A systematic sample would select the first element and thereafter the k^{th} term on the list afterwards until the required sample has been selected in the whole population. The interval between the selected elements would then be the population size/ calculated sample size [15]. The calculated k^{th} term gave the value 2.73. This therefore makes the value three the k^{th} term for the systematic sampling i.e. in all strata. This resulted in the sample size of 245. However, 244 was used in accordance to the calculation using equation 2. Similarly, this was conducted for the non-sterile products to select the sample size of 325 letters.

$$n* = \frac{N*}{kth} \ldots \textit{Equation (3)}$$

$$kth = \frac{N*}{n*} \quad \textit{...Equation (4)}$$

$$= \frac{667}{244} = 2.73$$

Table 1: The different strata (pharmacological classifications) generated for sample selection of sterile products.

Pharmacological classification (Therapeutic categories)	Population (*N**)	%	Sample (n∗)
Central nervous system depressants	138	21	52
2.1 Anaesthetics			
2.2 Sedatives, hypnotics			
2.5 Anticonvulsants, including anti-epileptics			
2.7 Anti-pyretic or anti-pyretic and anti-inflammatory analgesics			
2.8 Analgesic combinations			
2.9 Other analgesics			
3.2 Non-hormonal preparations	12	1.8	4
4.0 Local anaesthetics	22	3.3	8
Medicines affecting autonomic function			
5.2 Adrenolytics (sympathicolytics)	62	9.3	23
5.4.1 Anti-parkinsons preparations			
5.7.1 Anti-histaminics			
5.7.2 Anti-emetics and anti-vertigo preparations			
5.10 Serotonin antagonists			
Vasodilators, hypotensive medicines			
7.2 Vasoconstrictors, pressor medicines	33	5.0	12
7.10.3 Other hypotensives			
Medicines acting on blood and haemopoietic system			
8.1 Coagulants, haemostatics	28	4.2	10
8.2 Anticoagulants			
8.3 Erythropoietics (haematinics)			
8.4 Plasma expanders			
Medicines acting on respiratory system			
10.2.1 Inhalants	6	1.0	2
Medicines acting on gastro-intestinal tract			
11.4.3, Antacids, other	10	1.5	4
Ophthalmic preparations			
15.4 Ophthalmic preparations. other	32	4.8	12
Medicines acting on muscular system			
17.1 Peripherally acting muscle relaxants	12	1.8	4
Medicines acting on genito-urinary system			
18.1 Diuretics	29	4.3	10
18.3 Ion-exchange preparations			
18.7 Contraceptive preparations	14	2.1	5
19.0 Oxytocis	22	3.3	8

Antibiotics and antibiotic combinations			
20.1.1 Broad and medium spectrum antibiotics	99	15	37
20.1.2 Penicillins			
20.2.2 Fungicides			
20.2.3 Tuberculostatics			
20.2.8, Antiviral agents			
hormones, antihormones and oral hypoglycaemics			
21.1 Insulin preparations	59	8.9	22
21.2 Oral hypoglycaemics			
21.4 Parathyroid preparations			
21.5 Cortico steroids			
21.10 Trophic hormones			
21.12 Hormone inhibitors			
26.0 Cytostatic agents	61	9.0	22
28.0 Contrast media	12	1.8	4
32.15 radiopharmaceuticals	2	0.3	1
34, other	14	2.1	5
	667	**100**	**245**

The full history of all the products finalised between the 7-year period (2011-2017) were collected. The history comprises of all communication between the authority and applicants in order to reach finalisation. The documents include the recommendations sent to the applicant and the response received, as well as the evaluation reports of responses in the form of amendment schedules. These paper documents were obtained from the committee meeting minute documents and the registry files where all documents relating to the product are placed. The investigation process involved obtaining the type and extent of the deficiencies raised in the first deficiency letter following the initial evaluation process, thereafter, extracting all the responses and feedback during the multiple rounds of communication. During collection of the deficiencies, those with a frequency that was observed as less than five were categorised under "other" in the tables and calculated in the relevant section or subsection. The understanding was that these would not be classified as common due to the low frequency.

The study focuses mainly on the FPP which is presented as Module 3.2.P part of the CTD structure of the dossier as stipulated in Table 2, Module 3.2.P entails eight sections in which five consists of subsections. The 3.2.P sections are applicable for all types of medicines including the sterile and non-sterile products.

Table 2: FPP (3.2.P) Sections and Subsections for Classification of observations**.**

CTD sections and subsections	Content
3.2.P.1	**Description and Composition**
3.2.P.2	**Pharmaceutical development**
3.2.P.2.1	Components of the pharmaceutical product
3.2.P.2.2	Final pharmaceutical product
3.2.P.2.3	Manufacturing process development
3.2.P.2.4	Container closure system
3.2.P.2.5	Microbial attributes
3.2.P.2.6	Compatibility
3.2.P.3	**Manufacture**
3.2.P.3.1	Manufacturer(s)
3.2.P.3.2	Batch formula
3.2.P.3.3	Description of manufacturing process and process control
3.2.P.3.4	Control of critical steps and intermediates
3.2.P.3.5	Process validation and/or evaluation
3.2.P.4	**Control of inactive pharmaceutical ingredients**
3.2.P.4.1	Specifications
3.2.P.4.2	Analytical procedures
3.2.P.4.3	Validation of analytical procedures
3.2.P.4.4	Justification of specifications
3.2.P.4.5	Excipients of human origin
3.2.P.4.6	Novel excipients
3.2.P.5	**Control of finished pharmaceutical product**
3.2.P.5.1	Specifications
3.2.P.5.2	Analytical procedures
3.2.P.5.3	Validation of analytical procedures
3.2.P.5.4	Batch analysis
3.2.P.5.5	Characterisation of impurities
3.2.P.5.6	Justification of specifications
3.2.P.6	**Reference standard or materials**
3.2.P.7	**Container closure system**
3.2.P.8	**Stability**
3.2.P.8.1	Stability summary and conclusions
3.2.P.8.2	Post approval stability protocol and stability commitment
3.2.P.8.3	Stability Data

The deficiencies obtained were reviewed and the frequency of each listed per section and subsection of the 3.2.P section together with the percentage frequency of the total deficiencies per section and subsection of the CTD, which was calculated as follows:

- Percentage frequency of deficiency identified per section = (frequency of specific deficiency / Total number of deficiencies per section of CTD) x 100.
- Percentage frequency of deficiency identified per overall 3.2.P = (frequency of specific deficiency / Total number of deficiencies per overall 3.2.P section of CTD) x 100.

The deficiencies were collected and information such as charts and graphs was generated using Microsoft Office Excel® 2016 (Microsoft Corporation, USA).

4.3 RESULTS

4.3.1 Deficiencies from non-sterile products

The 325 applications contained a variety of dosage forms which are: film-coated and uncoated immediate release tablets (48%), immediate release capsules (23%), orodispersible tablets (8.0%), extended-release tablets (8.0%), extended-release capsules (3.5%), chewable tablets (1.2%), powders for suspensions (5.1%) and other (3.2%). The dosage forms which fall under the "other" category included oral solutions, creams, nasal spray, immediate release granules, gels, ointments, suppositories, lozenges and nose drops. A total of 3253 FPP deficiencies were collected from the 325 letters. Table 3 shows all deficiencies observed from generic non-sterile products that were finalised in the 2011-2017 period by the P&A pre-registration Unit. Figure 2 shows the distribution of the deficiencies and further highlights the 3.2.P sections in the CTD with the most deficiencies. The sections with the highest deficiencies are Module 3.2.P.3 Manufacture of the FPP, (23%) followed by Module 3.2.P.5 Control of the FPP (21%) and 3.2.P.8 Stability (15%). These three sections are considered the most critical sections in the CTD under Module 3.2.P as observed from reports by other regulatory authorities while reporting on common deficiencies [6-10].

Table 3 specifies all the deficiencies observed in 3.2.P section of the dossier. The deficiencies were calculated as percentage of the deficiencies in each subsection per overall 3.2.P section. For example, there were 274 deficiencies on the pharmaceutical development section, 3.2.P.2, pharmaceutical development, which is granulated as 3,8 % for 3.2.P.2.1 components of the pharmaceutical product, 1,4% for 3.2.P.2.2, final pharmaceutical product, 2,0% for 3.2.P.2.3, manufacturing process development and 1,2% for 3.2.P.2.4 container closure system for each subsection in the table.

Table 3: List of FPP common deficiencies in the 3.2.P section of the CTD recommended by SAHPRA in the non-sterile products finalised by the pre-registration unit between 2011-2017.

Subsection	Deficiency	amount	% overall
3.2.P.1 **Description and Composition of the FPP**			
3.2.P.1	Include an indication that water or other solvents are not present in the FPP since they have been eliminated during the manufacturing process.	34	14
3.2.P.1	State the polymorphic form of the API(s) used in the unitary batch formula.	52	
3.2.P.1	If a potency adjustment for the API has to be made, a statement to the effect that the actual quantity of the active will depend on the potency and the Pharmaceutical ingredients Inactive (IPI) that will be used to adjust the bulk quantity should be made. The manner in which the adjustment will be made should also be specified.	48	
3.2.P.1	Include the grades of all the IPIs used in the formulation, or the functionality specification of the IPI, if applicable. Indication that it is a pharmaceutical grade is not sufficient.	101	
3.2.P.1	The purpose of each IPI should be stated briefly. If the IPI is used for multiple purposes in the formulation, each purpose should be mentioned.	31	
3.2.P.1	The Colour Index Numbers (Foodstuffs, Cosmetics and Disinfectants Act, 1972 Regulation Food Colourants) or the colourant reference number in accordance with the European directive of colourants for those used in the formulation.	26	
3.2.P.1	The theoretical quantity of the base of the active pharmaceutical ingredient (API) should be stated if a compound, e.g. hydrate, solvate, salt is used.	19	
3.2.P.1	The description of the FPP (including scoring) is incomplete and does not concur with other relevant sections in the dossier such as 3.2.P.5.1 and Module 1.3.	32	
3.2.P.1	The theoretical mass must be indicated for uncoated tablets. In the case of coated dosage forms, the theoretical mass of the core, coating material, as well as the total mass of the dosage form/unit should be indicated.	48	
3.2.P.1	Fill mass, type of gelatine used as well as the capsule size, composition and mass of the capsule should be indicated.	21	
3.2.P.1	The overage used for the active pharmaceutical ingredient (API) should be indicated as a footnote and justified in 3.2.P.2.2.	12	
	Other	19	
		443	
3.2.P.2 **Pharmaceutical development**			
3.2.P.2.1 Components of the pharmaceutical product			
3.2.P.2.1	A Pharmaceutical Development Report (generally of not more than 25 A4 pages) should be submitted with each application.	13	3.8
3.2.P.2.1	Provide a brief summary of the synthesis of the API including a brief discussion of the physico-chemical characteristics of the API which are relevant to the final product.	23	

3.2.P.2.1	Include a discussion of the stability of the final product formulation and conclusion on stability and shelf-life allocation in accordance with the P&A CTD guideline.	10	
3.2.P.2.1	Explain the difference in specific excipients between the test and reference product.	11	
3.2.P.2.1	Submit the compatibility studies of the API-IPI used in the formulation to confirm that these are compatible with each other.	23	
3.2.P.2.1	Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g. bioequivalence) should be discussed.	45	
3.2.P.2.2 Final pharmaceutical product			
3.2.P.2.2	The reason for the overage should be stated / justified, e.g. with reference to batch results, in 3.2.P.2.2.2.	21	1.4
3.2.P.2.2	Justify the choice and quantity of excipients used in the formulation.	23	
3.2.P.2.3 Manufacturing process development			
3.2.P.2.3	The discriminatory nature of the selected dissolution medium should be illustrated.	32	2.0
3.2.P.2.3	Provide justification of the selected dissolution Quality Control (QC) medium with the inclusion of a surfactant.	34	
3.2.P.2.4 Container closure system			
3.2.P.2.4	Submit the discussion on the suitability of the formulation with the primary packaging system to confirm the acceptability of the proposed primary packaging.	34	1.2
	Other	5	
		274	
3.2.P.3 **Manufacture of the FPP**			
3.2.P.3.3 Description of manufacturing process and process controls			
3.2.P.3.3	The description of the manufacturing procedure must include duration of treatment, manufacturing conditions (temperature and humidity) and specifications for machine settings and capacity.	83	13
3.2.P.3.3	No provision has been made to bulk storage before packaging. Indicate the nature of the containers and maximum period the core and/or film-coated tablets may be stored (bulk) before final packaging. Submit information and provide supporting data with regards to holding time studies. This includes bulk holding time for cores prior to coating as well as container used.	97	
3.2.P.3.3	The manufacturing process flow chart is inadequate, include the in-process controls, hold times for processing steps and other additional controls to ensure completeness.	23	
3.2.P.3.3	The proposed holding times for intermediate products should to be included in the calculation of the shelf-life; they should not exceed 25% of the shelf life and if more than 30 days stability data should be submitted.	29	
3.2.P.3.3	Describe the tablet compression procedure and compression speed included as well as coating parameters used.	7	
3.2.P.3.3	The leak test, sealing test and adhesiveness for the blister packs must be described.	11	
3.2.P.3.3	Drying time must be indicated and moisture content to which the granules are dried must be stated.	24	

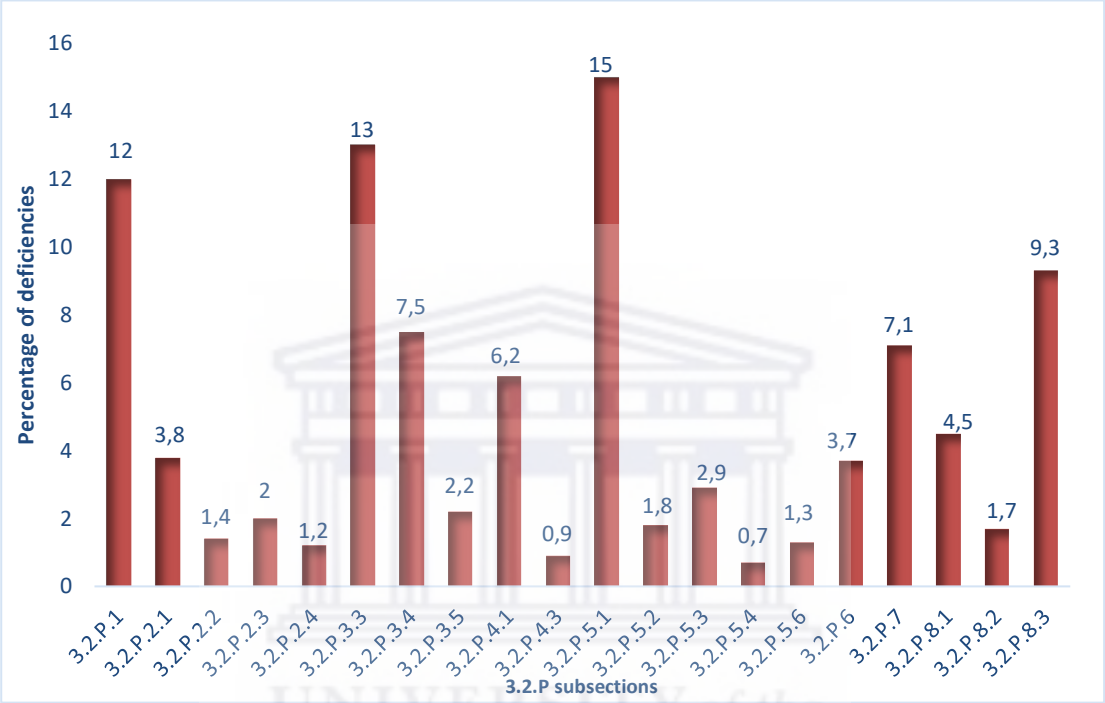
3.2.P.3.3	State the sieve sizes and mixing/blending speed during manufacture of the product as well as duration of stirring and drying temperature.	76	
3.2.P.3.3	A brief description of the packaging procedure must be provided.	33	
3.2.P.3.3	Fluid bed drying conditions must include inlet and outlet air temperature.	6	
3.2.P.3.3	The manufacturing process outlined is inaccurate in comparison to the description and validation report.	17	
3.2.P.3.4 Control of critical steps and intermediates			
3.2.P.3.4	The in-process control tests & frequency must be included as well as expansion of specifications for the granulate to include moisture content.	88	7.5
3.2.P.3.4	Specification for uniformity of content of the divided tablet must be included and blend uniformity as an in-process test.	41	
3.2.P.3.4	The limit for tablet hardness must be included as an in-process test and limits should be expressed in Newton and inclusion of the friability test.	43	
3.2.P.3.4	Include the test for friability for uncoated tablets as an in-process control or in the final specifications.	24	
3.2.P.3.4	Confirm that Batch Manufacturing records and packaging documents will be available upon request or during inspection.	10	
3.2.P.3.4	Limits proposed on the critical steps were not accepted and further justification is required.	32	
	Other	6	
3.2.P.3.5 Process validation and/or evaluation			
3.2.P.3.5	Submit a bulk formula for each batch size for each strength as three master manufacturing batch records were submitted with different batch sizes.	4	2.2
3.2.P.3.5	Include validation report for three commercial batches to confirm reproducibility and batch to batch consistency of the manufacturing process.	43	
3.2.P.3.5	Provide validation protocol and/or report for the proposed batch size.	25	
		722	
3.2.P.4 **Control of inactive pharmaceutical ingredients**			
3.2.P.4.1 Specifications			
3.2.P.4.1	Quantitative and qualitative composition of the colourant must be included.	26	6.2
3.2.P.4.1	Provide a declaration that the IPI e.g. talc is asbestos free.	7	
3.2.P.4.1	Submit the certificate of analysis for each of the IPIs used.	32	
3.2.P.4.1	Include specifications and control procedures of the IPIs used in the formulation for non-pharmacopoeial.	32	
3.2.P.4.1	Provide evidence that the IPIs are Transmissible Spongiform Encephalopathies/ Bovine Spongiform Encephalopathies (TSE/BSE) free.	44	
3.2.P.4.1	The related substances controlled in the IPIs should be quantified.	45	
3.2.P.4.1	Provide the identification used for the colourant or dye, for example a UV spectrum.	16	
3.2.P.4.1	Confirm that the colourant complies with purity criteria of the Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972 or with directives of the European countries or the register of the USFDA.	32	

3.2.P.4.3 Validation of analytical procedures			
3.2.P.4.3	Validation data was not submitted for analytical testing methods of non-pharmacopoeial substances. Submit.	16	0.9
	Other	13	
		263	
3.2.P.5 **Control of FPP**			
3.2.P.5.1 Specifications			
3.2.P.5.1	The dissolution specification must be brought in line with the profiles of the biostudy and reference products for this parameter. All the strengths of both test and reference products demonstrated very rapid dissolution whereas the specification is not in line with the definition of rapid dissolution.	139	15
3.2.P.5.1	The dissolution specification for release and shelf-life must correspond.	16	
3.2.P.5.1	Tighten the assay release and stability specification to 95-105% in accordance with the PA guidelines and include this as a percentage label claim.	80	
3.2.P.5.1	The final product specification must be expanded to include a limit for residual solvents and the relevant validated control procedure must be described.	16	
3.2.P.5.1	The FPP specifications should include an additional identification test.	23	
3.2.P.5.1	Include the leak test to confirm that the product is protected from moisture in the final FPP specifications or as an in-process control.	11	
3.2.P.5.1	Include all the parameters to be controlled for the Final product i.e. FPP specifications at release and shelf life.	9	
3.2.P.5.1	Tighten the specifications for water content taking into consideration the increased formation of impurities by water hydrolysis and the fact that the stability results do not justify the proposed specification.	22	
3.2.P.5.1	Include authorised documentation code and date of authorisation for release and stability specifications (version control).	19	
3.2.P.5.1	Bring the degradation/related impurity limits of the FPP in line with the ICH guideline Q3B.	16	
3.2.P.5.1	Tighten specifications for Total impurities to be in-line with the stability and batch analyses results.	48	
3.2.P.5.1	Tighten the shelf-life specification limits of the specified and unspecified impurities, as they appear to be wider.	45	
3.2.P.5.1	Tighten specifications for disintegration time since the final product is highly soluble.	11	
3.2.P.5.1	Include a test for microbial purity in the FPP specifications.	9	
3.2.P.5.1	Bring the FPP specifications in line with those indicated in a recognised pharmacopoeial monograph.	15	
3.2.P.5.2 Analytical procedures			
3.2.P.5.2	The pore size of the filter must be stated in the dissolution method description or justified.	21	1.8
3.2.P.5.2	Dissolution method should specify inline filtration or filtered immediately. The method for withdrawal and filtration of samples must ensure that dissolution of undissolved particles does not occur after sampling.	38	
3.2.P.5.3 Validation of analytical procedures			

3.2.P.5.3	Submit validation data for the assay method of the API, residual solvents and related substances/degradation products.	28	2.9
3.2.P.5.3	The following inconsistencies were observed in the submitted validation data which required clarification: nature of stress used in stress samples used in validation not confirmed, reference standard not calibrated against an internal standard; linearity of potency assay not conducted, detection limit for some specified related substances/residual solvents, acceptance criteria for system suitability tests and other parameters not justified.	32	
3.2.P.5.3	Representative chromatograms should be submitted for validation of analytical methods.	21	
3.2.P.5.3	Submit validation data of forced degradation studies in the assay method.	12	
3.2.P.5.4 Batch analysis			
3.2.P.5.4	Submit a complete analysis data of at least two batches.	23	0.7
3.2.P.5.6 Justification of specifications			
3.2.P.5.6	Justification of specifications was not submitted and requested.	11	1.3
3.2.P.5.6	The proposed justification of specifications is inadequate and not accepted. An amendment is proposed in 3.2.P.5.1.	21	
	Other	11	
		697	
3.2.P.6 **Reference standard or materials**			
3.2.P.6	Supply information on the primary reference standard used to confirm traceability if pharmacopoeial and describe how the secondary reference standards were established.	19	3.7
3.2.P.6	Provide Certificate of analysis (CoAs) of the reference standards used.	32	
3.2.P.6	Provide the CoAs showing the results of the identification, purity and content of the reference standards used.	43	
3.2.P.6	Characterisation of the reference and impurity reference standards not complete or inadequate.	12	
	Other	14	
		120	
3.2.P.7 **Container closure system of the FPP**			
3.2.P.7	Include an identification test e.g. IR of the immediate container closure system.	31	7.1
3.2.P.7	Give a specification and demonstrate the integrity for the heat seal bond strength as well chemical nature and identification test for this heat seal lacquer in the aluminium foil.	27	
3.2.P.7	Specify the printing details on blisters and give a control test for the quality of the printing.	7	
3.2.P.7	The chemical nature of the desiccant must be disclosed.	13	
3.2.P.7	Identification, chemical nature and density of the container closure must be included as well as specifications and the relevant control procedure included. This includes colour, dimensions and thickness.	38	
3.2.P.7	The manufacturers of the primary packaging materials should be included.	23	
3.2.P.7	Information included in the packaging insert/ patient information leaflet (PI/PIL)/Label is not in accordance with	21	

	the packaging presentations contained in this section. Correct.		
3.2.P.7	The Certificates of analysis (CoAs) for the immediate container closure(s) used were not provided.	43	
	Other	28	
		231	
3.2.P.8 **Stability of the FPP**			
3.2.P.8.1 Stability summary and conclusions			
3.2.P.8.1	Provide a justification for the out of trend assay results.	28	4.5
3.2.P.8.1	The shelf-life specifications are incomplete or have missing criteria or parameters. Include these or provide a justification for not including the parameters listed in 3.2.P.5.1.	32	
3.2.P.8.1	Indicate the date of initiation of the stability studies.	15	
3.2.P.8.1	Include the minimum and maximum size of the batches placed under stability study.	32	
3.2.P.8.1	Submit stability data for an alternative local packer for final products manufactured in a different country to the manufacturer, on the product packed in bulk containers over a suitable period covering the relevant transport conditions.	29	
3.2.P.8.1	Indicate the type of batch e.g. pilot/production/experimental as well as the batch size. For pilot batches, a provisional shelf life of up to 24 months is allocated.	11	
3.2.P.8.2 Post approval stability protocol and stability commitment			
3.2.P.8.2	The proposed post-approval stability study did not include the batches being placed on stability annually or how many batches per strength are annually put on stability testing.	34	1.7
3.2.P.8.2	The proposed stability programme commitment is not in accordance with the stability guideline; Summary tables with test results from stability studies conducted under accelerated and stressed conditions were not submitted.	21	
3.2.P.8.3 Stability Data			
3.2.P.8.3	Correct the container closure system to correspond with that indicated in the container closure section, Module 3.2.P.7.	36	9.3
3.2.P.8.3	Impurity/degradation shelf-life limits should be tightened from a quality perspective in view of the results observed for commercial batches.	56	
3.2.P.8.3	Critical stability indicating parameters such as related substances and dissolution are not included in the stability testing. These should be included.	54	
3.2.P.8.3	The proposed shelf life is not supported by the submitted studies, provide additional data to support the proposed shelf life, which should now be reasonably available.	98	
3.2.P.8.3	Stability studies for different manufacturing sites were not provided, confirming similar stability. Submit.	34	
3.2.P.8.3	Submit photostability data under normal conditions which show that secondary packaging protects the Ultra violet ray (UV)-sensitive API and that unrelated impurities did not increase with exposure to light and UV.	14	
	Other	9	
		503	

The results in Table 3 are depicted in a chart form in Figure 3 to clearly show which subsection exhibits the highest and the lowest deficiencies. Subsection 3.2.P.5.1 has the highest deficiency covering 15 % (71% of the 3.2.P.5 section). Module 3.2.P.1, description and composition of FPP, has the second largest number of deficiencies and takes up 14%. Module 3.2.P.3.3 (13%) description of the manufacturing process has the third highest percentage of deficiencies with Module 3.2.P.8.3 on Stability data of the FPP at 9.3% (66% of the 3.2.P.8 section) slightly lagging behind as forth highest.



Modules: 3.2.P.1 description and composition, 3.2.P.2.2 final pharmaceutical product, 3.2.P.2.3 Manufacturing process development, 3.2.P.2.4 Container closure system, 3.2.P.3.3 description of the manufacturing process, 3.2.P.3.4 control of critical steps and intermediates, 3.2.P.3.5 process validation and/or evaluation, 3.2.P.4.1 specifications of IPIs, 3.2.P.4.3 validation of analytical procedures of IPIs, 3.2.P.5.1 specifications of the FPP, 3.2.P.5.3 validation of analytical procedures of FPP, 3.2.P.5.4 batch analysis of the FPP, 3.2.P.5.6 justification of specifications, 3.2.P.6 reference materials, 3.2.P.7 container closure system, 3.2.P.8.1 stability summary and conclusions, 3.2.P.8.2 Post approval stability protocol and stability commitment, 3.2.P.8.3 Stability data.

Figure 3: The distribution of all the deficiencies found in the 3.2.P sections and subsections for non-sterile applications submitted to SAHPRA.

4.3.2 Deficiencies from sterile products

A similar investigation as for the non-sterile products indicated above was conducted on sterile products. The 244 sterile product applications consisted of the following dosage forms: Concentrate for injection (35%), powder for injection (17%), lyophilised powder for injection or infusion (42%), ophthalmic solutions (4.8%), irrigation solution (0.8%) and a minority of other comprising of the remaining 0.4%. These dosae forms were sterile suspensions and chelating agents. A total of 2742 FPP deficiencies related to sterile products were collected from the 244 letters.

The 244 letters were obtained and deficiencies outlined in Table 4 below. Note that the CTD has different requirements in specific sections depending on the dosage form. For example, the sterilisation method selected for sterile products would need to be clearly indicated and justified in accordance to the decision trees for selection of the sterilisation methods (CPMP/QWP/054/98) [22] under 3.2.P.2.2, while this is not a requirement for non-sterile products. There are a number of these sections in the CTD and those deficiencies are listed in the Table 4. There are also a number of common sections where the requirements are the same whether a product is sterile or not, for example, 3.2.P.6 reference materials, 3.2.P.5.4, batch analysis, 3.2.P.5.5 characterisation of impurities etc. Therefore, the deficiencies for sterile products are over and above those listed under Table 2 for non-sterile products depending on their applicability to the dosage form.

Table 4: List of FPP common deficiencies in the 3.2.P section of the CTD recommended by SAHPRA for sterile products finalised by the pre-registration Unit between 2011-2017.

Section/subsection	Deficiency	amount	% overall
3.2.P.1 **Description and Composition of the FPP**			
3.2.P.1	Nitrogen is used as pressure source for filtration it must be indicated in the list of excipients and controlled in 3.2.P.5.	74	3.1
	Other	12	
		86	
3.2.P.2 **Pharmaceutical development**			
3.2.P.2.2 Final pharmaceutical product			
3.2.P.2.2	The product development report is insufficient. It does not address the development of the buffered blend for filling, neither does it address aspects such as choice of container closure system, filter media, sterilisation methods.	39	13
3.2.P.2.2	It is stated that sterile filtration is chosen as method of sterilisation without justification. The choice of sterilisation by filtration as the method of sterilisation must be scientifically justified in terms of the decision tree for sterilisation choices for aqueous products (CPMP/QWP/054/98). Terminal sterilisation should normally be the method of choice if the product is expected to be heat stable.	106	
3.2.P.2.2	Discuss the selection and effectiveness of preservative.	34	
3.2.P.2.2	Include the pore size of the filter used for the method of sterilisation.	67	
3.2.P.2.2	The volume of overfills were unjustified in pharmaceutical development. Provide data to support that the indicated total fill volume sufficient to administer nominal dose.	34	
3.2.P.2.2	Provide results of tests on extractable volume and the API content after reconstitution of the FPP with the selected solvent.	76	
3.2.P.2.3 Manufacturing process development			
3.2.P.2.3	Justify sterilisation by filtration. Heat instability during autoclaving has been determined at 121 °C/20 min. Have studies	45	1.6

	been done at reduced F_o – values to confirm that terminal sterilisation is not possible.		
3.2.P.2.4 Container closure system			
3.2.P.2.4	Submit in-use stability testing method and results in this section to confirm integrity of the container closure system to prevent microbial contamination.	32	1.9
3.2.P.2.4	The consistency for droplet size for the dropper used should be conducted to ensure that the same API/FPP is ejected at each drop.	21	
3.2.P.2.6 Compatibility			
3.2.P.2.6	Extractability and leaching studies of the selected filter should be submitted.	45	6.3
3.2.P.2.6	The studies to confirm the compatibility of the product with the recommended intravenous (IV) solutions was not conducted.	54	
3.2.P.2.6	Provide compatibility studies of the formulation with the equipment used in the manufacturing process.	31	
3.2.P.2.6	Compatibility and leaching studies of the formulation with the coated rubber stoppers to demonstrate that these do not cause leaching should be submitted.	23	
	Other	19	
		626	
3.2.P.3 **Manufacture of the FPP**			
3.2.P.3.3 Description of manufacturing process and process controls			
3.2.P.3.3	The information must include an inspection flow diagram describing both processes, the batch manufacturing formulae, a comprehensive flow diagram and a comprehensive description detailing the various stages of both steps in the manufacturing process including environmental classification of areas, sterilisation methods and conditions of containers and equipment.	54	13
3.2.P.3.3	Nitrogen is used as pressure source for filtration, it must be indicated in 3.2.P.3.3 and should be indicated in the formula and controlled in 3.2.P.5. In addition, the method of sterilisation used for nitrogen should be stated.	43	
3.2.P.3.3	Confirm that the filter integrity is confirmed before and after filtration. Reference to the process procedure only to conduct filter integrity test is inadequate.	23	
3.2.P.3.3	State the type and size (porosity) of the filters used for filtration of the solution.	45	
3.2.P.3.3	Describe the grades of clean areas for manufacture and filling process of water for injection/diluent.	82	
3.2.P.3.3	Provide lyophilisation conditions of the cycle used and confirm that the lyophiliser is sterilised after each cycle.	68	
3.2.P.3.3	Proof of efficacy of the sterilisation of the dead space in the connecting tube and twist off ports of the bags must be provided.	27	
3.2.P.3.4 Control of critical steps and intermediates			
3.2.P.3.4	Bioburden testing and the acceptance criteria for bioburden must be included as an in-process control measure.	59	2.2
3.2.P.3.5 Process validation and/or evaluation			
3.2.P.3.5	Provide summary reports on the validations for the sterilisation of the rubber closures and for the lyophilized powder.	76	17
3.2.P.3.5	The validation of sterilisation and depyrogenation processes with conditions and determination of maximum holding/processing times must also be included.	83	

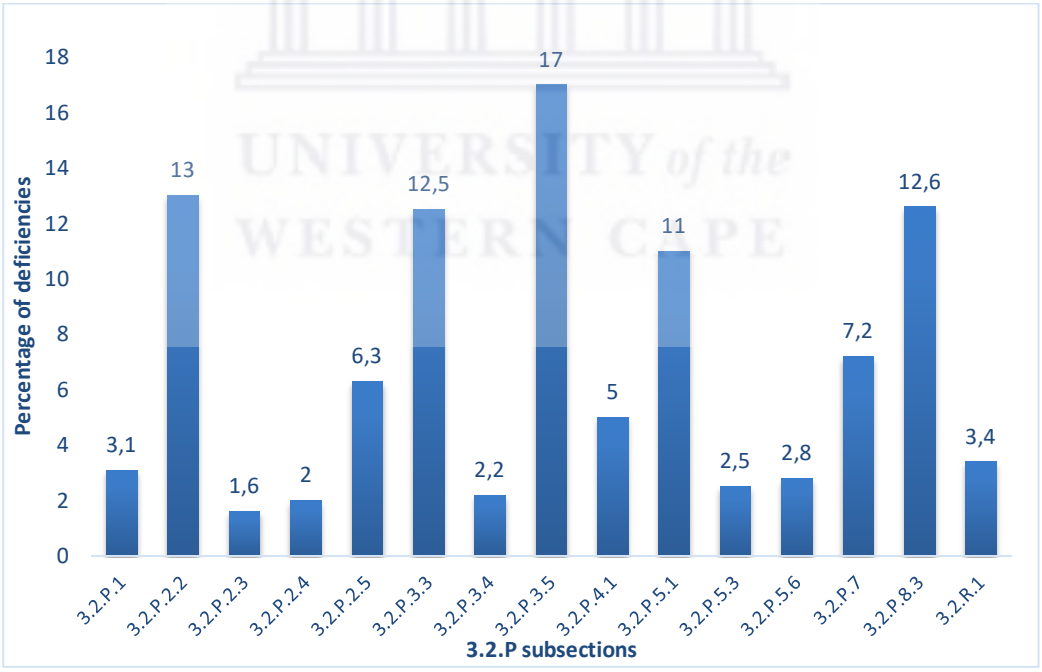
3.2.P.3.5	The hold time validation data should include hold time before and after filtration of final product bulk or hold time within lyophiliser chamber after cycle completion.	34	
3.2.P.3.5	Provide summary reports on the validations of depyrogenation of the glass vials and sterilisation of the rubber closures and for the water for injection/diluent.	23	
3.2.P.3.5	Submit a summary report of the validation (qualification) of the sterilisation cycle of the final product including the loading patterns.	23	
3.2.P.3.5	Submit a summary report of the validation of the selected filter.	16	
3.2.P.3.5	Provide a protocol or report of the validation of autoclaves and sterilisation/ depyrogenation tunnels.	23	
3.2.P.3.5	Provide a protocol or summary report of the media fill procedures and validation of holding times.	43	
3.2.P.3.5	Include a summary report on autoclaving of production equipment.	45	
3.2.P.3.5	A number of issues on the media fill validation including; Media fill validation not covering all product volumes and container types, details of the media fill conditions were not described, Aseptic process not validated by media fill to name a few.	65	
3.2.P.3.5	The validation process should contain storage and shipping conditions linked to process validation results.	25	
	Other	16	
		873	
3.2.P.4 **Control of inactive pharmaceutical ingredients**			
3.2.P.4.1 Specifications			
3.2.P.4.1	Nitrogen is used as pressure source for filtration. Provide specifications and control procedures.	56	4.5
3.2.P.4.1	Indicate the leak test performed on the container-closure system during filling.	45	
	Other	23	
		124	
3.2.P.5 **Control of FPP**			
3.2.P.5.1 Specifications			
3.2.P.5.1	Seal integrity testing (leak testing) of ampoules must be included as a final product control.	23	11
3.2.P.5.1	Visible particulate matter should be included as a specification either as final product release specification or as in-process control.	54	
3.2.P.5.1	Bacterial endotoxin Test (BET) should be included as a specification either as final product release specification or as an in-process control.	80	
3.2.P.5.1	In view of the batch release data and stability data provided for related substances the justification of the specifications for Total impurities based on batch release data is not accepted and should be reconsidered.	34	
3.2.P.5.1	Include a specification for preservative effectiveness. The test is not required for routine analysis provided that the preservative effectiveness has been established at the lowest limit specified, however, the specification should be retained as a skip test.	43	
3.2.P.5.1	The following were missing from the specifications and should be submitted: preservative efficiency testing at the end of shelf life; active content in reconstituted solution; product-related impurities in specifications considered as too wide; acceptance	22	

	and extractable volume after reconstitution as well as uniformity of mass.		
3.2.P.5.3 Validation of analytical procedures			
3.2.P.5.3	Provide validation data for the sterility test method. If a pharmacopoeial method from a recognised pharmacopoeia is used partial validation data will suffice.	23	2.5
3.2.P.5.3	Provide validation data for the bacterial endotoxin test method.	45	
3.2.P.5.6 Justification of specifications			
3.2.P.5.6	There were unjustified items: bacterial endotoxin limits; pH specification limits; active salt selection; omission of impurities in specifications and missing container closure test.	54	2.8
	Other	22	
		400	
3.2.P.7 **Container closure system of the FPP**			
3.2.P.7	Consistency of the droplet size should be confirmed.	45	7.2
3.2.P.7	Coating composition of the stoppers used was not included.	27	
3.2.P.7	The CoAs for glass and rubber stoppers used were not provided.	17	
3.2.P.7	Sterilisation of primary packaging components was not satisfactorily described.	13	
3.2.P.7	Compatibility of the stopper material with the final product was not demonstrated on potential extractables. Extractability and leaching study is therefore requested.	39	
3.2.P.7	Leachability study of the leachables originating from the container closure system should be investigated.	34	
	Other	21	
		196	
3.2.P.8 **Stability of the FPP**			
3.2.P.8.3 Stability data			
3.2.P.8.3	Provide results of the stability studies on the diluted solution in selected diluent for infusion confirming the recommendations in the PI.	28	13
3.2.P.8.3	The results of the photo stability studies showing no effect to impurity values and thus no requirement for protection from light during storage of the product should be provided.	45	
3.2.P.8.3	The results of the in-use stability study confirming stability of the product at a specific temperature for specified amount of time as indicated in the PI and in accordance with the guidelines should be provided.	38	
3.2.P.8.3	The results of the transportation stability test at specified elevated storage condition for a sufficient amount of time should be submitted.	23	
3.2.P.8.3	Provide stability results to confirm the effectiveness of the preservative.	43	
3.2.P.8.3	Stability studies should be conducted in upright and inverted positions, the results were only submitted for samples stored in an upright position. Submit for the inverted position.	34	
3.2.P.8.3	There were missing tests during stability studies, for example, volume in container, sterility and BET. This should be conducted in the next testing and submitted.	44	
3.2.P.8.3	Missing or insufficient data for aspects such as vacuum stress for container closure ingress testing; supporting storage out of Refrigeration; potency test performance during stability control; chromatograms from final product long-term, accelerated, and	38	

	stressed stability studies and sterility tests on preservative efficiency.		
3.2.P.8.3	Stability studies for temperature excursions at the end of the shelf-life should be submitted.	36	
	Other	15	
		344	
3.2.R.1	Pharmaceutical and Biological availability		
3.2.R.1*	Data to substantiate efficacy has been provided in Module 3.2.P.2 where essential similarity of the innovator and test product was proven however, a request for exemption from submitting proof of Biological availability based on the Biostudies Guidelines was not stipulated. Exemption will only be considered when motivation and comparative data has been submitted in Module 3.2.R.1.	93	3.4
		93	

Note that there are deficiencies applicable to sterile products already included in Table 3, these were not included in this table to avoid duplication and quantified as other in the table due to the low frequency.
* A regional requirement for sterile and liquid dosage form to request exemption from submitting proof of efficacy studies, only essential similarity with an SA innovator product is required in such cases.

The Figure 4 below highlights the most frequently observed deficiencies from the sterile products. It shows that FPP sub-sections Module 3.2.P.3.5, process validation and/or evaluation (17%), Module 3.2.P.2.2, development of FPP (13%), Module 3.2.P.8.3, stability data (12.6%), Module 3.2.P.3.3, description of the manufacturing process (12.5%) and Module 3.2.P.5.1, specifications (11%) fall under the top five most common deficiencies requested by SAHPRA for sterile products.



Modules: 3.2.P.1 description and composition, 3.2.P.2.2 final pharmaceutical product, 3.2.P.2.3 Manufacturing process development, 3.2.P.2.4 Container closure system, 3.2.P.2.5 Compatibility, 3.2.P.3.3 description of the manufacturing process, 3.2.P.3.4 control of critical steps and intermediates, 3.2.P.3.5 process validation and/or evaluation, 3.2.P.4.1 specifications of IPIs, 3.2.P.5.1 specifications of the FPP, 3.2.P.5.3 validation of analytical procedures of FPP, 3.2.P.5.6 justification of specifications, 3.2.P.7 container closure system, 3.2.P.8.3 Stability data, 3.2.R.1 Pharmaceutical and Biological availability.

Figure 4: The distribution of deficiencies relating to sterile products.

4.4 DISCUSSION

4.4.1 Deficiencies in Module 3.2.P

The most frequent common deficiencies observed by SAHPRA in the submitted non-sterile and sterile products are extensively discussed below as depicted Figures 3 and 4.

4.4.1.1 Deficiencies in Module 3.2.P.3., manufacture of the FPP

The highest section reported as per Figure 2 was Module 3.2.P.3. Further analysis (Figure 3) reveals that 13% of the overall deficiencies were due to Module 3.2.P.3.3 - Description of manufacturing process and process control, 7.4% on Module 3.2.P.3.4 - Control of critical steps and intermediates and 2.2% on Module 3.2.P.3.5 - Process validation and/or evaluation. Concerning sterile product deficiencies, a similar trend is witnessed where the highest reported section is Module 3.2.P.3, manufacture of the FPP. Module 3.2.P.3.5, process validation and/or evaluation, constitutes 17% of the deficiencies, followed by 12.5% from Module 3.2.P.3.3, description of the manufacturing process and lastly 2.2% from Module 3.2.P.3.4, control of critical steps and intermediates.

The common deficiencies observed in the manufacturing process of non-sterile products included: insufficient information being provided on the manufacturing process such as duration of treatment, manufacturing conditions (temperature and humidity), specifications for machine settings, capacity of equipment, compression procedure & speed, sieve sizes used, duration of stirring and drying temperatures. These and more are critical parameters that should be included in the process to provide the evaluator with comprehensive description of the manufacturing process. The second deficiency was on the hold time period not being indicated as well as the bulk containers used for the intermediates and final product before packaging. The proposed holding time is dependent on the shelf life, whereby a holding time exceeding 25% of the shelf life [23] should be supported by accelerated and long-term stability data for approval. There were a large number of deficiencies where applicants did not indicate the proposed period, did not provide a hold time study report in Module 3.2.P.3.5, process validation and/or evaluation and supporting data in 3.2.P.8.3, stability data, if the proposed period exceeds the acceptable conditions as indicated above.

The common deficiencies witnessed from the sterile products in this prevalent section was on subsection, Module 3.2.P.3.5 Process validation and/or evaluation. The deficiencies included issues on the validation and outstanding summary report on validation of; the sterilisation method used, media fill procedures, depyrogenation of glass containers and sterilisation for rubber stoppers and autoclaving of production equipment. These are a requirement and should normally be submitted by the manufacturer when the product is considered sterile using aseptic processing or terminal sterilisation. It is imperative that the container used, the excipients, the FPP and container closures be sterile or sterilised for these products, therefore, summary reports on how the validation is conducted is vital. Media fill simulations are also of importance as they assess the performance of an aseptic manufacturing procedure using a sterile microbiological growth

medium, in place of the FPP solution, to test whether the aseptic procedures are adequate to prevent contamination during actual FPP production [24-26]. The section comprised of 54% of these deficiencies.

A common deficiency in the section, 3.2.P.3, Manufacture of the FPP, is also the lack of inclusion of environmental classification of areas in the manufacture of sterile products. The classified rooms help the sterile pharmaceutical industry to manufacture products that are free from particulate and microbial contamination [26, 27]. The areas have a controlled contamination level, which is specified regarding the number of particles for every cubic meter for a specified particle size. The restricted areas are constructed with strict humidity, temperature and pressure control condition to minimise the generation, introduction and retention of particulate matter inside the rooms [27, 28]. The classifications are either A, B, C and D with sterile environments normally using Class A or B or a combination of both. This requirement is therefore very critical in the manufacture of the sterile product and should be specified in the process. These deficiencies comprised of 16% of the section.

4.4.1.2 Deficiencies in Module 3.2.P.5., control of the FPP

The section with the second highest deficiencies is Module 3.2.P.5, control of the FPP, (21%) as depicted in Figure 2. Figure 3 further shows that subsection 3.2.P.5.1, specifications, had the most deficiencies in the whole 3.2.P reported for non-sterile products. Missing dissolution profiles and/or unacceptable dissolution limits were observed from nearly all the evaluations. Multimedia dissolution profile data on the biostudy test product is critical and used as reference data set that is used to support and assign dissolution limits in accordance to the EMA reflection paper [29]. The reports indicate that manufacturers often assign dissolution limits that are wider than the biostudy test product. This leads to back-and-forth communication between the applicant and the authority. Applicants often justify the widened limits based on the results of the stability results, however, this is not accepted since the acceptance criterion set should be based on the biostudy product. The behaviour should not change during stability as any deviation confirm deterioration of product quality. This is also part of the reason why the proposed dissolution specifications for release and shelf life should not differ as the product quality is expected to remain the same throughout shelf life as per the biostudy test product.

Module 3.2.P.5.1, specifications, contains a number of deficiencies (58%) involving the request to tighten the proposed specifications based on batch analyses data, stability results and limits on ICH guidelines. For degradation/related impurities manufacturers are required to ensure that the proposed specifications are in line with the recognised pharmacopoeia or that the limit is in accordance with the ICH guidelines Q3B (R2) [11], the limit should be below the calculated qualification threshold or reporting threshold. It was also observed that the acceptance criteria set for any other unknown impurities did not conform to ICH requirements. Impurities that are structural alerts for genotoxicity need to be controlled at the Threshold of

Toxicological Concern (TTC) of 1.5 mcg/day, as found in the European Medicines Agency (EMA) [30] and draft FDA guidance [31]. However, a higher limit may be proposed based on safety studies demonstrating that the proposed limit does not pose a safety concern. Other limits such as water content, assay, disintegration time are based on the batch analyses and stability results observed. A reasonable proposed limit would need to be justified by supporting data for acceptability if not already indicated in the pharmacopoeia or guidelines.

The most frequent deficiency observed for sterile products in this subsection is the request to include the limit for bacterial endotoxin in the FPP specifications. Endotoxins released from Gram-negative Bacteria are the main reason of contamination in pharmaceutical products and as a result of this, an endotoxin test is required to be performed on sterile products especially those which are to be injected in the body so as to avoid bringing adverse effects to human [32].

4.4.1.3 Deficiencies in Module 3.2.P.8, stability

The section with the third highest deficiencies is Module 3.2.P.8, stability of the FPP, (15%) for non-sterile products. It comprises of Module 3.2.P.8.1 (7.6%) – stability summary and conclusions, Module 3.2.P.8.2 (1.8%) – post approval stability protocol and stability commitment and Module 3.2.P.8.3 (9.3%) – stability data. The frequent deficiencies in subsection 3.2.P.8.3, stability data, were on the limits proposed on degradation impurities and total impurities being too wide and applicant requested to tighten them in reference to the stability results, this relates to subsection 3.2.P.5.1, specifications, as discussed above. The other deficiency was on the applicant omitting critical stability indicating parameters such as dissolution, total impurities or degradation impurities in the stability testing. Acceptance of a product cannot be granted if the stability testing does not include these critical parameters which determine the behaviour of the product throughout its shelf life.

There were 12.6% of the additional deficiencies specific to sterile products also witnessed from subsection 3.2.P.8.3, stability data. The deficiencies were on the request for results of the in-use stability study confirming stability of the product at a specific temperature for specified amount of time as indicated on the Professional Information (PI). Since the products are sterile, there is a requirement that if the product is not for single use such as ophthalmic solutions, lyophilised powders for infusion etc., stability results should be conducted to confirm that the product quality is not compromised while in-use. Another list of stability data required involved studies to confirm compatibility of the selected diluent used for infusion solutions, photo stability studies to confirm the effect of light on the final product and transportation stability test at specified elevated storage conditions.

4.4.1.4 Deficiencies in Module 3.2.P.1, description and composition of the FPP

There is 14% of deficiencies attributed to Module 3.2.P.1, description and composition of the FPP, from the whole 3.2.P section. The deficiencies in the section comprised of requests for the potency adjustment calculation to be included. This equation clearly outlines the quantities required for the API depending on the assay of the API batches used. It also factors the water content present in the API and corrects to provide the acceptable quantity to be used. This should be included as a footnote under the composition table in 3.2.P.1. The other common deficiency in this section was on the indication of the polymorphic form used. The FPP manufacturer has to include the type of polymorphic form used in the batch formula as well as studies conducted to confirm the polymorphic form. They are required to provide the physico-chemical properties of the API in Module 3.2.P.2, pharmaceutical development, which will include polymorphic form investigation, particle size distribution and solubility. It should be noted that these parameters are not critical and may not be controlled by the final product manufacturer if the manufacturing process employs the following techniques which enhance the solubility as a result of the formation of the amorphous form of the product:

- Complete dissolution of the API in a diluent – results in the formation of an amorphous form [33].
- hot melt extrusion which forms a solid dispersion of the API resulting in the formation of an amorphous polymer with enhanced solubility and bioavailability [33, 34].

The most common deficiency witnessed from sterile products in this section is on the request to include the pressure source used for filtration in the batch formula or composition list. The pressure source commonly used is Nitrogen gas. It is also imperative that the pressure source used be sterile, this can be indicated in Module 3.2.P.4.

4.4.1.5 Deficiencies in Module 3.2.P.7, container closure system of the FPP

The most common deficiencies in the section included the request for the following regarding the immediate container closure system:

- CoAs of the immediate container closure system (CCS),
- Identification, chemical nature and density of the container closure as well as specifications and the relevant control procedures,
- colour, dimensions and thickness of the container closure system,
- the integrity for the heat seal bond strength (See Table 5).

Manufacturers are required to include the testing parameters used for the container closure system as well as analytical procedure used to do the test. Further description of the CCS is also frequently requested such as colour, dimensions and thickness. This needs to concur with the description in the PI and Patient Information Leaflet (PIL). This section also relates to Module 3.2.P.2.4 where developmental studies on the CCS should be conducted and the most common deficiency is that the manufacturers do not provide or poorly

documenting the suitability of the container with the final product. This should include performance studies, suitability, compatibility and safety of the CCS. The common deficiency is frequently cited for sterile products in the section since compatibility studies with all components the final product is in contact with should be provided. For non-sterile, a frequent response normally refers to the stability data provided in 3.2.P.8.3 or the confirmation that the reference product also uses the identical CCS. SAHPRA accepts these justifications.

4.4.2 Comparison with other authorities

The reported deficiencies listed in Table 4 and 5 have been compared with those published by other authorities and discussed below.

4.4.2.1 Comparison of deficiencies, SAHPRA vs USFDA

The USFDA published a four-part series on common deficiencies witnessed in the ANDA applications they received before 2010. Part 2-4 includes the common deficiencies found in the 3.2.P section of the CTD with Part 2 covering Module 3.2.P.1 and 3.2.P.4 on description, composition and excipients [5]. Part 3 covers Module 3.2.P.5 and 3.2.P.8 Control of the final product and stability [6] while Part 4 covers the common deficiencies on Module 3.2.P.2/3 and 3.2.P.7, Manufacture and Container closure system [7]. A quantitative comparison cannot be made since USFDA did not quantify the frequency of deficiencies. Some of the common deficiencies highlighted in 3.2.P.3 were on the in-process controls and tests (3.2.P.3.4, control of critical steps and intermediates) which is also 37% of deficiencies in the subsection by SAHPRA. Queries on granulation process was also reported to be significantly high and manufacturers were requested to provide a definitive quantitative end-point. A deficiency is included if no control or justification is provided by the applicant and the sole control proposed is a subjective, visual observation. For high shear processes, suitable controls may be related to the change in power consumption with respect to the granulation equipment (e.g. amperage). For fluid bed processes, moisture content can be a suitable control for end point of the desired granules [7]. There were 5.9% of the deficiencies in the subsection requesting this by SAHPRA. For sterile products, the reported common deficiency was on excess fill volume and studies on extractable volume. A justification should be provided under manufacturing development based on data of multiple containers demonstrating that the intended volume can be extracted. Large overfills exceeding the required limit according to the USP 1151 general chapter [35], should be appropriately justified as this may pose potential safety concern. There were 9.6% of these deficiencies reported by SAHPRA for the applicable dosage forms. The most prevalent deficiency from part 3 was on the control of the final product, specifications (3.2.P.5.1) which is also one of the highest common deficiency observed by SAHPRA at 58% in the subsection. The reported deficiencies are confirmed to be similar to those included in this study by SAHPRA.

4.4.2.2 Comparison of deficiencies, SAHPRA vs TFDA

A report by TFDA was made for applications submitted between June 2011 to May 2012 [8]. Deficiencies in the specification of the final product were the most prevalent in the final quality assessment reports. Issues regarding the specification of the final product were mainly related to the test item, related substances, or degradation products [8]. The second deficiency was regarding the validation of analytical procedures and mainly related to the validation for related substances/ degradation products. The issues were mainly about the inadequate range/linearity incomplete information about the characteristics (specificity, accuracy, precision, etc.) evaluated [8]. This deficiency comprised of 46% in the subsection Module 3.2.P.5.3 for SAHPRA submissions. The other deficiency witnessed was regarding the manufacturing process which included inappropriate overages applied, an unjustified change in the manufacturing process, unclarified batch sizes, and others. These are similar to those reported by SAHPRA as seen from Table 4 and 5 above. The top five deficiencies reported by SAHPRA are very similar to those reported by the TFDA.

4.4.2.3 Comparison of deficiencies, SAHPRA vs EMA

The study by the EMA was conducted on applications finalised by the Committee for Medicinal Products for Human Use (CHMP), during 12 consecutive plenary meetings held in 2007 and 2008. The concerns raised by the Committee were on control of FPP (32% for 3.2.P.5.1), followed by concerns on the manufacturing (21% for 3.2.P.3), product development (17% for 3.2.P.2) and stability (17% for 3.2.P.8) [9]. This is similarly observed by SAHPRA as shown on Table 5, which compares the frequent deficiencies with what other authorities and organisations reported.

Table 6: Comparison of the top five common deficiencies from the five regulatory bodies listed below.

SAHPRA#	**TFDA**	**USFDA***	**EMA**	**WHOPQTm**
3.2.P.5.1	3.2.P.5.1	3.2.P.3.3	3.2.P.5	3.2.P.3
3.2.P.3.3	3.2.P.5.3	3.2.P.5.1	3.2.P.3	3.2.P.4
3.2.P.1	3.2.P.3.3	3.2.P.8	3.2.P.2	3.2.P.5
3.2.P.8.1/3	3.2.P.3.4	3.2.P.2.2	3.2.P.8	3.2.P.8
3.2.P.7	3.2.P.6	3.2.P.4	3.2.P.4	3.2.P.7

* USFDA did not report on the deficiency quantitatively # Sequence included is for non-sterile products, the sequence is different for sterile products. *Modules: 3.2.P.1 composition and description, 3.2.P.2 pharmaceutical development, 3.2.P.3.3 description of the manufacturing process, 3.2.P.3.5 process validation or evaluation, 3.2.P.8 stability data, 3.2.P.2.2 pharmaceutical development, 3.2.P.5.1 Specifications, 3.2.P.4 control of the IPIs, 3.2.P.7 container closure system, (see Table 2 for further descriptions)*

With respect to stability (3.2.P.8), 32% of concerns were regarding the lack of data submitted by the applicant to substantiate the proposed shelf-life of the FPP. For pharmaceutical development (3.2.P.2), 16% of

concerns had to do with the results from comparative *in vitro* studies (for example the dissolution) or comparative *in vivo* studies (e.g., bioequivalence) requiring further discussion as well as a lack of information on the discriminatory power of dissolution method used [9]. These deficiencies were also observed by SAHPRA in the respective sections. EMA also published a recent study reporting on common deficiencies witnessed in Biosimilars [14] Although these are different to orthodox medicines with respect to the API synthesis in most cases, there is similarity of these products with sterile products since most Biosimilars are sterile. There were a number of similar deficiencies reported with those reported by SAHPRA. The deficiencies are; variety of media fill validation issues, validation of depyrogenation of glass vials and hold time validation issues in 3.2.P.3.5 (47% in the section), filter material and filter pore size not included in 3.2.P.3.3, lyophilisation conditions of the cycle used not indicated in 3.2.P.3.3 (28%) and compatibility studies of the FPP with the equipment not indicated in 3.2.P.2.4 (17%) [15]. Table 4 on the additional sterile product deficiencies also highlights these in the respective sections thereby confirming similarity.

4.4.2.4 Comparison of deficiencies, SAHPRA vs WHO PQTm

The WHO PQTm published on the FPP deficiencies observed in applications submitted between April 2007 and December 2010. The deficiencies reported were on missing executed and blank manufacturing records (BMRs), inadequate description of equipment, process parameters and end-point determination, inadequate description of sterile processes, unsatisfactory in-process tests and their frequency or acceptability of intermediate product specification, for Module 3.2.P.3 [3]. All the above have also been requested by SAHPRA as observed in Tables 4 and 5. Previously, SAHPRA only requested the BMRs and packaging records when the need arose from the evaluations since they were the principle requirement during inspections. However, this condition was amended in 2020 by SAHPRA and is now a requirement during evaluations. Inadequate or poorly defined end-point for wet granulation process was another common deficiency as well as hold time related deficiencies from the guidance document [10]. These were also observed by SAHPRA and discussed in previous sections.

4.5 CONCLUSION

The main objective of this study was to provide a comprehensive list of common deficiencies encountered by SAHPRA from the submitted 3.2.P section of the CTD dossiers. The issues raised stem from product development, production and control of FPPs. The list is aimed at assisting manufacturers and applicants who submit future products to anticipate and avoid common pitfalls in regulatory. Thus, as a result, this study will help pharmaceutical companies and manufacturers in reducing unnecessary and avoidable delays in the registration of these products to the benefit of accelerated access of medicines to patients. Comparisons with other regulatory authorities showed that other international regulatory agencies also observe similar common deficiencies as SAHPRA. This confirms the similarity in the extent of scientific assessments by the authorities, thus ensuring that quality, safe and efficacious medicines is available to the patients.

4.6 LIMITATIONS OF THE STUDY

The study could not be conducted for applications finalised in 2018-2020 due to the following: The authority transitioned from Medicine Control Council (MCC) to SAHPRA in 2018. In that time, SAHPRA staff continued to be housed in Civitas building in Pretoria with the NDoH employees. From April 2018, the department employees working in the Civitas building embarked on a protest action because of concerns about working conditions in the building. In the medium term, SAHPRA as a Section 3A public entity, moved into new premises at the end of 2018. In addition, a backlog project was initiated in 2020, which required SAHPRA evaluators to implement, induct and train the new evaluators involved in the project. As a result, information for 2018-2020 is not included in this study due to the disruptions caused by the protesting action, the move to the new premises and the initiation of the backlog project.

There are further investigations conducted on other sections within the CTD as this will assist in informing all relevant manufacturers and research organisations partaking in medicinal research in the pharmaceutical industry with the intent to obtain approval/registration from regulatory authorities.

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CHAPTER 5

Bioequivalence common deficiencies in generic products submitted for registration to the South African Health Products Regulatory Authority (SAHPRA)

Abstract

Background. The cost of healthcare has become expensive globally, of which the greater part of the money is spent on buying innovator medicines. In order to make medicine affordable, the development of generic medicines has become paramount. The science of bioequivalence studies of generic products to demonstrate therapeutic equivalence with innovator products has been developed over the last 50 years. These studies cost far less as compared to innovator products thereby reducing the cost of medicines. Accelerating access to medicines has become an increasing challenge due to insufficient resources from regulatory authorities while pharmaceutical industry continues to expand. An investigation on the deficiencies identified during scientific assessments by SAHPRA, in submitted bioequivalence studies is therefore paramount. Identification and publication of these deficiencies will assist in accelerating the access of medicines to patients.

Objective. The aim of the study is to investigate the types and frequency of the common deficiencies observed in the bioequivalence section of generic submissions to SAHPRA. The study was conducted retrospectively over a 7-year period (2011-2017) for generic products that were finalised by the Pharmaceutical and Analytical pre-registration Unit. A more recent analysis on common deficiencies witnessed for applications assessed between 2020-2021 was also done to illustrate the consistency in the evaluation practises adopted by SAHPRA.

Methods. There were 3148 applications finalised between 2011-2017 and to attain a representative sample for the study, statistical sampling was conducted. The multi-stage sampling called stratified systematic sampling was selected as the method of choice. The sample size was obtained using the statistical tables found in the literature and confirmed by a sample size calculation resulting in the selection of 325 applications (Fig 2a). Additionally, 300 master applications were assessed between 2020-2021 for up-to-date data (Fig 2b). All the deficiencies were collected and categorised according to the ICH E3 guideline and components relevant to biostudies.

Results. A total of 2458 deficiencies were collected from the selected sample size for applications finalised between 2011-2017 where a biostudy was submitted. The majority of the identified deficiencies were from

the following categories; *in vitro* dissolution testing and specifications (18%), study design (17%), details on the test and reference products (16%), issues on sample analysis (16%), and statistical analysis (10%) (Fig 3). From the applications assessed in 2020-2021, 492 deficiencies were identified with a similar trend compared to those finalised between 2011-2017. Comparison of the deficiencies with those reported by the USFDA and WHO PQTm are discussed with similarities outlined.

Conclusions. The five most common deficiencies observed were extensively discussed. The outcomes of this study will guide pharmaceutical companies, sponsors and Clinical Research Organisations (CROs) in submitting quality biostudies which will reduce turnaround times for registration and accelerate access to medicines for patients. In addition, the deficiencies identified will assist assessors from the different regulatory authorities to improve on their bioequivalence assessment.

5.1 Introduction

Innovator pharmaceutical products are New Chemical Entities (NCEs) that have received a patent on the chemical formulation or manufacturing process and obtained registration from a regulatory authority after extensive testing. [1] Innovator and generic products are both available on the market, but innovator products are usually more expensive compared to the generics due to extensive research conducted from discovery and development to marketing and promotion of the product. [2] For example, clinical trials which are the primary tool to assess safety, efficacy and clinical benefits of new Finished Pharmaceutical Products (FPPs) in humans tend to be time consuming, expensive and burdensome for subjects. These can be replaced by the cost-saving bioequivalence studies which ensures the progression of future therapeutic development. In 2017 alone, the United States of America (USA) government was able to save $265.1 billion due to the use of generic products, and an overall of $1.67 trillion was saved in the last decade. [2] In South Africa, the domestic manufacturing pharmaceutical industry almost exclusively produces generic products and the South African pharmaceutical sector is import-dependent. [3] In 2013, generic medicines accounted for 63% of the private pharmaceutical market and 80% of the market share in the South African government's pharmaceutical use. [3]

Bioavailability refers to the rate and extent to which the Active Pharmaceutical Ingredient (API), or its active moiety, is absorbed and becomes available at the site of action. [4] When two formulations of the same API or two FPPs are claimed bioequivalent, it is expected that they are therapeutically equivalent. [4-8] The generic products submitted to regulatory authorities must be both pharmaceutically equivalent and bioequivalent to the corresponding innovator product to establish that the two products are therapeutically equivalent. A biowaiver may also be requested instead of submission of the biostudies, when justified, in line with the Biopharmaceutics Classification System (BCS). [7]

The South African Health Products Regulatory Authority (SAHPRA) receives approximately 1200 applications per annum from pharmaceutical companies for registration into the market and 90% of these are generic products. Direct demonstration of therapeutic equivalence through a comparative clinical trial is rarely a practical choice, as these trials tend to be insensitive to formulation differences and usually require a very large number of patients. [7] Further, these studies in humans can be financially limiting, often unnecessary and may be unethical. [5] As a result, the science of bioequivalence testing has been developed over the last 50 years. [7]

Data from biostudies is received and evaluated by the Pharmaceutical Evaluations and Management (PEM), Pharmaceutical and Analytical (P&A) pre-registration Unit. SAHPRA mostly relies on external evaluators to execute biostudy evaluations. The P&A pre-registration Unit utilised five to eight external experts as biostudy evaluators. The experts formed part of the Pharmaceutical and Analytical (P&A) Committee, which provide the necessary support to the Unit and the meetings served as a quality assurance measure for all products. Committee members provide technical and scientific advice for evaluations in the pre-registration Unit. This meant that each biostudy report on the evaluation of the data provided in the dossier was discussed in the meeting before it can be communicated to the applicant. Due to the resultant backlog of applications over the years, SAHPRA embarked on a project called the Backlog clearance programme aimed at clearing the existing backlog over a specified time. Inherited processes and practices from the former Medicine Control Council (MCC) were re-assessed and the backlog project was initiated to support new methodologies required to achieve the goal of clearing the backlog of applications. [9] All applications received by SAHPRA prior to February 1, 2018 were considered to be part of the backlog project and ~ 8000 applications were in the pre-registration phase. [9] The authority, therefore, implemented a process that allows applicants to re-submit the dossiers, as some information may be required to be updated since the backlog applications were initially submitted as far back as 2008. Re-submission windows (RW) were created based on the importance of therapeutic categories of medicines to the country. Re-submission window one (RW1) consisted of medicines in the therapeutic category of Human Immunodeficiency Virus (HIV), Tuberculosis (TB), Vaccines and Hepatitis while re-submission window two (RW2) was for medicines in the therapeutic category, oncology medicines. [10] Re-submission window five (RW5) was for medicines targeting Diabetes, Malaria, maternal and newborn health as well as all the priority APIs. [10] The inclusion of the backlog applications in this study is to identify the biostudy deficiencies and establish if there are any differences in the outcomes from the newly developed biostudy assessments practices.

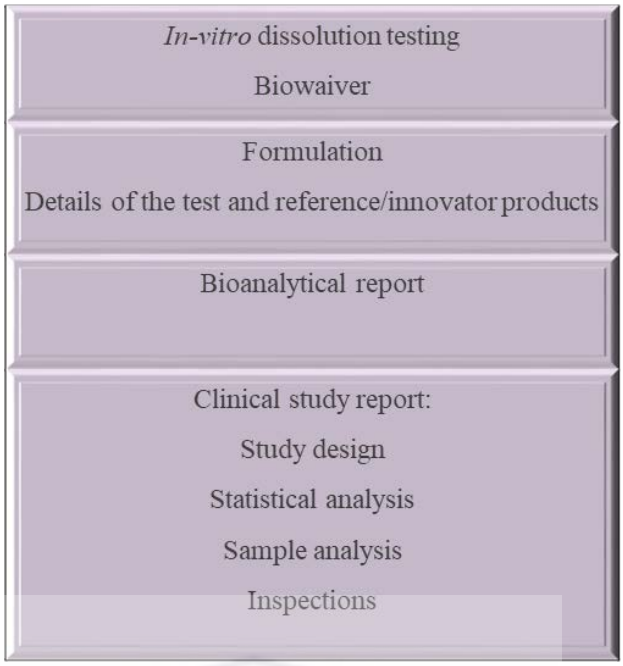

Fig. 1 Four groups of bioequivalence study components with nine categories for the deficiencies observed in biostudy submissions.

The four major study report components for biostudies and evaluations are as follows: *in vitro* dissolution testing, bioanalytical validation and analysis, clinical study reports, and details of the test and reference products used as illustrated in Fig 1. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use (ICH) E3 guideline provides the structure and content of the clinical study reports. [11] In an effort to improve the quality of biostudy submissions by the applicants, different regulatory authorities developed additional guidelines. [4-8] The United States Food and Drug Administration (USFDA) published guidance documents on General Bioavailability and Bioequivalence (BA/BE) Guidance [6], Statistical Approaches to Bioequivalence Guidance [12], and creation of the online Dissolution Methods Database (November 2005) to name a few. The USFDA noted that although there has been an improvement in the overall quality of the submissions with the employment of the guidelines and the Dissolution Methods Database, [13] there was still some recurring deficiencies that may be associated with one or more of the components of the biostudy reports of the applications. This resulted in authorities publishing common deficiencies observed in biostudy evaluations to the industry in order to avoid future delays in submissions and promote access of medicine to patients. Thus far, reports on common deficiencies were published by the USFDA [14] and the World Health Organisation Prequalification Team: Medicines (WHO PQTm). [15] This current study therefore aims to identify and quantify common deficiencies in the biostudy section of generic products finalised by SAHPRA's PEM pre-registration Unit between 2011-2017. In addition, deficiencies identified in applications assessed between 2020-2021 were also investigated. The

transparency between the authority and industry on common deficiencies in the biostudy section will assist in reducing the scientific review process and thereby accelerate the access of medicines to patients.

5.2 Methods

Over the 7-year period (2011-2017), 3148 applications were finalised by the P&A pre-registration Unit within SAHPRA. The sterile products (667), Veterinary (68), Biologicals (86), Medical Devices (5), and New Chemical Entities (NCEs) (233) were also finalised by the P&A Committee in the period as shown in Fig 2 but were not included as part of this study. NCEs require the submission of clinical trial data assessed by the Clinical Evaluation Unit within SAHPRA. Solutions for oral use, aqueous solutions administered by parenteral routes, powders for reconstitution, otic, ophthalmic, nasal, topical and cutaneous products containing the API in the same molar concentration as the reference product are considered to be equivalent without further documentation of equivalence. [5] The applicant should demonstrate that the excipients in the pharmaceutically equivalent product are essentially the same and in comparable concentrations as those in the reference product. [5] Sterile products are normally classified in the above dosage forms, thus, biostudies are not required and not submitted for these. The biological products also use sterile preparations due to the criticality and nature of the active moiety. The veterinary products were not included in the study since the P&A Committee only provided support to the veterinary Unit on each application in terms of quality assessments only. The veterinary applications require the submission of clinical trial data due to the diversity across animal species' physiology and the numerous dosage forms used in veterinary practice resulting in unique formulations and dosage routes. [16] As such, technical requirements for registration of veterinary medicines are constantly evolving as a result of scientific developments. [16] Lastly, medical devices were not included in this study because the sample size was too small to render the deficiencies common.
The distribution clearly shows that SAHPRA receives a large number of generic products since 90% of the finalised products are generic products and 66% of those are non-sterile (Fig 2a).

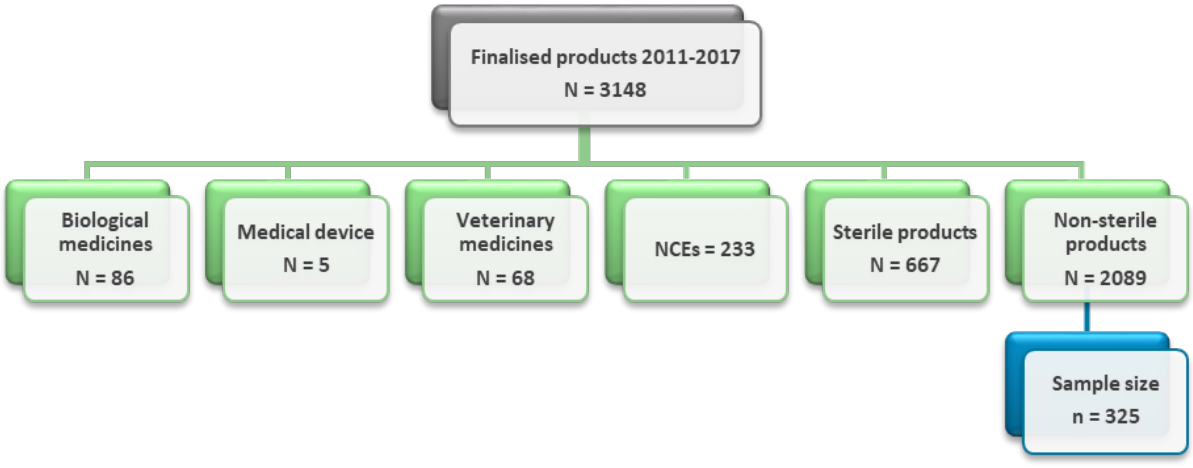

Fig. 2a Categorisation of products finalised by the P&A pre-registration Unit within SAHPRA.

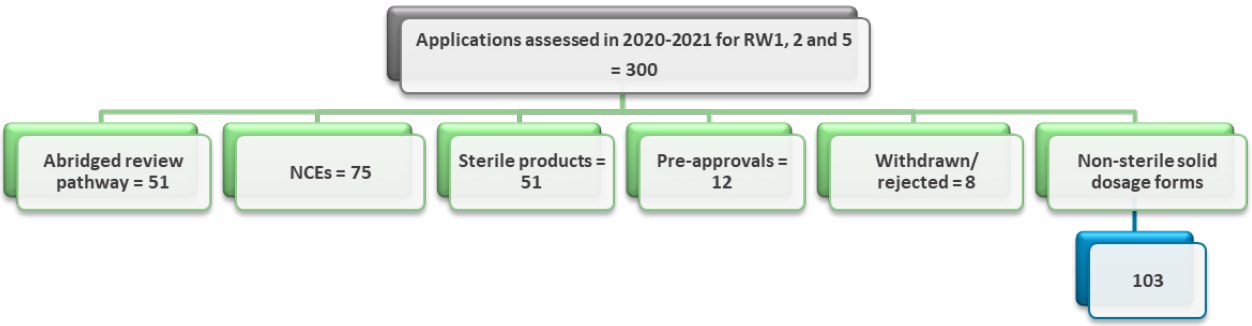

Fig. 2b Categorisation of products received in the respective re-submission windows 1, 2 and 5.

Due to the large population size of the non-sterile products, a statistical sampling method became a requirement for this research. The sample selected needs to be a true representation of the population and the results of the study can be generalised to the population as a whole. Selection of the sampling method is crucial as different sampling techniques are used for specific research problems since one technique may not be appropriate for all problems. [17] The sample size determination and sample selection for the non-sterile products have been well described in the findings on common deficiencies in the Active Pharmaceutical Ingredient section by SAHPRA. [18] Stratified systematic sampling is the selected sampling method and a sample size of 325 non-sterile applications was obtained (Fig 2a). [18]

For the study investigating applications assessed between 2020-2021, all applications received in re-submission windows one, two and five (300) (Fig 2b) where a biostudy was submitted, were used. An overall of 84 (RW1), 143 (RW2) and 73 (RW5) applications were received in the respective windows. Table 1 and Fig 2b illustrate the distribution of the pathways the applications undertook in the three windows. Abridged review pathway is an external reliance mechanism employed by the authority wherein reports from other authorities are received and comparison of the scientific content conducted instead of full scientific review. In addition, there were applications that were pre-approved by the PEM before the 1st of February 2018, these have been assessed and finalised by the Unit previously although not yet registered. Lastly, the first two windows consisted of NCE submissions as these are high priority and require the submission of clinical trial data. Thus, biostudy submissions were for a total of 103 applications between the three windows.

5.2.1 Collection of deficiencies

The full history of all the products finalised between the 7-year period (2011-2017) was collected which comprises of all communication between the authority and applicants in order to reach finalisation. The documents include the recommendations sent to the applicant and the responses received, as well as the evaluation reports of responses in the form of amendment schedules. These paper documents were obtained from the committee meeting minute documents and the registry files where all documents relating to the product are placed. The investigation process involved obtaining the type and extent of the deficiencies raised in the first deficiency letter following the initial evaluation process, thereafter, extracting all the responses and feedback during the multiple rounds of communication. For applications assessed between 2020-2021, the full history was obtained in the electronic database for SAHPRA applications. The deficiencies in the initial query letters were collected and quantified. The selected nine categories for the deficiencies are as illustrated in Fig 1 and Fig 3.

The deficiencies obtained were reviewed and the frequency of each biostudy component was listed with the percentage frequency calculated as follows:

- Percentage frequency of deficiency identified per biostudy component = (frequency of specific deficiency / Total number of deficiencies biostudy component) x 100.

All charts, graphs, and analyses were carried out with Microsoft Office Excel® 2016 (Microsoft Corporation, USA).

5.3 Results

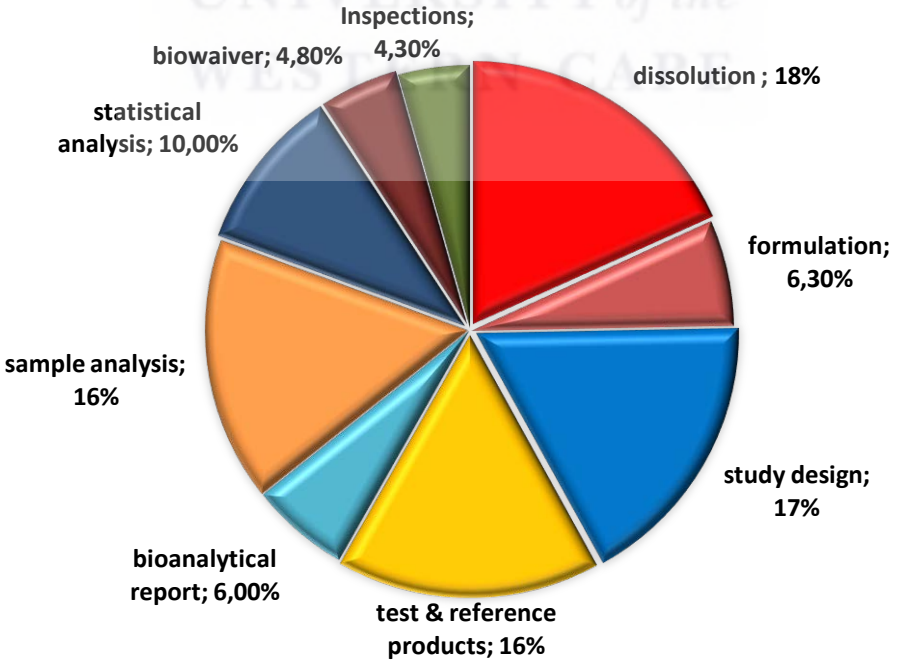

Fig. 3 Distribution of deficiencies from biostudies finalised between 2011-2017 by the PEM pre-registration Unit

From the stratified systematic sampling a sample size of 325 non-sterile applications was obtained and of those, nine were non-sterile products which do not require the submission of a biostudy such as oral liquids, topical products, etc. classified under "other" as indicated in the types of dosage forms below. The applications contained a variety of solid dosage forms, which are film-coated and uncoated immediate-release tablets, (48%), immediate-release capsules (23%), orodispersible tablets (8.0%), extended-release tablets (8.0%), extended-release capsules (3.5%), chewable tablets (1.2%), powders for suspensions (5.1%) and other (3.2%). There was an overall of 2458 deficiencies collected from the 316 initial letters from the biostudy sections.

Table 1: The illustration of applications received in re-submission windows 1, 2 and 5.

	Re-submission window 1 (RW1)	Re-submission window (RW2)	Re-submission window (RW5)
Total applications received	**84**	**143**	**73**
Abridged review pathway	8	22	21
Liquid dosage forms (biostudy not required)	5	29	17
Non-sterile solid dosage forms (biostudy required)	**31**	**48**	**24**
Pre-approvals (already assessed)	1	4	7
NCEs	39	36	-
Withdrawn/rejected	-	4	4

For the applications assessed between 2020-2021, there were 103 applications where a biostudy was submitted as outlined in Table 1. Of the 103, 50 were film coated- and uncoated immediate-release tablets (49%), 25 were immediate-release capsules (24%), 10 were powders for suspension (13%), eight were extended-release tablets and capsules (10%) and other (4.0%). This is a similar trend of the types of dosage forms received between 2011-2017 as indicated above. There were 492 deficiencies obtained as stipulated and discussed in the following section.

The deficiencies observed in the four components are expanded on Table 2-5.

Table 2: List of common deficiencies observed in *in vitro* dissolution testing and biowaivers identified by SAHPRA between 2011 - 2017.

Deficiencies			
***In vitro* dissolution testing**	Frequency (2011-2017)	% in the respective component (2011-2017)	Frequency (2020-2021)
Comparative dissolution studies must be conducted per the requirements in the guideline to include; the purpose of study, products batch information, full dissolution conditions, and method validation, as well as numbers of units per the study, how units were filtered, and any problem with pH related stability of the samples, should be indicated and discussed in terms of preventative handling measures, analysis and interpretation of data, analytical method or reference to part of the dossier, results (API dissolved): tabulated, graphically, similarity determination/f2 calculation if necessary.	64	15	2
The calculation of similarity factor values (f2) for profiles is not appropriate and should be corrected.	13	2.9	
The calculation on the similarity factor for the two profiles was not conducted and should be submitted.	10	2.3	
The submitted individual dissolution data are not accepted. There should be 12 units used for the comparative dissolution studies between the test and reference products.	21	4.8	5
Include the dissolution data for the innovator reference product (foreign and/or South African) as this was not submitted.	15	3.4	
Bring the final product release and stability dissolution specifications in Module 3.2.P.5.1 in line with the profiles of the biostudy test (and reference) products. A specific specification is proposed based on the results observed.	33	18	33
The dissolution profiles in the selected quality control medium were not included and should be submitted.	30	6.8	19
Describe the method for withdrawal and filtration of samples and how this ensures that dissolution of non-dissolved particles does not occur after sampling. Include in-line filtration for drawing the dissolution samples in the dissolution method in 3.2.P.5.2 to ensure that the dissolution of the sample is stopped immediately on withdrawal of the sample (USP "Test specimens are filtered immediately upon sampling unless filtration is demonstrated to be unnecessary"). If the method states that the samples should be drawn and filtered this does not necessarily imply or ensure that the dissolution of un-dissolved particles in the sample is stopped at the time of sampling.	46	11	19
Demonstrate the similarity of the dissolution profiles of the reference and corresponding test product or SA innovator in three of the physiological media and justify the use of other buffers apart from those in the guideline or the addition of a surfactant.	30	6.8	4
The sample withdrawal times and other aspects do not comply with the requirements stipulated in the dissolution guideline.	29	6.6	
Provide a statement on whether *in vivo* and *in vitro* correlation from the data were obtained.	09	2.0	
Indicate where the dissolution studies were conducted as well as the dates when the studies were conducted.	10	2.3	6
The submitted dissolution data is incomplete for the extended-release products as it is lacking dissolution data in multimedia and alcohol dose dumping data for extended-release products.	10	2.3	

Consider including an additional dissolution specification for the extended-release products with a longer release rate.	06	1.4	
Demonstrate the discriminatory nature of the dissolution method in 3.2.P.2 to ensure that it is sensitive to changes in manufacturing processes and /or in grades and/or amounts of critical excipients. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters.	59	13	24
Other	09	2.0	
	442		**112**
Biowaiver			
Provide evidence to show the proportional similarity of the different strengths. Fully address biowaiver requirements for the lower strength(s) by including confirmation that all strengths are manufactured using the same process, similar equipment, similar dissolution profiles, linear pharmacokinetics, etc.	38	32	15
The BCS classification of the API has not been identified and all requirements according to the guideline regarding the appropriateness of the BCS biowaiver have not been addressed, evidence that the API is fully absorbed upon oral administration is also required.	31	26	
According to pharmacopoeial monograph, the API is poorly soluble and poorly permeable therefore BCS II/IV. Therefore, the API will not be considered by SAHPRA for biowaiver.			10
Provide permeability studies to confirm the indicated BCS classification of the API.	41	34	5
A biowaiver for the additional strength cannot yet be granted until data for dissolution at pH 1.2 is also provided, or the omission justified.			10
For a BCS based biowaiver application, comparison should have been demonstrated for each strength of the test product with the corresponding strength of the foreign reference product. In addition, the following documentation for the reference products should have been submitted: a. Copies of product labelling (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate. b. Copies of the comparator products carton outer boxes. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling. c. Copies of CoAs for the comparator products			3
A volume of 1000ml was used for the dissolution comparative dissolution studies for biowaiver purposes. This volume may be acceptable for release testing however this is not acceptable for biowaiver purposes. You should submit new comparative dissolution data in 900ml of media (pH 1.2, 4.5 and 6.8) and at release conditions.			6
Other	09	7.6	
	119		**49**

Table 3: List of common deficiencies in the bioequivalence clinical study reports identified by SAHPRA for non-sterile products finalised by the pre-registration Unit between 2011 - 2017

Deficiencies			
CLINICAL STUDY REPORT			
Study design	Frequency (2011-2017)	% in the respective component	Frequency (2020-2021)

		(2011-2017)	
3.0. Include a comprehensive table of contents (ToC) for the Overview. General information guideline 3.1.2 and Biostudies guideline 3.9. (currently not relevant since SAHPRA allows only electronic submissions)	30	7.1	
5.1. Submit the ethical approval letter by the Ethics Committee or Institutional review board (IRB) for the approved protocol and the subject consent forms.	26	6.1	
9.1. The meal composition employed in fed studies should be consistent with the description in the labelling i.e. Profession Information (PI)	23	5.4	
9.1. The Summary of product characteristics (SmPC) of the reference product indicates that the product should be taken with food, therefore submit the appropriate biostudy i.e. fed study.	09	2.1	
9.1. Justify the inclusion / explain/clarify the relevance and appropriateness of the proposed pharmacokinetic information in the professional information with reference to the results of the bioequivalence study, by a comparison of the results (including mean values, inter- and intra-individual variability, of this study with published results (literature, product information of reference product (innovator), WHOPARs). Copies of these references should be provided as well). The submitted fasting study does not appear to support the pharmacokinetic values for plasma concentration in the proposed PI, and no statement regarding the effect of food on the bioavailability of the final product is included.	09	2.1	2
9.1. Evidence of food effect must be included for fed studies. Alternatively: The biostudy employed an open label, randomized, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study in healthy adult male human subjects under fed conditions, because the comparator product in the European Union is taken with food. However, the claim that it can be taken with and without food requires that the biostudy should be conducted in fasting conditions.	34	8.0	13
9.2. Include the complete dates of the treatment schedules, ensure that the washout period is not excessively larger than five times the largest expected half-life.	32	7.5	
9.3.1/2. The inclusion and exclusion criteria could not be located in the protocol.	14	3.3	
9.4.5 The proposed sampling times are found inadequate and not sufficient to cover the Cmax.	10	2.4	
9.4.5 Provide clarity on the dates of the study reports and analytical reports.	27	6.4	
9.4.5 The lowest Cmax is at a specified time based on the submitted concentration-time data. This means that there is only one post dose time point before the Cmax. Provide evidence to show that no Cmax happened between the 1st sampling time and the lowest Cmax.			2
9.7.2. Ensure that the number of additional subjects added to the sample size to compensate for potential dropouts or withdrawals are realistic and consistent with the study design.	12	2.8	
9.7.2. Provide the parameters and method that were used to determine the sample size.	25	5.9	
9.7.2. Provide justification for the proposed sample size as it is lower than the minimum requirement.	12	2.8	
10.2. Insufficient information provided on the protocol e.g. address deviations in the submitted and approved protocol.	35	8.2	
14.1. Submit individual subjects' demographic profiles i.e. age, race, ethnicity, gender, and body mass.	25	5.9	9

14.1. Submit the number of females and males participating in the study.	25	5.9	
16.1.1. Provide the protocol for the study which includes the protocol final version number.	19	4.5	
16.1.1. The protocol should indicate the software that will be used for the statistical calculations and factors to be included in the Analysis of Variance (ANOVA) should be well defined.	24	5.6	
16.1.2 Confirm that case report forms will be available upon request or for inspection. (this is now a requirement by SAHPRA, case report forms should be included in the submissions) 2011-2017	21	4.9	
16.1.2 Provide copies of Case report forms (CRFs) completed at screening for the volunteers recruited for inclusion in the fasting study. A blank copy of the CRF was found in 16.1.2 for all studies, this is noted but not adequate to address this requirement. 2020-2021			2
16.1.2 Tabulate the respective laboratory results against the normal ranges for any results that were outside of study site normal values. Further, the case report form for respective study participants must also be provided.			4
Other	13	3.1	
	425		**32**
Sample analysis			
9.5.4. Provide the temperature of the water bath in which the samples were defrosted before testing.	46	11	
9.5.4. Demonstrate the long-term stability of the plasma samples in the study under the correct study conditions for the period between centrifuging and analysis.	59	15	20
9.5.4. Provide a description of the sample transportation, transport temperature recording from the clinical site to the analytical site.	39	9.7	10
9.5.4. Provide or justify why no definitive time, temperature, and speed is given for the centrifuging of samples after receiving the blood samples.	25	6.2	15
9.5.4 Calibration data, i.e. raw data and back-calculated concentrations for standards, as well as calibration curve parameters, for the entire study should be provided.	11	2.7	7
12.2. Provide a discussion on the selection of samples for repeat analyses as these could not be located.	15	3.7	5
12.2 Provide the SOP specifying the criteria for reanalysis and reporting of reanalysed samples.			2
12.2. Plasma samples from subjects who dropped out or were withdrawn due to an adverse event should be analysed for a complete safety analysis of the data.	31	7.7	
14.2. Submit 20% of chromatograms in accordance with the SAHPRA biostudies guideline 3.9.2.e. The chromatograms must have a table of contents indicating the subject and page numbers. The legend or sample coding system must be included and clearly identified and sampling time given.	76	19	10
14.2. Submit the mean and all individual plasma concentration versus time profiles presented on a linear/linear as well as log/linear scale.	40	10	9
14.2 Provide evidence that the analytical method used was able to detect and resolve the primary analyte from possible metabolites.			3
14.2 A discussion of sensitivity in terms of signal-to-noise ratio determined at Lower limit of quantification (LLOQ) concentrations including the signal-to-noise ratio values should be provided for the methods used to analyse the APIs in the plasma.			4

14.2. Provide legible concentration vs time plots and Certificates of Analysis (CoAs).	29	7.2	8
14.2. Submit complete documentation with respect to subject sample analyses.	26	6.5	6
Note that samples from all dosed subjects should be analysed for safety evaluation.			20
Other	06	1.5	
	403		**119**
Statistical analysis			
11.4.1. Comment on the high standard deviation (SD) of the area under the curve (AUC).	25	9.9	
11.4.1. The submitted pharmacokinetic/statistical calculations are incorrect and require revision and re-calculation.	27	11	
11.4.1. The criteria for selection of samples for reanalysis are not objective, unscientifically sound or potentially biased toward a favourable bioequivalence outcome. Provide adequate justification for the selection reanalysed samples.	19	7.5	
11.4.1. The biostudy submission consists of missing data files required for statistical analysis. Submit the missing data files.	12	4.7	
11.4.1. Indicate how sampling deviations were handled in the statistical analysis.	11	4.3	
11.4.1. Correct/justify the statement in the PI under pharmacokinetic properties where it is stated that peak plasma is reached after a specified time while data presented in the biostudy shows peak plasma is reached well within a different time.	19	7.5	
11.4.1. Address and justify the high point estimates that have been obtained on the results.	21	8.3	
11.4.1. Provide a justification of the extended bioequivalence criteria of 80-125%.	22	8.7	
14.2. Provide adequate justification for subjects that are excluded from the statistical analysis.	48	19	
14.2 The matrix effect should be evaluated by analysing at least 3 replicates of low- and high-quality controls (QCs), each prepared using a matrix from at least 6 different sources/lots. The accuracy should be within ±15% of the nominal concentration and the precision (percent coefficient of variation (%CV)) should not be greater than 15% in all individual matrix sources/lots as per International Council for Harmonisation (ICH) acceptance criteria.			11
14.2 Provide the complete statistical software printouts of the analysis made on log transformed data for AUC0-t and Cmax to help justify your findings reported in the ANOVA table.			4
14.2 The statistical output of Statistical Analysis Software (SAS) system in appendix 16.1.9.2 does not include the calculation of the 90% Confidence interval (CI) for the ratio test/reference of the primary pharmacokinetic parameters when the conventional ANOVA with subject, sequence, period and subject (sequence) factors are analysed. Provide new statistical analysis including the raw SAS output taking into account the recommendations above.			8
14.2. Submit the calculated point ratios of the AUC0-t, AUC0-inf, and Cmax.	23	9.1	
16.1.11. Provide a discussion of the study results with available literature references.	12	4.7	10
Other	14	5.5	
	253		**33**
Inspections			

16.1.8 Provide a GMP/GLP compliance declaration by the laboratory, including reference to the availability of validation records of test methods and procedures for and records of calibration of instruments and maintenance of equipment.	24	23	
16.1.8 Provide auditing and monitoring activities that took place in relation to the studies undertaken.	25	24	15
16.1.8 Confirm that the Sponsor and investigational sites, facilities and laboratories, and all data (including source data) and documentation and reports concerning the data including participant files are available for verification by the Inspectorate and indicate the facility where all the relevant study documentation is available for inspection by the Good Clinical Practice (GCP) inspectors.	47	44	10
16.1.8 Submit a declaration that all the biostudy documents are available for inspection by the Inspectorate and indicate the facility at which they may be inspected.	17	16	7
Provide the executed Batch Manufacturing Records (BMR) for the biobatch used in the biostudy.			9
Ensure that the Bioequivalence Trial Information Form (BTIF) is adequately and accurately completed to reflect the same data as on the submitted dossier			15
Ensure that all documents are adequately bookmarked with appropriate titles/document names.			10
Other	10	9.4	
	106		**66**

Table 4: Common deficiencies witnessed in aspects relating to the reference and test product including formulation comparisons.

Deficiencies			
Formulation	Frequency (2011-2017)	% in the respective component (2011-2017)	Frequency (2020-2021)
Confirm that the formulation being applied for is the same as that of the biostudy test product. The data should include unit formula, manufacturing procedure, equipment, site of manufacture, source of raw material, overall product specifications, and other relevant information.	41	26	6
Provide a comparison of the qualitative formulation of the test and reference products.	21	13	2
Provide justification for the major differences observed in the formulation for the test and reference products.	22	14	
For studies five years and older, submit data to confirm that the product being applied for is identical to the test product used in the bioequivalence study. The data should include but not be limited to the following: • Unit formulation, manufacturing procedure, and equipment • Site of manufacture of final product and manufacturer of the API • Overall product specifications and • Other relevant information	67	42	6
Other	07	4.4	
	158		**14**
Details of the reference and test products			

Provide a justification for the use of the biostudy reference product fully complying with the requirements stipulated in the SAHPRA guideline.	48	12	5
The potency and/or content uniformity data for the test product was not submitted.	33	8.5	
Provide further literature information to support the proposed reference product.	13	3.4	
Provide a justification for the proposed batch size, which is smaller than the recommended batch size in accordance to the biostudy guideline.	33	8.5	6
Provide detailed CoAs for the biostudy reference and the corresponding innovator product in South Africa which include the dissolution, assay and impurity results.	13	3.4	20
Evidence to show that the reference product used in the study is equivalent to the innovator product registered by SAHPRA must be submitted.	54	14	4
Submit the corrected complete overview 3.2.R.1 according to the guideline.	25	6.4	
The biostudy test batch and that used in the validation and stability batches are from two different manufacturing sites. The equivalence or essential similarity of the two products manufactured by the stated final product manufacturers has not been adequately addressed and is not accepted. Demonstrate essential similarity between the product manufactured by manufacturer 1 and the product manufactured by the final product manufacturer being applied for, i.e. manufacturer 2.	15	3.9	
Provide certified copies of invoice/ purchase documents as proof of receipt of the reference product and South African (SA) innovator product used in the bioequivalence study as well as copies of immediate container label and carton which visibly includes the name of the product, name and address of the applicant, batch number, and expiry date.	19	4.9	2
The shipment and storage of the reference product should be submitted and properly documented.	34	8.8	6
Ensure and confirm that the final product release and stability specifications for total impurities are in line with the impurity profile of the reference product.	19	4.9	
Batch size, manufacturing date (test product) and expiry date of the biostudy reference and test products must be included.	39	10	
Submit CoAs of the foreign reference and the SA innovator products.	33	8.5	
Other	10	2.6	14
	388		**57**

Table 5: Deficiencies observed by SAHPRA on the bioanalytical report submitted for the bioequivalence studies.

Deficiencies			
Bioanalytical report issues	Frequency (2011-2017)	% in the respective component (2011-2017)	Frequency (2020-2021)
The bioassay validation report must be submitted.	12	8.2	
Submit the analytical method report and bioanalytical method standard operating procedure (SOP) which could not be located.	36	25	10

Submit the detection and quantification limits of the parent and metabolites of the analytical methods.	34	23	
The biological matrix used was not clearly indicated in the report.	12	8.2	
The reasons for the high rate of failures of control samples could not be located. This should be justified.	23	16	
Provide a discussion of the preparation of the calibration curve standards and the quality control samples.	20	14	
Other	10	6.8	
	147		**10**

5.4 Discussion

Fig 3 clearly depicts the distribution of the deficiencies observed in the biostudies. It shows that the highest deficiencies, 18%, were from dissolution testing. This component is followed by study design (17%), queries on the test and reference products (16%), sample analysis (16%), and statistical analysis (10%). The common deficiencies observed in the categories are further discussed below.

5.4.1 *In vitro* dissolution testing and biowaivers

Dissolution testing is an essential part of product development and serves as a quality control measure once the composition and the manufacturing process are defined for the scale-up of production batches to ensure batch-to-batch consistency. [5, 6, 19-22] It is also used in support of a biowaiver of bioequivalence testing to demonstrate the similarity between different product formulations of an active substance and the reference medicinal product and to indicate potential problems with bioavailability. Thus, issues regarding comparative dissolution details between the test and reference products used in the biostudy are assessed in this component as well as the appropriateness of the proposed dissolution specifications.

For biowaivers, the Biopharmaceutics Classification System (BCS) waiver is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the API and is intended to reduce the need for *in vivo* bioequivalence studies. [21] This is confirmed by comparison of the proportional additional strength(s) and similarity of the dissolution profiles in the three physiological media with the reference product. [4, 5] The deficiencies observed in the biowaiver requests are therefore investigated in this component.

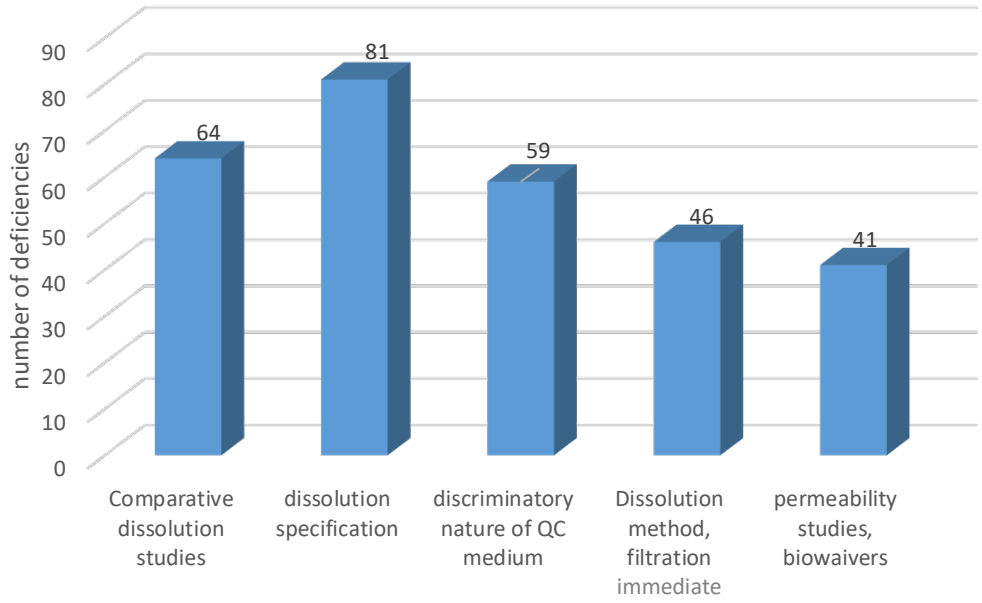

Fig. 4 Distribution of the five highest deficiencies observed in the *in vitro* dissolution testing and biowaivers section.

The dissolution of a product is important for its bioavailability and therapeutic effectiveness and is therefore considered a critical parameter in biostudies. [23] The deficiencies observed in these components are listed in Table 2, and Fig 4 further highlights the five most frequent deficiencies observed in the sections. Dissolution testing requires the development of a robust and rugged dissolution method that is adequately discriminating to distinguish any changes that could affect the product. [22, 23] As depicted on Table 2 there was 13% of deficiencies relating to the discriminatory nature of the selected dissolution method not having been demonstrated and was therefore requested. The choice of an adequate medium that can discriminate between critical manufacturing variables is crucial in such cases. [24, 25] The changes may include quantitative formulation, material specifications, and/or using slightly modified process parameters. [25]

When a dissolution test is not defined in the monograph of the product, or if the monograph is not available, a comparison of product dissolution profiles is recommended in three different dissolution media at physiological pH ranges, that is, 0.1 N Hydrochloric acid - pH 1.2, Acetate buffer - pH 4.5 and phosphate buffer - pH 6.8. [21, 22] Table 2 clearly shows that there were 6.8% of these deficiencies from the dissolution testing category. If the API is poorly soluble, appropriate concentrations of a surfactant is recommended, therefore comparative dissolution results should also be submitted in the selected medium with the surfactant [21]. A clearly described justification is required for these products since this is not encouraged. The comparative dissolution study results should be submitted in accordance with the SAHPRA dissolution guideline which is in the three media as described above, specified dissolution vessel, media volume and agitation speed between the test product and reference product [24, 26], there were 15% of the deficiencies

requesting this. The 15% also comprised of deficiencies such as lack of submission of the method validation, inadequate numbers of units used for performing the study, how the units were filtered, similarity determination (f2) calculation where necessary. The complete list of deficiencies for this component are included in Table 2. In the case where the reference product used in the biostudies is not procured in South Africa (SA), SAHPRA requires a comparative dissolution study report between the foreign reference product and the SA innovator product to confirm equivalence. [21] The results of the biostudy test product are therefore used to determine the dissolution specification for the product in Module 3.2.P.5.1. The deficiency where an incorrect or unacceptable dissolution specification is proposed (18%) for the final product is very common and leads to the back-and-forth communication between the applicants and the authority thus delaying registration. The dissolution specifications should be based on the results of the biostudy test product since the manufacturer needs to ensure that the manufacture of the proceeding batch continues to meet the standard of the biostudy test product. If the product is unable to meet these specifications in the stability results, it illustrates the deterioration of the quality of the product which should therefore be addressed by investigating the product development. The justification of changing the dissolution specification based on the stability results is therefore not acceptable.

Dissolution testing can also be used to support the bioavailability of a new pharmaceutical product in which case a biowaiver is requested. The frequent deficiency on the biowaivers was on the request of permeability studies to confirm BCS class I or III. Class I and III APIs are considered highly soluble while Class II and IV have low solubility. With regards to permeability, Class I and II have high permeability while III and IV have low permeability. Thus, when a BCS-based biowaiver is requested, it is imperative to support the classification of the API with solubility and permeability studies.

5.4.2 Clinical study reports

The conduction of bioavailability studies in humans requires that the FPP be administered to a group of individuals and that the time-course of the concentration of the API in the blood be evaluated. [28] The clinical study reports provide a summary of this scientific data. The clinical study report section is divided into four sub-categories based on the common deficiencies observed. These are further described in detail below and the quantification is depicted in Table 3 and Fig 5.

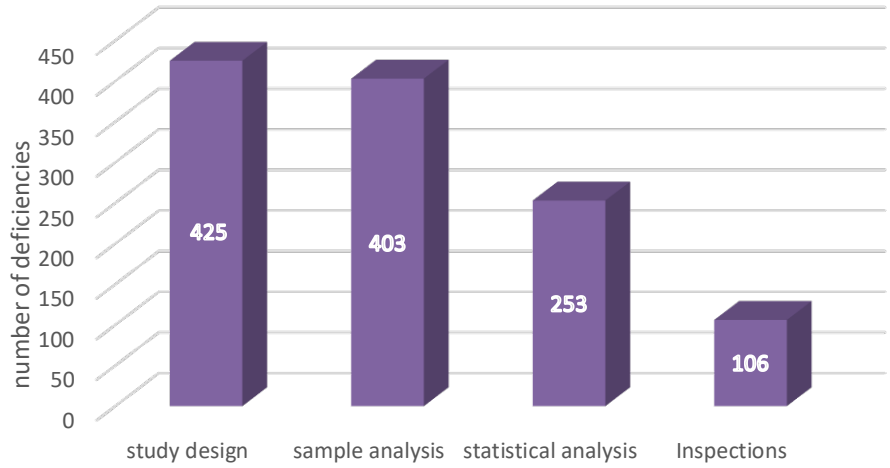

Fig. 5 Categorisation of the deficiencies in the bioequivalence clinical study reports

5.4.2.1 *Study design*

Study design involves the adequacy and appropriateness of the bioequivalence study design selected covering aspects such as the following:

- Selection and appropriateness of single-dose-, multiple dose- or steady state studies.
- Selection and appropriateness of a two-period, two-sequence, crossover design or a parallel design.
- Appropriateness and acceptability of the dose selected to conduct the biostudy.
- Selection and appropriateness of the study selected to investigate food effects, if relevant, thus whether under fed or fasting conditions depending on the molecule and medicine under investigation.
- Acceptability of the number of subjects proposed to conduct the study.

The study design selected for 91% of the 316 applications was simple single-dose, randomised, two-treatment, two-period, crossover biostudies. The most common experimental plan for comparing the bioavailability of two products is a simple crossover study as outlined above. [5-8] In this design, each individual in a group of subjects receives both FPPs at different times so that there is a direct comparison of the absorption of each product in the same individual. Special care must be taken to allow sufficient time to elapse (washout period) between the administration of the first and second final product so that there is no carryover effects. [5] In order to minimize the influence of such effects on the outcome of the study, good experimental design requires that each final product be administered initially to half of the subjects, hence this being the most common study design selected. There are however special cases where this study design cannot be employed depending on the behaviour of the API under investigation, in such cases a different study design such as parallel design, steady state studies, multiple dose studies are selected. [5] The study

design deficiencies as depicted in Table 3 included deviations witnessed in the protocol which differ from the approved protocol (8.2%). The protocol should be approved by a reputable ethics Committee or Institutional Review Boards (IRB) before the study commences, should there be any amendments or deviations to the protocol these should also await approval by the Committee. The deficiencies noted were not stated in the approved version of the protocol, therefore the latest protocol was required. Other deficiencies also involved applicants not including the Ethics approval letter (6.1%). Ethical approval is an integral part of the research process and aims to protect both researchers and participants who should have enough details to make informed and autonomous decisions. [29] The details on the study design also did not include critical aspects such as demographic details of the subjects i.e. age, race, ethnicity, body mass and description of the gender of subjects used in the study (12%), the inclusion and exclusion criteria employed (3.3%), and instances where an incorrect study has been included between the fed- and fasting study (7.5%). If the reference product's labelling instruction includes that the product should be taken with food or an extended-release product is applied for, a fed study should be submitted. [30]

5.4.2.2 *Sample analysis*

The third component with the highest deficiencies is sample analysis comprising 16% as seen in Fig 3 with the deficiencies listed in Table 3. This covers issues observed relating to the sample analysis procedure such as the appropriateness of the sample collection and sampling times selected, stability of the plasma sample, assurance that the Clinical Research Organisation (CRO) follows Good Clinical Practice in the sample collection and storage, and appropriateness of the bioanalytical analysis of the samples. [5]

The most frequent deficiencies in the section (41.9%) are on sample handling before the analysis. This is a critical aspect in biostudies since during storage the final product may undergo chemical degradation, adsorption on the walls of the container, etc., thus, storage of plasma samples is important. [5, 6] Complete information on the long-term stability data of the samples was either not included or insufficient (15%), or details on the transportation and transport temperature recordings of the sample from the clinical site to the analytical site (9.7%), or the details of centrifugation of the blood samples (6.2%) or the details of the treatment of the frozen samples before testing (11%) were not provided. These are critical parameters that need to be safeguarded and adequately documented to ensure that the quality of the samples is maintained throughout the biostudy. Other deficiencies witnessed include the submission of chromatograms which should be 20% of consecutive subjects involved in the study. There was also a deficiency observed on the request to analyse samples for subjects who initiated the study and dropped out or were withdrawn due to adverse events (7.7%). This remains a requirement in order to obtain a complete safety analysis.

5.4.2.3 *Statistical analysis*

This involves assessment of the issues associated with the statistical calculations of the pharmacokinetic parameters used to deduce bioequivalence. The statistical method for testing relative bioavailability is based on the 90% confidence interval for the ratio of the population means (Test/Reference) for the parameters under consideration. The pharmacokinetic parameters should be analysed using statistical software called Analysis of variance (ANOVA) to attain an acceptance criterion for the main bioequivalence. [4, 5] The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80 – 1.25 (80 – 125%) for the investigated parameters in order to confirm bioequivalence.

Deficiencies in statistical analysis accounted for 10% of the biostudies investigated. The most common deficiency was from the lack of justification for the exclusion of subjects from the statistical calculation which constituted 19%. It is important to include the results of all subjects that were dosed from the study to avoid bias. The calculation of the pharmacokinetic (PK) parameters should be accomplished from observed data instead of fitted data. Some deficiencies included incorrect calculations on the PK parameters noted by the evaluator which required correction. These constituted 11% of the deficiencies in the category.

For the biostudy to be established, 90% confidence interval for the ratio of the geometric least-square means of peak plasma concentration, AUC of test and reference products should be within 80 - 125%. [5, 24, 31] Closer limits are considered for products that have a narrow therapeutic index, serious dose-related toxicity, steep dose effect curve, and nonlinear pharmacokinetics within the therapeutic dose range. European guidelines also provide a tightened acceptance interval of 90.00-111.11% for narrow therapeutic index drugs (NTIDs) as well as highly variable products which SAHPRA has adopted. [24, 31] A wider acceptance range is admissible if it is based on a sound clinical justification. [6] This justification was not included in some biostudies submitted with the extended range (10%) and this was requested.

5.4.2.4 *Inspections*

Deficiencies on inspection reports of the CRO conducting the biostudy as well as any outstanding audit and monitoring reports for the biostudy are required in order to confirm that the biostudy was conducted in line with Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) requirements. Confirmation that the sponsor, investigational sites, facilities, laboratories, all data (including source data), documentation and reports concerning the biostudy including participant files must be available for verification by the Inspectorate Unit. This was queried and comprised of 44% of the deficiencies in this section as illustrated in Table 3. Over and above the biostudy information being submitted to the authorities, it is critical that the raw and complete data sets for the study be archived for the Inspectorate Unit to request upon inspections.

5.4.3 Aspects relating to the reference and test products

One of the critical aspects in selecting a reference product is ensuring that the assay content and dissolution data are similar to the test product. For example, the assayed content of the batch used as a test product should not differ by more than 5% from that of the batch used as the reference product. [7] Acceptability of the source of the reference product is also assessed, this should be sourced from an authority SAHPRA aligns itself with, thus all supporting documentation and testing of the test and reference product should be included. [5] Deficiencies relating to outstanding documentation or details regarding the test, foreign reference, and SA innovator product were investigated in this component.

The common deficiencies in this category as highlighted in Table 4 include the request to justify the proposed reference product in accordance with biostudy guidelines and available decision trees on the selection of the appropriate reference product. These comprised 12% of the deficiencies identified in this category. In the case where the reference product is not procured in SA, the following supporting information on the foreign reference product is required:

- The name and address of the manufacturing site where the reference product is manufactured.
- The qualitative formulation of the reference product. (3.9%)
- Certificate of Analysis of the reference product. (8.5%)
- Shipment and storage details of the reference product to the sponsor. (8.8%)
- Copies of the immediate container label as well as the carton or outer container label of the reference product. (4.9%)
- The method of manufacture of the reference product is claimed by the applicant to be the same.
- Procurement information of the reference product:
    - Copy of licensing agreement/s if relevant
    - Distribution arrangements / agreement/s if relevant
    - Copy of purchase invoice (to reflect date and place of purchase) (4.9%) [5]

The above deficiencies were the largest observed in this category and were quantified as 31%.

The bioequivalence study aims to confirm the similarity of two formulations of the test and reference product. Formulation comparison is imperative, as there may be formulation effects, which alter the bioavailability of the test product, therefore qualitative comparison with the reference would need to be assessed. There was 42% of the deficiencies depicted in Table 4 requesting the confirmation of similarity between the formulation of the test and reference products as well as any changes which have been made to the biobatch if the submission received was older than five years. The data requirements are confirmation of the following to ensure no significant changes occurred: unit formulation, manufacturing procedure and equipment, site of manufacture of final product and manufacturer of the API and overall product specifications. This is to ensure

that there were no major amendments made to the product which may negatively impact on the quality of the product compared to the biobatch.

5.4.4 Comparison with RW1, RW2 and RW5 applications (2020-2021)

Table 2-5 also illustrates the similarities on the common deficiencies witnessed in applications finalised between 2011-2017 and those assessed between 2020-2021. The additional row indicating the frequency of deficiency in 202-2021 shows all the deficiencies that were identified. This confirms that the standards of assessment have been maintained as the identified deficiencies comprised of more than 80% of the deficiencies already identified in the 2011-2017 sample. The distribution of deficiencies is also similar to that observed in Fig 3 with dissolution as the highest category (23%) and sample analysis (24.2%) followed by inspections (13.4%). The deficiencies that were observed only in the 2020-2021 applications are largely on the request of Case reports forms and the Statistical Analysis Software (SAS) report for raw data as well as the executed BMR (batch manufacturing records) of the biobatch. These were previously not a requirement. The Case report forms were assessed during inspections as well as the executed BMRs and therefore not incorporated in the quality and bioequivalence assessments, however these are now requirements by SAHPRA and relevant documents should be included in the dossiers.

5.4.5 Comparison of the deficiencies with those of other well-known regulatory authorities

Only a few reports have been published on biostudy common deficiencies from other regulatory authorities. The USFDA reported on these in 2012 using Abbreviated New Drug Application (ANDA) applications received between 2001 and 2008 to identify the most commonly occurring biostudy deficiencies. [14] The two most common deficiencies related to dissolution are method and specifications which constitute 23.3% of the applications and bioanalytical method validation and/or report found in 16.5% of the applications. [14]

The USFDA noted that the establishment of an online dissolution method database has helped greatly in improving the quality of the ANDA submissions. Reducing the deficiencies to 15.5% in 2006-2008, thus accelerating the approval of generic products. [14] The observed deficiency on *in vitro* dissolution testing is comparable to the deficiency recorded as the highest in SAHPRA applications at 18%.

On bioanalytical method validation and/or report, the USFDA found the most frequent deficiencies include a lack of SOPs, no data showing long-term stability of API in frozen samples of biological fluid, and incomplete sets of bioanalytical raw data. [14] These are similar to those observed in Tables 3 and 5 for sample analysis and bioanalytical report issues witnessed by SAHPRA. Issues relating to the lack of inclusion of relevant SOPs in the bioanalytical report and the raw data of the bioanalytical report were observed as 23% by SAHPRA. The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP) and Good Clinical Practice (GCP). The Bioanalytical methods used must have adequate sensitivity and accuracy, as well as selectivity that will make

it possible to quantify the API in the presence of its metabolites or of endogenous compounds that may interfere with the determination of the compound in biological fluids. [28] The samples should be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted. [6] This section, therefore, covers this aspect to ensure the appropriateness of the bioanalysis and reliability of the validated methods.

The other components reported by the USFDA were: potency and formulation, unjustified exclusion of subjects, analytical issues, and long-term stability. [14] This confirms the similarity in the quality of evaluation of the submitted biostudies between SAHPRA and the USFDA.

WHO PQTm also conducted a study for applications submitted between April 2007 and December 2010. [15] The deficiencies observed were categorised as follows: clinical study information, subject sample analysis, audit and monitoring information, statistical calculation, analytical method validation issues and an unacceptable reference product. [15] The deficiencies were quantified according to the therapeutic category of the submission, for example, 15% of the dossiers on reproductive health (treatment category) included incorrect pharmacokinetic/statistical calculations that required revision and re-calculation. The deficiencies observed from the components mentioned were very similar to those reported in Table 2-5 confirming the similarity of the quality of evaluations. The similarity is also witnessed in the work published by WHO PQTm in 2020 which stipulates an update on the qualitative common deficiencies in the biostudy reports submitted. [32]

5.5 Conclusion

The study included the collection of a list of common deficiencies on biostudies from applications finalised over a seven-year period and highlighted the most common deficiencies requested by SAHPRA. In addition, a recent study was conducted which confirms that the standards of assessments have been maintained as the deficiencies reported between 2011-2017 are similar to those observed in the 2020-2021 assessments. This, therefore, provides transparency to pharmaceutical companies on deficiencies to address before biostudy submissions are made to SAHPRA. The findings also show that the evaluation standards employed by SAHPRA are similar to other international regulatory agencies such as the USFDA and WHO PQTm. These findings will guide pharmaceutical companies, manufacturers and CROs in submitting quality biostudies in the future which will thereby allow accelerated access to medicine for patients. This in turn will reduce the turnaround product registration timelines for SAHPRA. Moreover, the deficiencies identified will assist assessors from the different countries to improve on their bioequivalence assessments.

5.6 References

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CHAPTER 6

The implementation of a risk-based assessment approach by the South African Health Products Authority (SAHPRA)

Abstract

Background An extensive backlog of pending regulatory decisions is one of the major historical challenges that the South African Health Products Regulatory Authority (SAHPRA) inherited from the Medicine Control Council (MCC). Revising and implementing new regulatory pathways is one of the strategic mechanisms that SAHPRA employs to circumvent this problem.

Objectives To alleviate the backlog, the use of a new review pathway termed the risk-based review on the scientific quality and bioequivalence assessments was explored. The objective of the study is to articulate the risk-based assessment (RBA) pathway, to determine robust criteria for the classification of the levels of risk for medicines and to define the improved process to be followed in the assessment and approval of medicines

Methods In 2015, an extensive exercise was conducted by SAHPRA to identify the unknown status of in-process applications. The RBA pilot project commenced in 2016 and further piloted in 2021 using the knowledge gained from the 2016 study for optimisation of efficiency.

Results By 2015 the backlog was quantified as 7902 applications in the pre-registration phase. The 2015 project entailed two phases. The initial phase was conducted to identify the status of 3505 in-process applications, which resulted in the registration of 198 applications. The second phase commenced in 2016 on 4397 applications not yet reviewed whereby RBA approach was explored. With the developed criteria for risk classification and refined end-to-end registration process, the pilot resulted in a finalisation time with a median value of 90 calendar days and a median approval time of 109 calendar days. The throughput of the RBA pilot study conducted in 2021 was 68 calendar days finalisation time for the 63 applications used. These finalisation times are lower in comparison to the 501 calendar days for the current process employed by SAHPRA for the backlog clearance programme initiated in 2019. Both the 2016 and 2021 studies had similar approval times calculated from the date of allocation of scientific assessments. The reported evaluation timelines for both studies were within 6-7 hours for a low-risk quality assessment, 9-10 hours for a high-risk quality assessment, 7-8 hours for a bioequivalence assessment and 2-3 hours for a biowaiver and initial response assessment.

Conclusions The refined processes used in the risk-based pilot studies to alleviate the SAHPRA backlog are described in detail. The process managed a reduction of the finalisation time to 68 calendar days in

comparison to 501 calendar days for the current process that was employed by SAHPRA for the backlog clearance programme initiated in 2019. The RBA approach, therefore, reduces the finalisation and approval times for quality and bioequivalence assessments for regulatory authorities without compromising on the quality, safety and efficacy of the medicinal products. In addition, the approach provides a prototype solution to counteract the influx of medicinal product applications received by the regulatory authorities.

Key Points:

The South African Health Products Regulatory authority (SAHPRA) had accumulated a backlog of 7902 medicinal product applications in the system in 2016 and by 2018, this had escalated to 8 220. In addition, a median approval time of 1622 was reported between 2015-2018. The growing application backlog in SAHPRA demonstrates the need for drastic interventions; hence the development of the risk-based assessment approach aimed at alleviating the current and continuously forming backlog by reducing overall approval timelines.

The risk-based assessment approach is a robust end-to-end registration process which would be a new alternative regulatory review pathway that has been developed to alleviate the backlog and reduce overall approval times. This process includes a risk classification applied before assessments, improved overall registration process, improved evaluation tools and amended peer review process. The pilot studies conducted using this new regulatory review pathway confirmed the reduced approval timelines.

6.1 Background

In the effort to protect public health, access to free or affordable essential medicines is one of the main obligations by Governments to fulfill the right to health [1]. The World Health Organisation (WHO) has reported that one-third of the world's population does not have timely access to such medicines and has encouraged countries to amend their national legislation or constitutions to provide for this right [2]. Regulatory authorities are established by Governments with a mandate to safeguard the patients by ensuring that safe, efficacious and quality medicine is accessible at an accelerated rate [2]. The median approval times by several regulatory authorities are outlined in Table 1 for the period of 2015-2019 [3-6]. The table illustrates the median approval times reported with the lowest as 247 calendar days for 48 applications by the United States Food and Drug Administration (USFDA) [3], and the highest with a median approval time of 1622 calendar days for 121 New Chemical Entity (NCE) applications by the South African Health Products Regulatory Authority (SAHPRA) [6]. In 2020 a study was conducted by SAHPRA and a median approval time of 790 calendar days was reported for 244 generic applications [7]. Table 1, therefore, demonstrates that SAHPRA has significantly longer approval times compared to other Authorities. The large influx of medicines from pharmaceutical companies due to the emerging pharmaceutical market as a result of the increasing disease burden and the growth of the pharmaceutical generic sector amongst others has made access to medicines a challenge to regulatory authorities in low to middle-income countries [4, 8].

Table 1 Median approval times: The reported median approval times from various regulatory authorities between 2013-2019.

Authority	**Country**	**Median approval times (calendar days)**	**Number of applications**
United States Food and Drug Administration, 2017-2019	United States of America (USA)	247	48
Health Canada, 2015-2019	Canada	347	30
Australian Therapeutic Goods Administration (TGA), 2015-2019	Australia	351	25
European Medicines Agency (EMA), 2015-2019	European countries	433	27
Swiss Medic, 2015-2019	Switzerland	527	28
Agência Nacional de Vigilância Sanitária (ANVISA), 2013-2016	Brazil	795	138
SAHPRA, 2015-2018	South Africa	1622	121

Regulatory authorities in developing countries such as SAHPRA face a number of resource constraints with the main one being insufficiently skilled individuals for dossier assessments and manufacturing site

inspections. The delays were also attributed to deficient operational processes and increased volume of applications for registration. The long regulatory decision timeframes have serious public consequences, as these delay access to life-saving medicines. In addition, the Medicines and Related Substances Act, 1965 (Act 101 of 1965), Section 22F [9], did not prevent or state how many generics the regulatory authority should register per active pharmaceutical ingredient (API). This Act encouraged "dossier farming" within the industry which created a significant backlog within the Regulator [10, 11]. SAHPRA received an average of 1200 applications annually between 2006-2015 and the authority could therefore not evaluate all the applications received within the period due to resource constraints and other factors as mentioned above. This resulted in the formation of a backlog of applications, delaying access to medicines for patients.

6.1.1 SAHPRA's organisational structure

SAHPRA, with internationally recognised standing, is aimed at facilitating the availability, evaluation and approval of the quality, safety and efficacy of medicinal products and related substances intended for humans and animals. In the years in which SAHPRA (formerly Medicine Control Council, MCC) has been in effect, over 20 000 medicinal products have been registered [12]. SAHPRA assumed the roles of both the MCC as well as the Directorate of Radiation Control (DRC) which were housed at the South African National Department of Health (NDoH) [13]. Subsequently, SAHPRA was constituted as an independent entity that reports to the National Minister of Health through its Board [13]. The organisation is headed by the Chief Executive Officer (CEO) with support from the Chief Financial Officer (CFO), Chief Operating Officer (COO), Chief Regulatory Officer (CRO) and the Human Resource Executive who all form part of the Executive Committee of the organisation (See supplementary material page 274). Within the office of the CRO lies the programmes; Pharmaceutical Evaluation Management (PEM), Clinical Evaluation Management, Inspectorate and Regulatory Compliance, and Medical device and Radiation control as illustrated in the supplementary material (page 275).

The programmes are in turn subdivided into Units responsible for coordination and execution of various activities. Within the PEM programme, lies the Pharmaceutical and Analytical (P&A) pre-registration Unit. The work of the Unit involves the evaluation of the quality and efficacy (bioequivalence) aspects of products submitted as a dossier in the Common Technical Document (CTD) format by pharmaceutical companies. The clinical aspects i.e., to confirm that the labelling of the generic products is in accordance with the registered innovator products and efficacy of the NCEs is evaluated by the clinical evaluations pre-registration Unit. Inspection of manufacturing sites is conducted by the Inspectorate Unit. Appropriate naming and scheduling status of the products is conducted by the Names and Scheduling Unit (Supplementary material 275) [14]. The PEM, P&A pre-registration Unit has proven to be the rate-limiting part of the registration process since the bulk of the evaluations which include quality and bioequivalence assessments are conducted in the Unit. The growing application backlog in SAHPRA demonstrates the need

for mechanistic interventions such as the RBA approach to alleviate the backlog by reducing the scientific evaluation timelines.

6.1.2 Risk-based assessments

Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm [15, 16]. The evaluation of risk requires the identification of a hazard and the likelihood of its occurrence [17, 18]. In pharmaceuticals, managing risk is of prime importance to ensure that the patient gets medicines/products of acceptable safety, efficacy and quality, according to WHO standards, as set out in WHO guidelines [15-16, 18-19]. Risk assessment is applied on the diseases to be treated as well as in the technology involved in the development and manufacture of the pharmaceuticals. The technology level affects the feasibility of the manufacturing process, including packaging and quality control testing, the overall quality assurance system of the manufacturer, as well as the capacity of the local National Regulatory Authority (NRA) to effectively assess the resultant dossier [20]. Thus, one of the main factors that affect the quality of the product is the quality of the manufacturing process which produces both the API and the Final Pharmaceutical Product (FPP). Hence, sound and reliable processes produce quality products. Quality cannot be tested into the product, but it is to be built into the product during its manufacturing.

In order to expeditiously provide the public with access to quality, safe and efficacious medicines, a risk-based approach to the assessment of a pharmaceutical product should be explored. This approach is discussed in the publication by the Centre of Innovation in Regulatory Science (CIRS) which describes measures that regulatory authorities should consider to apply in the risk-based approach [21]. The review highlights the importance of the level of experience of the evaluators used and the assessment tools employed during assessments to ensure that there is no compromise in the quality and that all critical components are appropriately detailed in the assessments. The component of the level of experience of the evaluators used in the assessments of the dossiers is supported by the results of the project previously undertaken by SAHPRA. In July 2009 - September 2010, the Regulator had a backlog of 2114 applications and initiated a project aimed at alleviating the backlog of applications. Only 16.6% of the products were registered while 1.6% were rejected and 6% were cancelled or withdrawn [22]. The reason for the unsatisfactory results were due to substandard reports that were submitted by inexperienced evaluators which required re-assessment by the PEM, P&A pre-registration Unit. This, therefore, illustrates the importance of experienced evaluators who are well knowledgeable with vast experience in the field of regulatory science and scientific assessments with a thorough scientific understanding of the benefit and risk involved [23].

The second component mentioned in the CIRS article is the scientific review tools which play a major role in the efficiency and effectiveness of the authority and could result in delayed registration, depending on the tools and strategies used to conduct scientific assessments [21]. In the effort to attain shorter registration

turnaround times, authorities need to incorporate the benefit-risk factors at the assessment stage. This entails adopting and implementing a systematic process of assessment of the dossier that builds quality into the assessment. Understanding what critical information is needed to reach an acceptable level of certainty to resolve scientific questions and meet regulatory standards for registration is important [23]. Therefore, identification of critical aspects in the Common Technical Document (CTD) and International Conference for Harmonisation (ICH) E3 bioequivalence structures is paramount.

Risk-based assessments, involving the thorough evaluation and reporting of only critical sections in the dossier which affect the quality of the specific product, are now commonly applied by a number of regulators [24, 25]. By applying a risk-based assessment, the following are questions to be considered:

- What is the risk to the user and how serious is it?
- What is the weight of evidence that supports that a risk exists?
- What is the expected and the actual benefit for a specific patient?
- Will the risk intensify over time?
- Does the risk outweigh the benefit? [26]

Both practical and theoretical knowledge of regulatory assessment is desirable to achieve a good understanding of the issues likely to be associated with the product under review and identify the risk and the critical aspects [16-17, 27].

6.1.3 Objectives

The objectives of the study are four-fold:

- quantification of the backlog that developed within SAHPRA,
- defining risk and developing robust criteria for risk classification of products,
- developing a new robust mechanistic review pathway called the risk-based approach and evaluate the review process based on the results of the pilot study conducted,
- detailed description of the implementation of the RBA process aimed at reducing the scientific evaluation timeframes and thereby reduce the overall registration turnaround time within SAHPRA.

6.2 Methods

6.2.1 The 2015 backlog project

The backlog project undertaken in 2015 was divided into two phases. The initial phase entailed the identification of the status of in-process applications and the second phase was on applications not yet allocated for review. The extensive planning of the backlog project required the collaboration of all Units

involved in the registration process which resulted in the formation of a backlog working group. The status of most of these applications by the different Units was unknown and required an extensive investigation in order to obtain the exact status of the products. The list was created, and the documents were titled in the backlog spreadsheet (Microsoft Excel® 2016, Windows 10) which consisted of all the in-process applications in the pre-registration phase.

6.2.1.1 Obtaining the status of in-process applications

SAHPRA initiated an overtime project during weekends to allow for the extraction of the information from the registry files, brown files, dossiers, Committee meeting minutes, applicants etc. For instance, if the product status is unknown, obtaining the information involved the following sequential order and if it is not obtained in one document area, it moves to the next:

- the brown files which should consist of the communications sent to the applicant;
- the Committee meeting minute documents which consist of the history and dates of each application discussed and the outcome thereof;
- registry files which contain the full history of documents received from applicants were checked to see the available history;
- if no information is obtained from the above, the applicant was contacted for a re-submission.

It was discovered from this process that a number of Units were not aligned when it comes to evaluations, i.e. one Unit would have finalised an application while another Unit was only at the initial evaluation stage. Therefore, although there might be finalisation in one Unit, registration cannot be executed because another Unit has not finalised the application. When documentation was obtained from the above four areas, it was promptly shared or communicated with the applicant to facilitate review and accelerated the registration process.

6.2.2 New applications – Risk-based review

The pilot project was initiated with the available new applications on a first come first served basis. During this time, the Authority was allocating applications received in 2011 while those received prior, were either registered or in the pre-registration phase under review. There were 208 line-item applications which equate to 150 master applications that were received towards the end of 2011 to 2012 that were not yet reviewed. These were used in the pilot study as they were next in the queue to ensure fairness to all applicants. The intent of the pilot study was to observe the effects of the proposed process with the aim of implementing it to all applications upon assessing the results. There were two separate phases within the project, the first one for the in-process applications which was initiated in 2015, and the second phase for the new applications initiated in 2016. For the 2021 pilot study, the applications that were next in line for allocation were in re-submission window eight (8) and were therefore used for further optimisation and efficiency of the process.

6.3 Results

6.3.1 The 2015 backlog project

For quantification of the backlog, Fig. 1 and 2 illustrates how the backlog resulted within SAHPRA in the period 2006-2015. For example, in 2010, SAHPRA received 1204 applications and could only register 425, resulting in 779 backlog applications. The collective backlog by May 2016 was 7902 applications and only 3779 were registered between 2006-2015 [28]. There were 3505 in-process applications in the initial phase for identification of the status of and 4397 applications not yet allocated for review in the second phase [28]. The results from these two phases were investigated and the outcomes are detailed below.

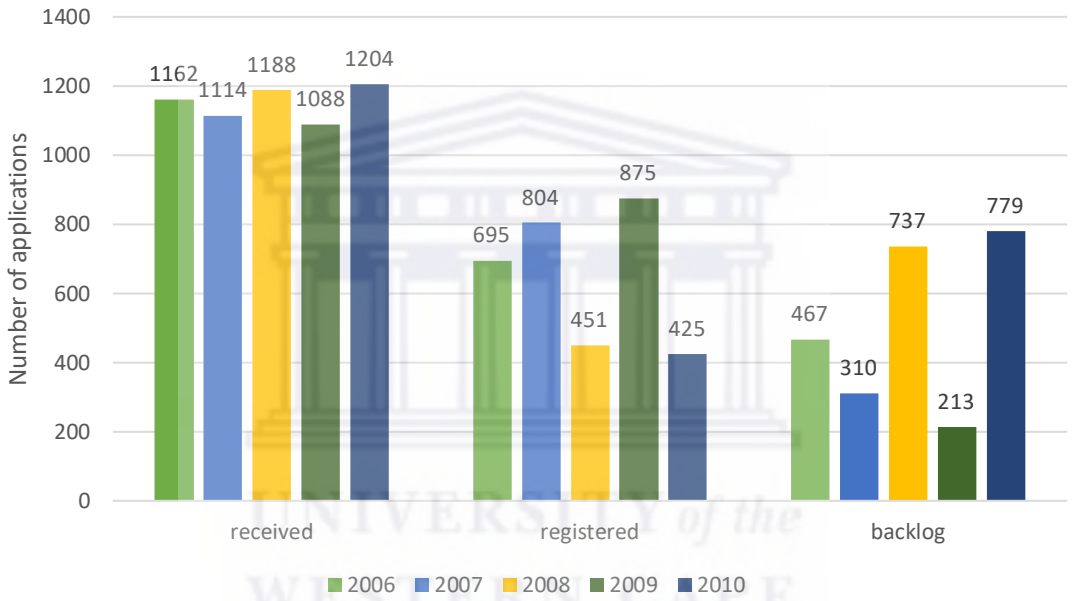


Fig. 1: A depiction of the registered products within SAHPRA between 2006-2010 resulting in the backlog.

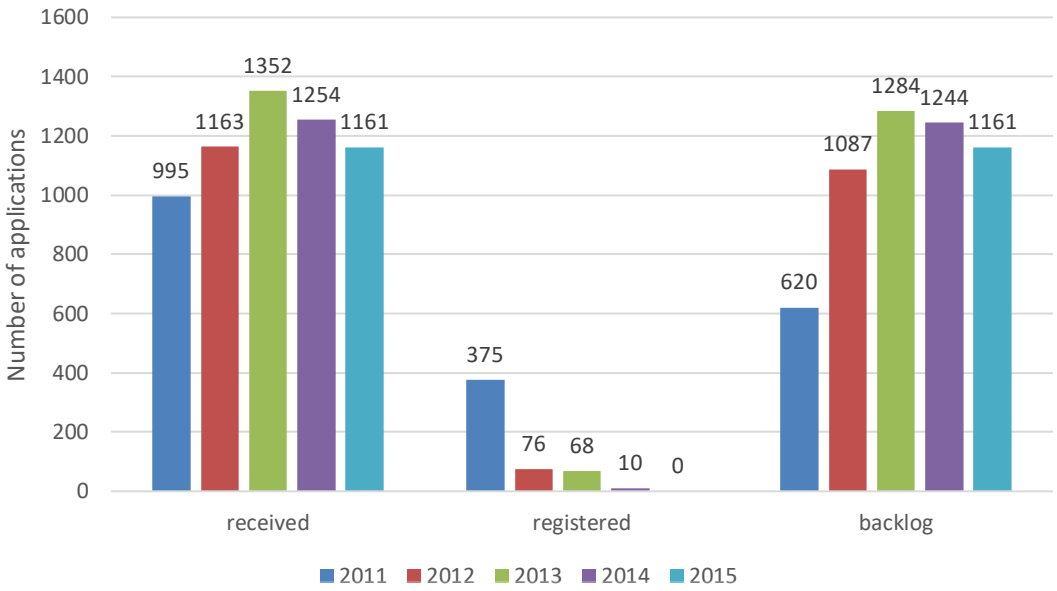


Fig. 2: A depiction of the registered products within SAHPRA between 2011-2015 further exacerbating the backlog.

The backlog pilot project on the in-process applications succeeded in the registration of 198 products, while 189 products were withdrawn by applicants after analysis of the business need. For the 2015/2016 cycle, in quarter one (April – June 2015) 34 products were registered, in quarter two (July – September 2015) 43 products were registered, in quarter three (October – December 2015) 88 products were registered and in quarter four (January – March 2016) 33 products were registered. The project achieved the clearance of 387 products in 2015 as well as obtaining the status of all the applications that were pending registration (see Fig. 3). The 448 registered applications include 250 registrations via the normal process that were not part of the pilot project.

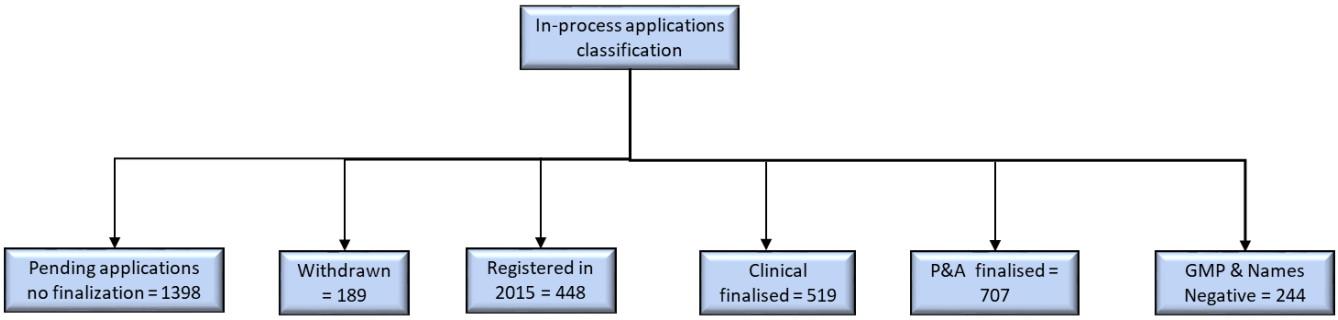


Fig. 3: Status classification and quantification of the in-process applications once phase 1 of 2015 project was concluded.

GMP – Good Manufacturing Practice

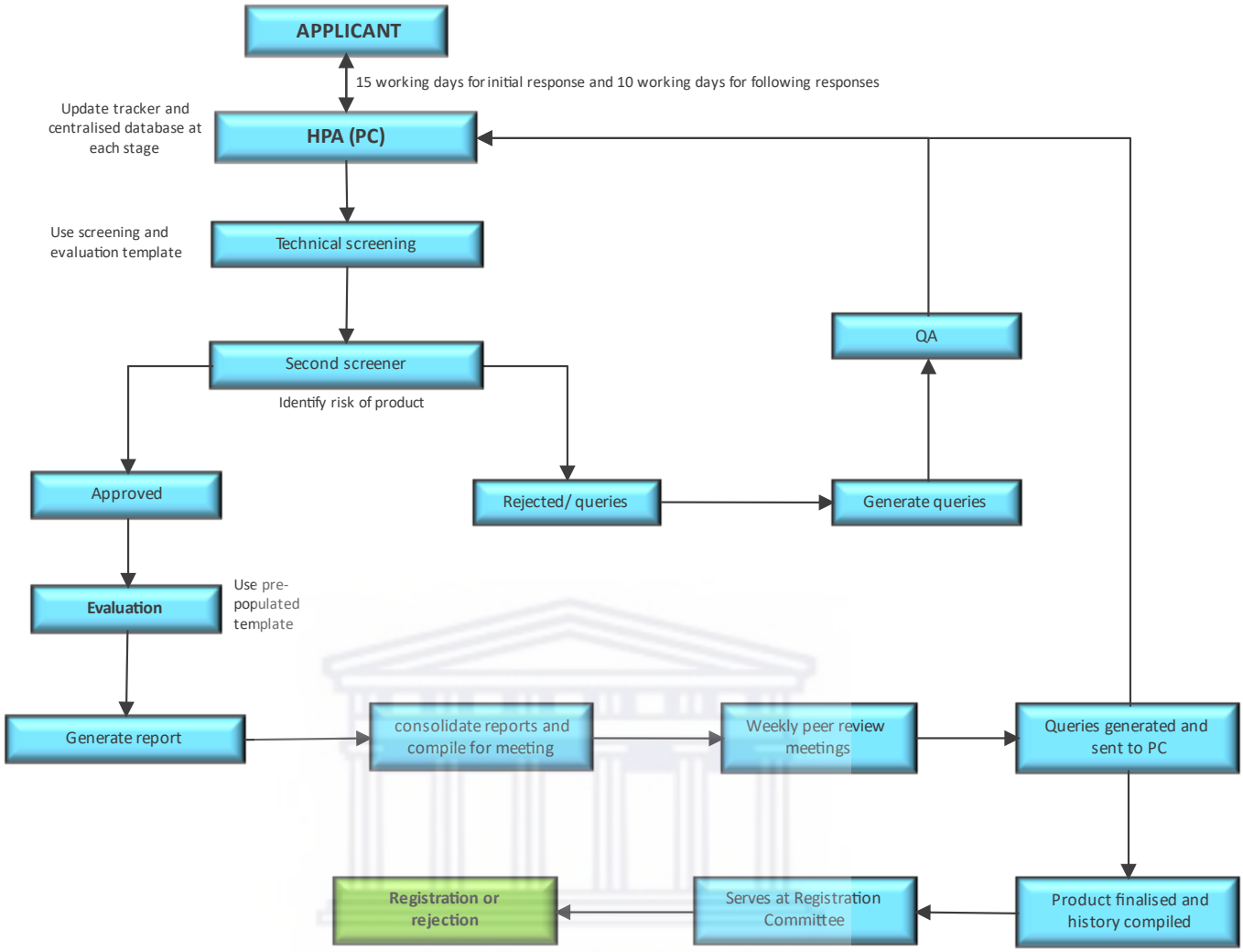
P&A – Pharmaceutical and Analytical pre-registration Unit

Fig. 3 shows the grouping of the status of applications obtained during the 2015 project. The exercise managed to identify and classify the status of all pending applications, a task that was historically difficult for the authority. The authority did not have a central database or tracker for applications and relied on individual Units to monitor the applications which led to misalignment within the Units as they were not communicating with one another on evaluations of applications. As a result, there were 707 applications with P&A finalised status, and 519 applications with Clinical finalised status. There were also 244 applications with P&A and Clinical finalised status, however, these could not be approved since the Inspectorate and Names and Scheduling Units had not finalised the applications. These applications were classified as "the low-hanging fruits" since they were near registration and only required finalisation by one or two Units. For the P&A finalised applications, it meant that other Units needed to focus on those products to attain registration and vice versa for the other finalised groups.

6.3.2 Risk-based assessment process

6.3.2.1 Registration process

Once the status of the pending applications was concluded, the authority moved on to reviewing the evaluation pathways for the new applications. Strategic planning over a two-year period between 2014-2016 was employed in order to alleviate the backlog by improving the existing registration process. It was important that the process be revisited to ensure that the proposed process is seamless and avoids the formation of a backlog in future. The overall developed and refined process as detailed in Fig. 4 involved changes to the previous practices thereby promoting efficiency and timely access of medicines to patients.



The process is repeated for the response cycle and only 10 working days are allocated for the second response cycle. PC = Portfolio Coordinator.

Fig. 4: Proposed risk-based assessment end-to-end registration process in the PEM, P&A pre-registration Unit for quality and bioequivalence assessments.

6.3.2.2 Risk classification

Upon re-assessment and refining of the two pilot studies for scale-up and implementation in the BAU section of SAHPRA, the risk classification template was refined through consultation with numerous experts and extensive literature review [20, 29-47]. This resulted in the developed risk classification template (Table 2) used for determining the risk of generic products including essential medicines that qualify to fall under this pathway. The model and structure detailed in the concept paper by the WHO was used whereby a scoring is assigned for each aspect to consider and the overall scores was used to determine the risk class of the product using Table 2 [20]. Table 3 indicates the risk classification matrix employed to deduce the overall outcome. Note that before the 2021 pilot study, it was decided that NCEs, biologicals medicines or biosimilars will not

be reviewed using this pathway, full review would be conducted for these applications. For the products that were part of the pilot studies, the overall risk classification of products was deduced using Table 3 and overall classification identified.

Table 2 risk classification template: The designed risk classification template used to determine the overall risk class of a generic medicinal product.

Item no	Aspects to consider	Dosage form affected	Risk assessment guide	Comments
	RELIANCE			
	API			
RA1.	CEP/CPQ submission, internal and external reports	All	CEP/CPQ submitted = 1 if not, are reports from the Authority's database available = 1 if not, is external reliance claimed = 1 if not, go to RA2	
RA2.	Specifications	All	CEP/CPQ submitted = 1 if not, are reports from the Authority's database available = 1 if not, is external reliance claimed = 1 if not, is pharmacopoeial monograph claimed = 1 if not, is pharmacopoeial monograph available and not claimed = 2 if not, is pharmacopoeial monograph not available = 3	If a monograph is available and not claimed, limits for degradants should be pharmacopoeial and process-related impurities should be according to ICH Q3A (R2) guideline. Applicant to provide cross-validation data to demonstrate equivalence.
	FPP			
RF1.	Internal and external reports	All	Are reports from the Authority's database available = 1 if not, is external reliance claimed = 1 if not, go to RF2	

Item no	Aspects to consider	Dosage form affected	Risk assessment guide	Comments
RF2.	Specifications	All	If the above is not applicable, are reports from the Authority's database available = 1 if not, is external reliance claimed = 1 if not, is pharmacopoeial monograph claimed = 1 if not, is pharmacopoeial monograph available and not claimed = 2 if not, is pharmacopoeial monograph not available = 3	If a monograph is available and not claimed, limits for degradants should be pharmacopoeial and process-related impurities should be according to ICH Q3B (R2) guideline. Applicant to provide cross-validation data to demonstrate equivalence.
	BE			
RB1.	Internal and external reports	All	Are reports from the Authority's database available = 1 if not, is external reliance claimed = 1 if reports not available = 2	
Decision point	If full internal or external reliance is identified, the risk assessment is herewith concluded. If partial reliance, such as in RA1, RA2, RF1 and RF2, is identified and reliance pathways are not identified, then move to non-reliance mechanisms below.			
	NON-RELIANCE			
	API			
A1.	Solubility BCS class	Solid oral dosage forms	BCS Class 1/3 = 1 BCS Class 2/4 = 4	If bioequivalence is submitted for BCS class 2/4 and equivalence is proven, then score = 2
A2.	Hygroscopicity	Solid oral dosage forms	Slightly to not hygroscopic = 1 Highly hygroscopic = 2	CCS is critical. If Alu-Alu or any blisters are used = 1 When bottles (e.g. HDPE) are used as CCS = 2

Item no	Aspects to consider	Dosage form affected	Risk assessment guide	Comments
A3.	Particle size	Solid oral dosage forms	No micronisation necessary = 1 If micronisation is conducted and specifications included = 1 If micronisation is required but not controlled (this will be requested) = 2	To check if micronisation is required, refer to ICH 3QA decision tree #3 (Only if API is BCS class 2/4); Not applicable if API is fully dissolved during FPP manufacture.
A4.	Polymorphism	Solid oral dosage forms	Amorphous form = 1 Consistent polymorphic form manufactured and controlled = 1 Different polymorphic forms produced as a ratio = 2	Only if API is BCS class 2/4, Not applicable if API is fully dissolved during FPP manufacture.
A5.	API load (Concentration)	Solid oral dosage forms and semisolids	High API load (more than 5% of the total mass) = 1 Low API load (less than 5 % of the total mass) = 2	For low API load, if the manufacturing process involves wet granulation, uniformity is assured = 1 If manufacturing process involves direct compression, in-process controls should be checked for content uniformity = 1 If content uniformity is not conducted, it should be requested and proven = 2
A6.	Therapeutic index	All	Wide therapeutic index = 1 Narrow therapeutic index, high load = 4 Narrow therapeutic index, low load = 5	Examples of narrow therapeutic index APIs = chloramphenicol, lithium, carbamazepine, phenytoin, digoxin, warfarin, rifampicin, phenobarbital, theophylline.[b]

Item no	Aspects to consider	Dosage form affected	Risk assessment guide	Comments
	Repeat for different APIs, if present			
	FPP			
F1[a]	Type of dosage form as per dosage form classification (Tran *et al.* [33])	All	Non-sterile solutions = 1 Immediate release solid oral dosage forms = 1 Powders for suspension, not sterile = 1 Semi-solids (Ointments and creams) = 1 Sublingual = 2 Buccal = 2 Modified release solid oral dosage forms = 4 Solid oral, immediate release dosage forms for treatment of chronic illnesses = 3 Transdermal = 4 Sterile products = 4 Injectables (products injected directly into the systemic circulation) = 4 Metered-dose inhalation (applied directly to the site of action) = 5	

F2[a]	Complexity of the manufacturing process	All	**Non-sterile solutions** Measuring; mixing blending = 1 **Immediate release solid oral dosage forms**, Compression (tablet); granulation (dry and wet); milling; measuring; mixing blending; coating; drying; encapsulation (hard gel) = 1 **Powders for suspension, not sterile** Milling; mixing blending; measuring = 1 **Semi-solids (ointments and creams)** Emulsification; mixing blending, Deaeration; heating, cooling; measuring = 1 **Sterile products, injectables** Aseptic filling-traditional method; form-fill seal, isolation, filtration; lyophilisation, mixing blending, terminal sterilisation, validation, in-process and testing conditions = 4 **Modified release solid oral dosage forms** Compression (tablet); granulation (dry and wet); milling; measuring; mixing blending, rate-controlling materials, release system; coating; drying; encapsulation (hard gel) = 4 **Transdermal** Active deposition; coating; extrusion, mixing blending, drying; measuring, primary packaging is critical to dose delivery = 4 **Metered-dose inhalations** Assembly; filling,	

Item no	Aspects to consider	Dosage form affected	Risk assessment guide	Comments
			Micronisation = 5	
F3.	Composition in relation to the reference product	All	If qualitative composition of the reference product is the same = 1 If qualitative composition differs from reference product = 2	For qualitative composition that differs from the reference product, assess API-excipient compatibility studies for excipients not in the reference product.
F4.	Excipients	All	Well-known and pharmacopoeial = 1 Novel = 5	A DMF is required for a novel (non-pharmacopoeial) excipient
F5.	Container closure system (CCS)	All	If CCS is the same as the reference product = 1 If the CCS is critical to accurate dosing = 5 (e.g. metered-dose inhalers) If the manufacturer cannot use the CCS as required by reference or other generic products = 2	For CCS that is not identical to the reference or other generic products, assessment of the stability data will prove suitability of container = 1
	Repeat for other FPP manufacturers, if present and different			
	BE			
B1.	Bioequivalence and comparative dissolution with the reference products	Solid oral dosage forms	Biowaiver submitted = 1 BE and dissolution submitted and bioequivalence proven = 2 If the API(s) is known for bio-inequivalence problems = 4	To confirm equivalence check section under results on the BE template to confirm a confidence interval of 80 – 125 %

[a]If F1 and F2 are scored as 4, then application is high risk as these aspects carry more weight
[b]For the comprehensive list see reference [48].
[c]The scores for all rows are assessed once template is completed and Table 3 used to obtain overall classification.
RA# = Reliance for API section, RF# = Reliance for FPP section, RB# = Reliance for BE section, A# = Aspect to consider under API section, F# = Aspect to consider under FPP section, B# = Aspect to consider under BE section. 5-point risk scoring scale: 1-very low, 2-low, 3-medium, 4-high, 5-very high.
API = Active Pharmaceutical Ingredient , BCS = Biopharmaceutics Classification System, CEP = Certificate of Suitability , CPQ = Certificate of prequalification, DMF = Drug master file, ICH Q3A = International Conference for Harmonisation Q3A , ICH Q3B = International Conference for Harmonisation Q3B , HDPE = High density polyethylene.

Table 3 deduction of overall risk classification: The risk classification matrix employed to deduce the overall outcome

Outcome of risk assessment	Risk classification
Any one aspect scoring 5	High-risk
Any three aspects or more scoring 4 or more	High-risk
Any four aspects or more scoring 3 or more	High-risk
Any three aspects scoring 3, rest 2 or below	Low-risk
Any two aspects scoring 3, rest 2 or below	Low-risk
All aspects scoring 2 or below	Low-risk

From the findings reported, evaluation templates were designed according to the level of risk for evaluators, clearly identifying critical sections for the different risk classifications. The templates are included as Supplementary material page 276 and 292. The sections that are critical are identified under the discussion section.

6.3.2.3 Summary of results on the risk-based assessment approach

Table 4 provides a summary of the results from the backlog pilot project conducted in September 2016 and September 2021 by SAHPRA. There were 10 evaluators used in both pilot studies; for the 2016 pilot, seven were external evaluators and three were internal evaluators while for the 2021 pilot study eight were external and two were internal evaluators. The reported finalisations times and approval times for both studies are depicted in Fig. 5 which illustrates the median values for the finalisation times in both pilot studies as well as the reported minimum and maximum times. A number of outliers are witnessed in the depictions for applications that took longer to finalise than the other applications due to applicants not addressing the queries as required. Delays in approval times after finalisations are attributed to other Units not yet finalising the products hence delaying registration. This also illustrates how the rate-limiting PEM, P&A pre-registration Unit managed to finalise applications before other Units which has always been a historic problem.

Table 4 pilot study summary results: The summary results of the backlog Phase 1 pilot projects conducted by SAHPRA in 2016 and 2021.

	2016 risk-based approach in P&A pre-reg Unit	**2021 risk-based approach in Backlog clearance program**
Time received to time when application was allocated	1542 calendar days	431 calendar days
Product total (master applications)	150	63 (RW 8)
Withdrawn (opted out)	51	6
Product used in the pilot project	99	57
Number of Evaluators used	10	10
Evaluation week (products evaluated)	54	Weekly meetings for 10 weeks
Finalisation time	median: 90 calendar days (3 months)	median: 68 calendar days (2.3 months)
Approval time[a]	median: 109 calendar days	median: 110 calendar days

[a]the approval time is calculated from date of initial allocation

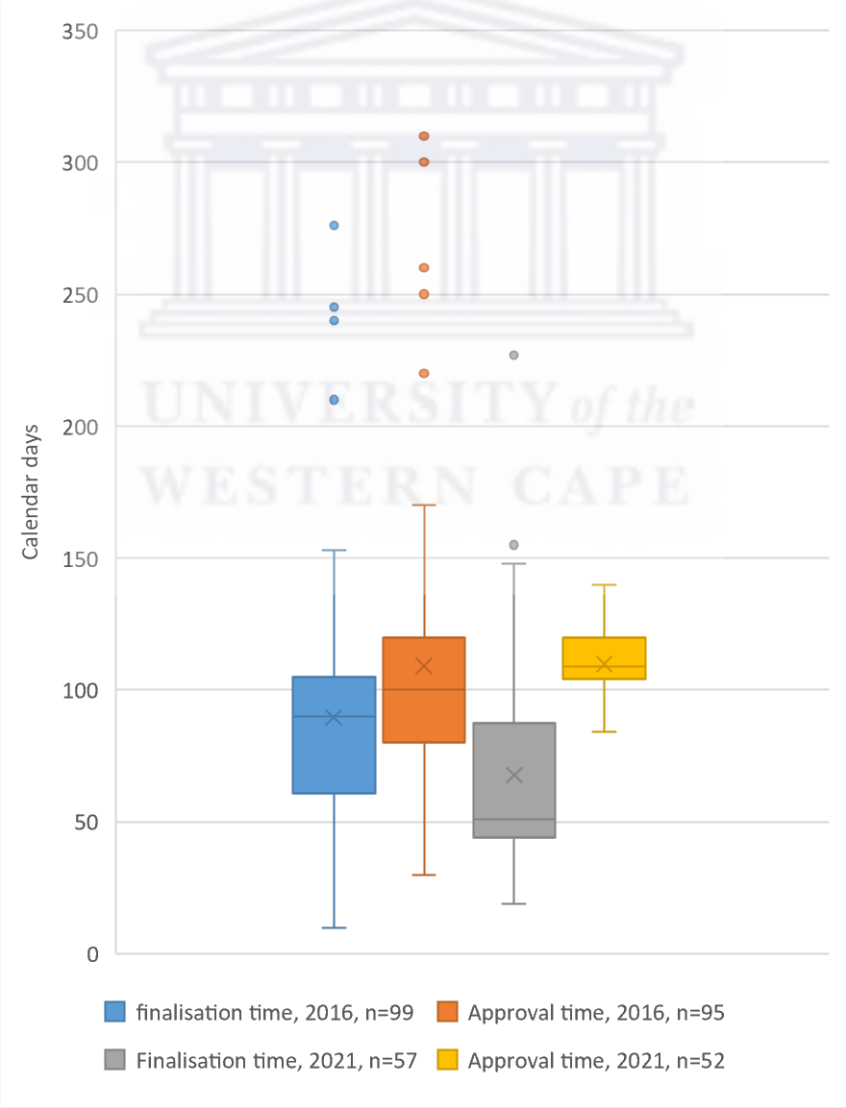


Fig. 5: The distribution of finalisation times and approval times for applications in the backlog Phase 1 (2016) and 2021 pilot studies. Box: 25th and 75th percentiles. Whiskers: 5th and 95th percentiles.

Table 5 risk classification outcomes of products: The risk classification outcomes for the products used in the pilot studies.

Dosage form	**Number of applications, 2016 pilot study**	**Risk classification**	**Number of applications, 2021 pilot study**	**Risk classification**
Immediate-release tablets	27	All were low-risk	30	All were low-risk
Immediate-release Capsules	21	All were low-risk	2	All were low-risk
Modified release tablets	10	All were high-risk	4	All were high-risk
Enteric-coated tablets	0	-	1	High-risk
Non-sterile powders	4	All were low-risk	2	All were low-risk
Eye drop solutions	5	All were high-risk	2	All were high-risk
Sterile IV or IM Solutions	13	All were high-risk	12	All were high-risk
Syrup	3	All were low-risk	4	All were low-risk
Topical Gel	8	All were low-risk	1	Low-risk
Transdermal patch	1	High-risk	1	High-risk
Mouth wash	0	-	1	Low-risk
Throat spray	0	-	1	Low-risk
Suppository	3	All were low-risk	1	Low-risk
Nasal spray	1	Low-risk	0	-
Anaesthetic inhalation, solution	0	-	1	High-risk
Medical device with API inside device	1	Low-risk	0	-
NCEs	2	All were high-risk	0	-

API = Active Pharmaceutical Ingredient, IM = intramuscular route, IV = intravenous route, NCE = New Chemical Entity

Table 5 provides the outcomes of the risk classification of the products that were in the two risk-based assessment pilot studies. This shows that the classification largely depends on the dosage form of the product and the manufacturing process of the final product as stated by Tran *et. al*. [33].

6.3.2.4 Assessment timelines

The assessment times were recorded for each application. Fig. 6 illustrates the median times obtained for assessment of a simplified low-risk application, high-risk application, bioequivalence assessment, biowaiver assessment and a response assessment. For the 2021 pilot study, four of the applications were omitted from the calculations since two were clones of already registered products and two had pre-approvals by the PEM, P&A pre-registration Unit before February 2018, and only minor variations were submitted for review. Hence, the total n value was 59 which is 38 low-risk applications and 21 high-risk applications (Fig. 6). It should be noted that a Phase 2 pilot study was conducted in 2022 in order to monitor upscaling of the number of applications to 156, a different template was used and included as supplementary material page 299 which was pre-populated by the applicant and used as an evaluation template for quality assessments. The reported evaluation times for the second phase in 2022 was a median time of 14 hours for high-risk and 10 hours for low-risk applications. The biostudy, biowaiver and response assessments remained the same as the templates remained the same as the 2021 pilot study results.

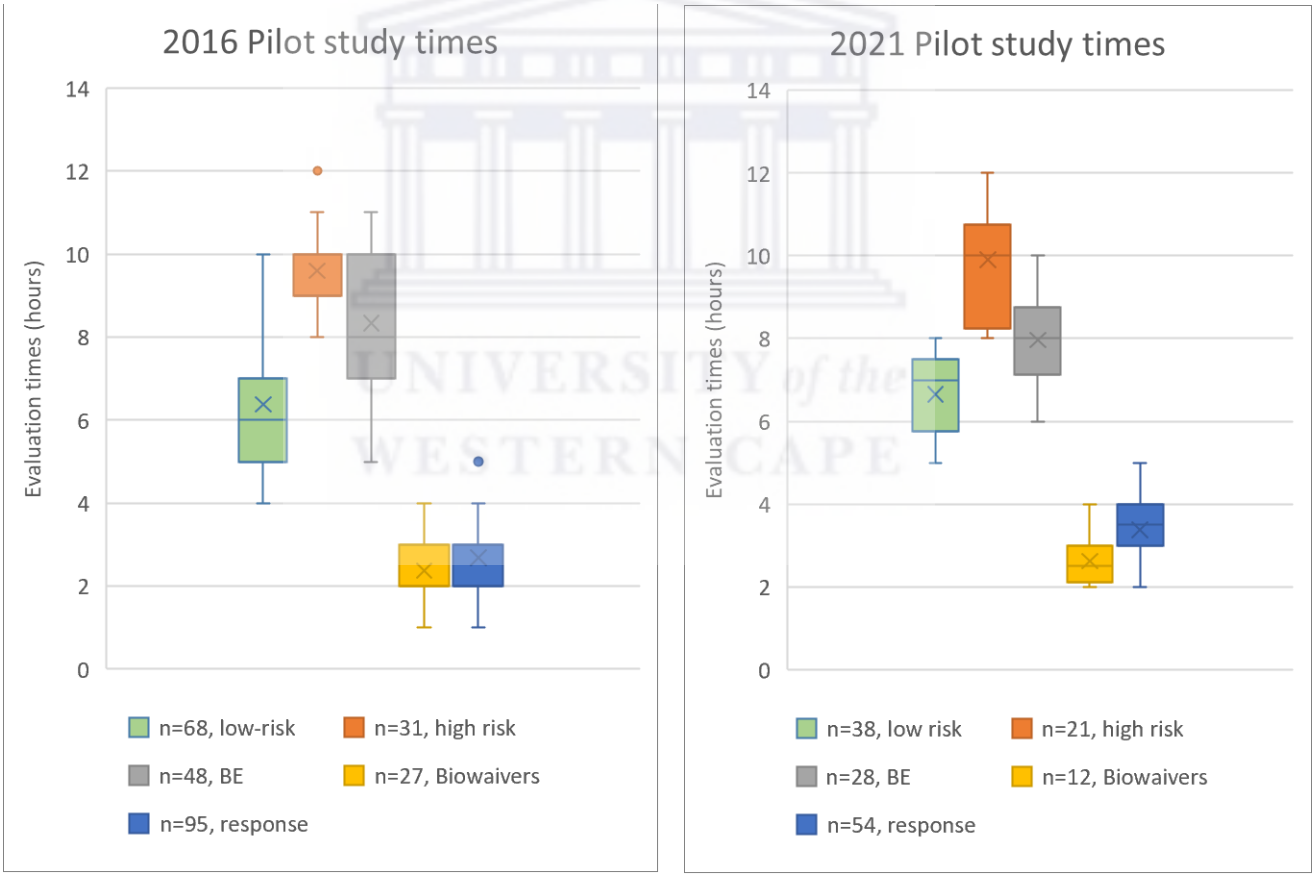


Fig. 6: Median evaluation times reported in the two risk-based assessment pilot studies for low-risk, high-risk, BE, biowaiver and responses. (n) = number of product applications. Box: 25th and 75th percentiles. Whiskers: 5th and 95th percentiles.

6.4 Discussion

6.4.1 The 2015 backlog project

For the initial phase of the project, the identification of the status of each pending application proved to be a success as it allowed for better coordination and management of applications. In addition, obtaining the status of the finalised products from each Unit provided a list of applications that each Unit can focus on (Fig. 3). Although allocation was conducted at the same time by the Health Products Authorisation (HPA) section, the Units did not initiate the evaluations at the same time. With the improved process this would be alleviated as communication to the applicant was synchronised for all the applications.

6.4.2 New applications – Risk based assessments

The planning of phase 2 of the 2015 backlog involved engagements with other stakeholders in order for the success of the project. The stakeholders such as the applicants and the Expert Committees were a wealth of knowledge regarding processes, historical information, industry insight and in the planning and execution of the project for new applications. It was therefore imperative that they were consulted in the decision-making of the project to allow for a seamless process to occur. The proposed process was outlined, and modifications were made where necessary until a consensus was reached to initiate the pilot project.

The proposed process was communicated with all stakeholders involved, which included the CEOs of the pharmaceutical companies in the pilot study, the P&A expert Committee members and the Unit, the Clinical evaluations expert Committee members and Unit, the members of the MCC registration Committee and the Industry Technical Group (ITG). It was agreed that all new applications not yet reviewed, should be resubmitted to facilitate review. This is because the submission for these products were between 2011-2012, thus, the information in the dossiers was outdated. It was observed that the frequent recommendations for the old applications, since five years had lapsed, were on updates of the stability data, updated Certificate of Suitability (CEP), changes in the methods of synthesis, changes in the API manufacturers, changes in the FPP manufacturers etc. This meant that several changes had occurred to a product over time and in some instances, the product was considered non-existent as the final product manufacturers were no longer in business or were no longer manufacturing it. Thus, after registration, the applicant would apply for post-registration amendments, and by registering the products that essentially no longer exist, MCC was shifting the work to the post-registration Unit without eliminating the burden the Authority faced. Hence, applicants were requested to uplift, update and re-submit the paper documents. Uplifting of the paper dossiers was conducted two months prior to the re-submission date, which gave applicants enough time to update their applications.

Consultation with the applicants resulted in withdrawal of 31% of the application due to the lack of business need for the product and only 99 master applications were left for the pilot study. The dossiers were re-submitted between 12-16 September 2016, distributed to the respective Units and evaluated by the PEM, P&A pre-registration Unit during evaluation week held on 19-23 September 2016.

Even with the two phases as detailed above, by 2018 the backlog of applications had increased to 8 220. In 2018, the authority embarked on a project called the Backlog Clearance Programme aimed at clearing the existing backlog over a specified time. The planning and development of the project was initiated in February 2018 through the assistance of a project consulting firm which assisted in the quantification of the backlog. Inherited processes and practices from the former MCC were re-assessed and the backlog project was initiated in August 2019 to support new methodologies required to achieve the goal of clearing the backlog of applications [7]. The project was initiated through the assistance of funding from government, development partners and donors [49].

The applicants were initially requested to indicate if they would like to include their applications in the Backlog Clearance Project. Upon analysis of the business need and proposed timeframe to submit there were 4 610 applications that opted out of the project and 99 applications were withdrawn. Not being part of the backlog project meant once the dossier was ready for resubmission with the new requirements, it would be submitted to the BAU section of SAHPRA. The in-process applications that were near finalisation, by either Units, were assessed in the BAU and concluded. Thus, SAHPRA initiated the Backlog Clearance Project in August 2019 with 3343 applications which translates to 1364 master applications.

The Backlog Clearance programme utilised 56 external domestic and international evaluators to conduct the scientific assessments as well as the internal evaluators from the BAU section working overtime to assist with the project. By May 2021, 34% of the applications had been cleared. This was nearly two years after the initiation of the project where the intent was to eliminate the backlog in two years. The program was extended by one year and five months to December 2022 and the delay in the clearance was attributed to the assessments conducted within the PEM, P&A pre-registration component due to the bulk of the work done in this Unit [50]. Hence, the necessity for the refinement of the risk-based assessment in September 2021 in effort to conclude the Backlog Clearance Project in the set time. The 63 applications that were next in line for allocation were in re-submission window eight (8) and were therefore used in the 2021 pilot study.

In 2019 when the backlog clearance programme was initiated, the business-as-usual (BAU) section was provided the opportunity to start on a clean slate while the backlog clearance programme dealt with all the ~8220 applications. In the period 2019 and 2022, SAHPRA amended its processes and put systems in place such as the inclusion of a tracker that allows all Units to monitor each other, however, even with that, a backlog has formed within the BAU section of SAHPRA. The tracker was aimed at providing transparency

and synchronisation within the Units, however, this did not correct the misalignment as Units could still allocate the same applications at different times and communicate the queries at different times. The solution to this would have been to have one set of queries from the different Units communicated at the same time by the PC, as conducted in the 2015 study to ensure alignment within Units at all times. This meant some Units would finalise applications before others which leads to the misalignment. It should be noted that the root cause of the backlog is not as a result of one factor such as the misalignment of Units only, there is a number of reasons which are detailed in the study which is why the risk-based assessment approach was developed as an end-to-end registration process providing corrective or preventative measures or solutions to prevent the root causes from occurring in future.

6.4.3 Risk-based assessment process

6.4.3.1 Registration process

A reassessment of processes was a necessity for the authority for improved efficiencies. An improved registration process was employed as detailed in Fig. 4.

The following were improved in the developed process illustrated in Fig. 4:

- Previously, the Units were only allocated an application by HPA, thereafter communication with the applicants would be made by the separate Units. There was an introduction of the Portfolio Coordinator (PC) responsible for coordinating and collating outcomes from the Units as one communication to the applicants.
- The introduction of the Inspectorate Unit confirming the Good Manufacturing Practice (GMP) status before allocation to other Units was included since previously, this would only occur once the scientific assessments have been concluded by the PEM, P&A and clinical evaluations of pre-registration Units. The inspections being conducted towards the end of the process would further delay the registration of applications.
- The use of a risk-based approach to conduct scientific assessments to reduce the assessment times by the PEM, P&A pre-registration Unit with assessments focused on the critical quality attributes of the product.
- The use of a pre-populated evaluation template to aid in the reduction of evaluation times. This allowed for the technical person to screen the applications to check if the updated information such as the updated stability data is as per the requested shelf-life, the updated Certificate of Suitability (CEP) is included etc.
- Frequent peer review meetings. For the 2016 pilot study, an evaluation week approach was used where a week was blocked for evaluation, wherein towards the end of each day evaluators discussed the reports and query letters sent to HPA. This promoted scientific knowledge sharing and ensured that queries going out to the applicants were critical aspects to be addressed in the dossier and that

the queries were standardised. This was only conducted once, and the rest of the applications awaited the P&A Committee meetings held on a six-weekly basis. This resulted in some delays.

In the refined process in 2021, there were weekly peer review meetings introduced which allowed for better throughput of query letters to the applicants. The selection of the date for each peer review session was based on the availability of evaluators using the When Available poll. The reports were then compiled into meeting documents and uploaded on Google Docs well in advance to allow evaluators to provide their comments. The living document would then show all comments in real-time, allowing all evaluators to see each other's comments. This assisted in drastically reducing the meeting sessions as only specific points of discussion, highlighted by the peer review panel, were discussed. Most other aspects were collaboratively deliberated on during the real-time discussions via the Google Docs.

- The response time was reduced from 90 calendar days to 30 calendar days and only two response cycles were allowed which the pharmaceutical companies agreed on for the 2016 study.

  In the refined process this was further reduced to 10 working days, however, applicants could request an extension if required. The requests for extension were for 41% of the responses, therefore the response timeline was increased to 15 working days for initial responses and 10 working days for further responses.

Once this robust process had been concluded, the products were classified according to risk.

6.4.3.2 Risk classification

Ahead of assessing the aspects of the API and FPP, prior work conducted by other NRAs or Regulatory Institutions should be considered. Recognition of the work previously done is termed as reliance. And, according to the WHO, reliance is defined as the act whereby one regulatory authority in one jurisdiction may consider and give significant weight to rely upon scientific assessments or inspection reports performed by another authority or trusted institution totally or partially in reaching its own decision [21]. The relying authority uses this work according to its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities. Historically, SAHPRA had not implemented this review pathway until 2019 when the backlog clearance programme was initiated [49]. The authorities which SAHPRA aligns itself with and uses the unredacted reports of are the European Medicines Agency (EMA), Health Canada, Medicines and Health Products Regulatory Agency (MHRA) in the United Kingdom, Ministry of Health, Labour and Welfare (MHLW) in Japan, Swiss Agency for Therapeutic Products (Swissmedic), Therapeutic Goods Administration (TGA), Australia and USFDA [51]. SAHPRA is also currently utilising partial reliance through the use of submissions such as CEPs by the European Directorate for the Quality of Medicines (EDQM) and Certificates of Prequalification (CPQs) of the API by the World Health Organisation Prequalification Team: Medicines (WHO PQTm). The developed template in Table 2 therefore accommodates the reliance aspect as well during risk classification.

The non-reliance critical aspects are also considered during quality and efficacy (bioequivalence) aspects of products submitted for approval and detailed below to assist in the overall classification of the product.
When it comes to defining the risk pertaining to the API, the following key aspects of the API are assessed:

- Availability of a valid CEP/CPQ (Certificates of Prequalification (CPQs)),
- Pharmacopoeial status of the API,
- Biopharmaceutics Classification System (BCS) of the API (in particular aqueous solubility),
- Solid state properties (solubility, hygroscopicity, particle size distribution (PSD) and polymorphism),
- The concentration of the API in the FPP.

The key aspects to be considered in the FPP are:

- Pharmacopoeial status of the FPP,
- Type of dosage form,
- Complexity of the manufacturing process,
- Excipients,
- Container closure system (CCS).

The key aspects in the bioequivalence study:

- The bioequivalence (BE) with the reference products and comparative dissolution with the reference products.

Based on the identified aspects to consider as stated in Table 2, a product could be classified as low- or high-risk.

6.4.3.3 Critical areas to be reviewed for low-risk products

A combination of literature reported by Tran *et. al.* [33] and the concept paper by the WHO [20], as well as a wide array of expert advice garnered on the approach, categorically assisted in the determination of the critical attributes of manufacturing and overall risk ranking of the product. With this information, the CTD sections and extent of evaluation thereof could be established. The areas of concern have been included below and will be thoroughly evaluated for low-risk applications. The relevant templates are used for assessment with the critical sections included.

The identified critical sections of the CTD for low-risk applications are as follows:

- Module 1.3 Labelling and packaging (Professional Information (PI), Patient Information Leaflet (PIL) and Label)
  Quantitative and qualitative composition

Storage conditions

Container closure system

Appearance

- Module 1.7.4.1 Batch Release

  API and Inactive Pharmaceutical Ingredient (IPI) batch release

  Release (Final Product Release Control (FPRC)/Final Product Release Responsibility (FPRR))

- Module 1.10 Foreign regulatory status

  Marketing authorisation information for reliance

- Module 3.2.S. Active Pharmaceutical Ingredient

  3.2.S.1.3 Physico-chemical properties (depending on dosage form)

  3.2.S.2.2 Method of synthesis (N/A if CEP/CPQ is submitted)

  3.2.S.3.2 Impurities (N/A if CEP/CPQ is submitted)

  3.2.S.4.1/2 Specifications (N/A if CEP/CPQ is submitted, however, assess the API specifications by the FPP manufacturer)

  3.2.S.7 Stability (N/A if retest period is stipulated on CEP/CPQ)

- Module 3.2.P Finished Pharmaceutical Product

  3.2.P.1 Components and composition of the final product

  3.2.P.3.3 Manufacturing process/Batch Manufacturing Record (BMR)

  3.2.P.5.1 Specifications

  3.2.P.7 Container closure system

  3.2.P.8 Stability

- Bioequivalence

  The sections proposed for the bioequivalence section are included below and are in line with ICH and EMA requirements [52-53]. In the case where a BCS-based biowaiver is requested (BCS class I and III applications), only two sections would be assessed. These include the details of the test and reference product used in the study and comparative dissolution profiles, thus reducing the assessment review times. This template, used as an evaluation tool, would reduce the current reported evaluation timelines, as it is designed to point out and discuss critical aspects of the biostudy.

The identified sections from the bioequivalence template are as follows:

- Details of the test and reference product used in the study (applicable for biowaiver request)
- Comparative dissolution profiles (applicable for biowaiver request)
- Study method and design
- Summaries of statistical and pharmacokinetic data
- Bioanalytical report parameters

Certain sections are excluded from evaluation for low-risk applications. The rationale for these exclusions, which addresses the risk mitigation for each, are as follows:

- Batch analyses (3.2.S.4.4 and 3.2.P.5.4) are not evaluated for low-risk applications because the stability results (3.2.S.7.3 and 3.2.P.8.3) at the initial time point essentially serve as batch analyses. In addition, the impurities section also includes profiling of the impurities and residual solvents formed, thus these sections mitigate the risk since they are assessed.
- Reference materials sections (3.2.S.5 and 3.2.P.6) are for documentation purposes and do not need to be assessed since the API would have been confirmed already in preceding sections, such as the method of synthesis, impurity section and specifications. In most cases, 3.2.P.6 refers to section 3.2.S.5 of the dossier. The working standard and primary standards are those manufactured by the applicant and synthesis would, therefore, be in line with the proposed methods.
- Pharmaceutical development (3.2.P.2) is not assessed for low-risk applications, because this is research and development conducted by the manufacturer for optimisation of the final manufacturing process for commercial product/s. The final proposed manufacturing process is then assessed in section 3.2.P.3.3 and the information is verified by the batch manufacturing records. In addition, for the oral solid dosage forms which require the submission of a bioequivalence study, certain critical aspects of the pharmaceutical development section are evaluated. These include *in vitro* dissolution studies as these are covered in the bioequivalence template for evaluation. For solid oral dosage forms, selection of inactive pharmaceutical ingredients (IPIs) is covered by the bioequivalence assessment where similarity to the reference product is reviewed, and in the case where the excipients are not similar to the reference product, API-excipient compatibility should be confirmed under 3.2.P.2. In the case of liquid dosage forms, excipient similarity to the reference is confirmed under Module 3.2.R.1.4.1 and in the case where the excipients are not similar to the reference product, API-excipient compatibility would be confirmed under 3.2.P.2. The designed templates therefore provide guidance for these.
- Module 3.2.P.3.1 details the full name and address of the final product manufacturer. The name of the final product manufacturer is confirmed in the administrative table at the beginning of the pre-populated template. In addition, the Inspectorate Unit confirms and validates this during inspections.
- Batch formula (3.2.P.3.2) is not assessed since it is confirmed during assessment of the batch manufacturing records, which consist of actual quantities of API/s and IPI/s used for the proposed batch(es).
- Validation of analytical methods (3.2.S.4.3 and 3.2.P.5.3) is not assessed because the product would either be pharmacopoeial and only verification is then required. In addition, specification limits provided found to be within ICH requirements will be confirmed since the specification

section is assessed for low-risk applications. At most, the evaluator may only confirm the submission of the reports for noting for low-risk applications.

6.4.3.4 Critical areas to be reviewed for high-risk products

If a product is classified as high-risk, additional sections over and above the ones identified for low-risk, would also require thorough evaluation and reporting on the respective templates. The additional sections to assess for high-risk products include the following:

- Module 1.3 Labelling and packaging (PI, PIL and Label) – same as low-risk
- Module 1.7 Good Manufacturing Practice – same as low-risk
- Module 1.10 Foreign regulatory status – same as low-risk
- Module 3.2.S Active Pharmaceutical Ingredient
  - 3.2.S.4.3 Validation of analytical methods for the API – additional section for high-risk applications
- Module 3.2.P Finished Pharmaceutical Product
  - 3.2.P.2 Pharmaceutical development of the FPP
  - 3.2.P.3.5 Process evaluation of the FPP validation
  - 3.2.P.5.3 Validation of analytical methods for the FPP
  - 3.2.P.7 Container closure system (for sterile applications)
- Bioequivalence
  - Details of the test and reference product used in the study (applicable for biowaiver request)
  - Comparative dissolution profiles (applicable for biowaiver request)
  - Study method and design
  - Summaries of statistical and pharmacokinetic data
  - Bioanalytical report parameters

The justification stated above for the sections that are not to be assessed are also applicable for high-risk applications. Note that risk classification will not be applied to NCEs and biological applications, instead full review will be conducted due to the criticality of the medicines.

6.4.3.5 Summary of results on the risk-based approach

In the second phase of the 2015 backlog pilot project for new applications, all 99 master applications were finalised within nine months, with the median time calculated as 90 calendar days. The outliers were noted as seven, eight and nine months as indicated in Fig. 5. These were due to the FPP manufacturers receiving a negative status and therefore inspection had to be arranged by the Inspectorate Unit before evaluation could take place. There were other instances where the applicants requested an extension to submit responses and

this led to the delay in finalisation. For the refinement of the process in 2021, a median finalisation time of 68 calendar days was obtained (Fig. 5). Of the 63 applications, 6 were withdrawn while in-process in the response phase. However, the initial evaluation was already conducted for these so they were included in the calculations of evaluation times.

From the 63 applications, 21 applications were classified as high-risk and 42 classified as low-risk as depicted in Table 5. From Table 5, it is observed that all immediate-release tablets and capsules were low-risk which constitute 51% of the applications. From the 90% generic applications that SAHPRA receives, most of these are pharmacopoeial and well-known with readily available extensive research conducted on them therefore due to this, classification would be low-risk. In addition, the dosage forms were not novel therefore overall classification was low-risk. The same applies for the other dosage forms classified as low-risk.

6.4.3.6 Assessment timelines

Fig. 6 illustrates the reported evaluation times by the evaluators who were part of the two risk-based assessment pilot studies in 2016 and 2021. The graphical depiction shows the calculated median values as 6.3 and 7.0 hours in 2016 and 2021 respectively for low-risk quality assessment timelines. As observed from Table 4, products classified as low-risk were immediate-release tablets and capsules, topical gels, mouth wash, throat spray, oral syrups and oral solutions. The median values for high-risk quality assessments were reported as 9.5 and 10 hours from the two pilot studies respectively. Products classified as high-risk were sterile intravenous injections and infusions, ophthalmic solutions, delayed-release tablets and sterile lyophilised powders. The bioequivalence study assessment times were 8.4 and 8.0 hours using the proposed template and biowaivers reported as 2.3 and 2.6 hours with initial response assessment times as 2.6 and 3.4 hours. The calculations above were based on a simplified submission that contains one API from one API manufacturer who submitted an Active Pharmaceutical Ingredient Master File (APIMF) with only one FPP manufacturer applied for. In a case where a CEP was submitted the median evaluation times were 5-6 hours for low-risk and 7-8 hours for high-risk, when two APIMFs were submitted, the evaluation times were 11-12 hours for low-risk and 13-14 for high-risk products. This resulted in the deduction that one APIMF assessment takes 4-5 hours and one FPP takes 5-6 hours to assess for high-risk applications. The reported medians have resulted in a reduction in the assessment times without the compromise to quality as only critical sections which will impact the quality of the product are adequately assessed.

For the Phase 2 pilot study conducted in 2022, the quality assessment timelines for high-risk is reported as a median of 14 hours and 10 hours for low-risk. The increased assessment timeline is due to the different quality template used which has been pre-populated by the applicant. The evaluators therefore would spend time validating the information populated by the applicant with the scientific information in the dossier to ensure that accurate information was completed.

Once applications that undergo the risk-based assessment pathway are registered, the following post-marketing-surveillance or monitoring procedures were proposed and will be conducted:

- The applicant will be requested to provide the Post-registration reports on a yearly basis to Pharmacovigilance and annual product review report to the Inspectorate Unit. Depending on the information submitted on the reports, the Inspectorate could perform inspections of the non-compliant manufacturer/applicant.
- Ongoing post-marketing surveillance will be conducted on the products by the Inspectorate Unit.
- Re-evaluation of the information (dossiers) after five (5) years will be conducted on all applications.

6.5 Conclusions

The large influx of applications as a result of "dossier farming" as well as resource constraints experienced by SAHPRA over the years resulted in the formation of a backlog as large as 8 220 applications. The organisation needed to implement drastic changes in order to reduce the timelines to promote timely access to medicines. A backlog pilot project was conducted in 2016 to alleviate the existing backlog of applications at the time. The pilot project consisted of 99 master applications and managed to reduce the finalisation timelines to a median value of 90 calendar days. The refined and efficient process was described in detail as well as the knowledge gained from the project. These learnings were used in the refined and optimised risk-based assessment pilot study in 2021. This pilot study was initiated with applications from re-submission window 8 of the Backlog clearance programme project initiated by SAHPRA in 2019. The study was resumed with 63 applications and a median finalisation time of 68 calendar days recorded which is significantly lower compared to the initial pilot study (90 calendar days) and the current process employed by SAHPRA for the backlog clearance programme initiated in 2019, which resulted in the finalisation time of 501 calendar days. The risk-based approach is discussed in detail as it involves the robust risk classification matrix to employ which allows for the categorisation of a product to the adequate risk class. The approach also details which sections of the CTD and bioequivalence study are considered critical for comprehensive assessment. The identified sections for the assessment of the two risk classes ensures that quality, safety and efficacy are not compromised while accelerating access to medicine for patients. The risk-based approach therefore essentially aims to reduce the finalisation timelines for quality and bioequivalence assessments for authorities which will greatly reduce the overall registration timelines. Implementation of this approach by other regulatory authorities will assist in the reduction of the backlog of applications created due to resource constraints and the large influx of applications that are of urgent need to the public.

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CHAPTER 7

Regulatory registration timelines of generic medicines in South Africa: Assessment of the performance of SAHPRA between 2011-2022

Abstract

Background. Various regulatory authorities are experiencing backlogs of applications which result in delayed access to medicines for patients. The objective of this study is to critically assess the registration process utilised by SAHPRA between 2011 - 2022 and determine the fundamental root causes for the formation of a backlog. The study also aims to detail the remedial actions that were undertaken which resulted in the development of a new review pathway termed the risk-based assessment approach for regulatory authorities experiencing backlogs to implement.

Method. A sample of 325 applications was used to evaluate the end-to-end registration process employed for the Medicine Control Council (MCC) process between 2011 and 2017; 129 applications were used for the backlog clearance project (BCP) between 2019 and 2022; 63 and 156 applications were used for the risk-based assessment (RBA) pilot studies in 2021 and 2022 respectively. The three processes are compared, and the timelines are discussed in detail.

Results. The longest median value of 2092 calendar days was obtained for the approval times between 2011-2017 using the MCC process. Continuous process optimisation and refinement are crucial to prevent recurring backlogs and hence implementation of the RBA process. Implementation of the RBA process resulted in a shorter median approval time of 511 calendar days. The finalisation timeline by the Pharmaceutical and Analytical (P&A) pre-registration Unit, which conducts the majority of the evaluations, is used as a tool for the direct comparison of the processes. The finalisation timeline for the MCC process was a median value of 1470 calendar days, the BCP was 501 calendar days and the RBA process phases 1 and 2 were 68 and 73 calendar days respectively. The median values of the various stages of the end-to-end registration processes are also analysed in order to build efficiency within the process.

Conclusions. The observations from the study have identified the RBA process which can be implemented to reduce regulatory assessment times while assuring the timeous approval of safe and effective, quality medicines. The continuous monitoring of a process remains one of the critical tools required to ensure the effectiveness of a registration process. The RBA process also becomes a better alternative for generic applications that do not qualify to undergo the reliance approach due to its drawbacks. This robust procedure can therefore be utilised by other regulatory agencies that may have a backlog or want to optimise their registration process.

7.1 Background

In the effort to reduce the likelihood of a backlog of medicinal product applications, which has the propensity to build up in medicine regulatory bodies globally, the performance of regulatory review should be measured and tracked [1]. The need for agencies to measure and improve their performance proactively and consistently against stated target times is one of the World Health Organization (WHO) global benchmarking tool parameters [2]. This is especially important for generic products as they increase accessibility and affordability in global healthcare systems. Generic products contain the same quantity of active substances in the same dosage form, meet the same or comparable standards and are intended to be administered by the same route as the innovator products [3]. In most countries, these generic products are marketed only after patent expiration and are normally cheaper than branded innovator medicines [4].

In 2015, China's Food and Drug Administration (CFDA) had more than 21 000 applications in backlog, most of which were generic products [5]. In 2019, the CFDA's 900-day approval period was shortened to 300 days [5]. Their Centre of Evaluation (CDE) employees expanded from 100 in 2015 to approximately 1000 by 2020; this was reported as one of the direct causes of the decline [6]. The increase in human resources, amendments to the 2007 administrative measures and processes for Drug Registration as well as the introduction of additional review pathways were implemented which accelerated access to medicines [6]. The regulatory authority in Brazil, Agência Nacional de Vigilância Sanitária's (ANVISA) also reported that in 2018 there were more than 800 New Chemical Entities (NCE) and generic applications in the backlog with the intent to clear the number by January 2019 with improved registration processes [7]. ANVISA had achieved an approval time of 795 days for generic products in 2013-2016 for 138 products. [1] The United States Federal Drug Administration (USFDA) on the other hand accomplished an approval time of 661 days in 2020 for 737 Abbreviated New Drug Applications (ANDA) approvals and 172 ANDA tentative approvals [8], while the Australian regulatory authority, Therapeutic Goods administration (TGA) accomplished an approval time of 244 calendar days for 85 generic products in 2021 [9]. This shows that the approval times are dependent on the number of applications received in that specific year and the resources available in the authority. The Taiwan Food and Drug Administration stated that they receive an estimated 400 generic applications per annum [10]. The Caribbean Regulatory authority received 11 generic applications in 2018 [11], TGA received 85 applications in 2021 [9] and South African Health products regulatory authority (SAHPRA) received an annual average of 1247 applications in 2019 [12]. It is therefore the duty of the authorities to ensure that the required measures, review tools and developed processes that best suit the situation they are faced with are continuously monitored and efficiencies applied.

The South African authority, SAHPRA, formerly named the Medicine Control Council (MCC) reported a backlog of approximately 8000 applications in 2016 which highlights the need to review the registration process and apply better efficiencies [13]. The authority had a fast-track process initiated in 2003 which only

focused on essential and critical medicines [14]. Due to the backlog that formed, a number of medicines in the essential list were fast-tracked, therefore only these products were allocated and evaluated while other products were allocated only when an evaluator was available. Given that the human resource was at a minimal and a registration process had not been reviewed for more than 20 years, the backlog increased [14]. The operational challenges and resource constraints faced by SAHPRA over the years resulted in the formation of a backlog of approximately 16 000 applications including variations by 2018 [15]. In 2019 when the backlog clearance project (BCP) was initiated, 15 domestic and 48 international evaluators were contracted to assess the quality and bioequivalence assessments while SAHPRA's business-as-usual section operates as normal with the new applications received [16]. This strategy would allow for the authority to function while the backlog is managed as a separate project with the required human resource employed to execute the required end-to-end backlog function. This was aided through the assistance of funding from various entities such as the Bill and Melinda Gate Foundation and the National Treasury of South Africa. This meant that careful monitoring and consistent reporting was required to ensure that the project's goal was executed. With funding acquired and after an in-depth analysis of SAHPRAs backlog by a project managing consulting firm, a target completion time of two years was predicted based on the available resources [16]. This was not executed as planned and it was extended by one year and four months [17].

This study, therefore, investigates the end-to-end registration process of generic products employed between 2011-2022 for the MCC process and the BCP process in the effort to assess the performance and identify the root causes of the backlog. In addition, the developed robust pathway called the risk-based assessment (RBA) process with remedial steps implemented to mitigate future backlogs is described and compared with the other processes.

7.2 Methods

The study assesses three different registration processes used between 2011-2022; the MCC process is assessed using a sample of finalised applications between 2011-2017; the BCP process is assessed using the applications from three re-submission windows (RW) evaluated in 2020; and the RBA pilot studies assessed in 2021 and 2022 using the sample of applications that were in RW8, 10, 11 and 12. The RBA approach is the robust process that was developed upon further refinement and optimisation of the MCC and BCP process and piloted in 2021 and 2022, titled the RBA pilot study phase 1 and 2.

7.2.1 MCC registration process, 2011-2017

Over the 7-year period, 3148 applications were finalised by the P&A pre-registration Unit within SAHPRA of which 2089 were non-sterile. Thus, due to the large application size at hand, a statistical sampling method became a requirement for this research. The sample selected becomes a true representation of the population

and results of the study can be generalised to the population. The method of selection and calculation of the representative sample is comprehensively described by Moeti et al. where a sample size of 325 non-sterile products is obtained and used in the study [13, 18, 19]. By comparing the quality requirements for sterile and non-sterile products it is witnessed that the sterile products require additional assessments in the pharmaceutical development section (3.2.P.2) as well as the process validation and or evaluation section (3.2.P.3.5). On the other hand, the non-sterile products would normally require additional assessment in the regional section on bioavailability, therefore, assessment times would be similar for both product types.

7.2.2 Backlog clearance project (BCP) registration process, 2019-2022

In order to eliminate the backlog, in 2019 SAHPRA started a project named the BCP [19]. The project was initiated with ~8220 applications in the pre-registration phase [16]. The implemented process allowed for applicants to re-submit the dossiers, as some information may be outdated since they were submitted as back as 2008. Resubmission windows (RW) were then created according to therapeutic categories with those considered essential in the earlier windows.

The applications selected from the BCP were from three RWs, i.e., RW1, RW5 and RW6. RW1 consisted of medicines in the therapeutic category of Human Immunodeficiency Virus (HIV), Tuberculosis (TB), Vaccines and Hepatitis, RW5 was for medicines targeting Diabetes, Malaria, maternal and newborn health as well as all the priority APIs and RW6 was for medicines targeting respiratory system diseases [20]. An overall of 129 applications from the three windows was employed and only the applications that utilised the full review pathway for quality and bioequivalence scientific assessments were selected. Note that other pathways include the reliance pathway [21] or applications that have previously received preliminary approval from the P&A pre-registration Unit, however, not yet registered and contained minor variations. Since the approval times for these pathways were shorter, this would alter the calculated timeframes, therefore, the applications that undertook the reliance route were not included in the study. The dates at each stage of the BCP registration process for each application were collected from the electronic database/tracker used by the authority.

7.2.3 Risk-based assessment (RBA) pilot study, phase 1 and 2, 2021-2022

The risk-based pilot project was initiated in September 2021 within the realm of the BCP using 63 applications from resubmission 8 (RW8) as they were next in line to be allocated for initial full review. RW8 comprised of medicines in the therapeutic category that treats haematological/immunological diseases as well as medicines that are analgesics and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). For further optimisation and reproducibility of the process, the RBA pilot study was up-scaled in April 2022 using 159 applications from RW 10, 11 and 12. The therapeutic categories are; endocrine, nutritional, digestive system and metabolic disease for RW10; skin, subcutaneous tissue, musculoskeletal system and connective tissue for RW11; and eye and ear diseases for RW12 [20]. The implementation was made as an intervention to

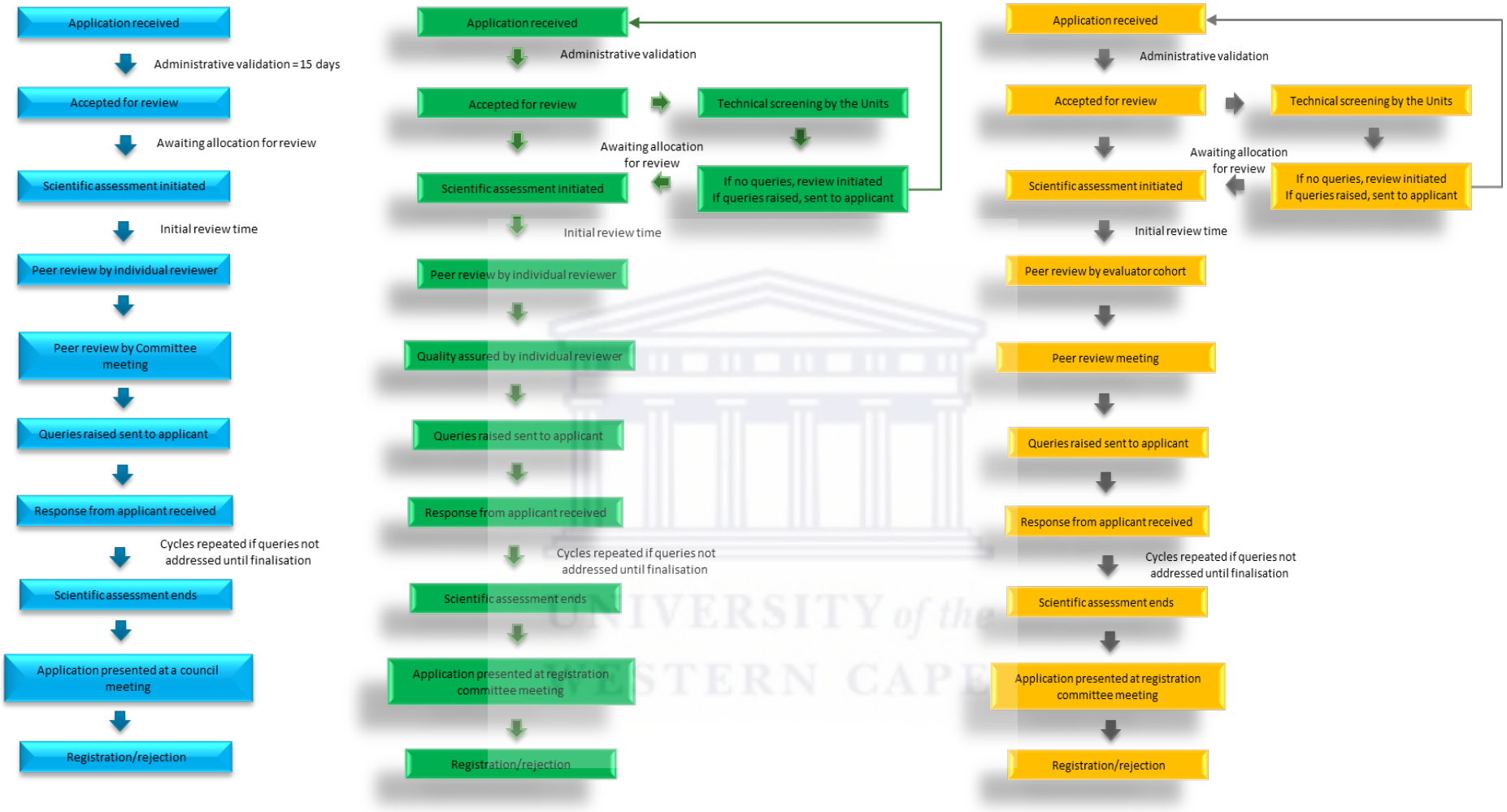
promote efficiencies within the existing registration process and allow accelerated access to medicines. The dates were collected from the database created during the initiation of the pilot studies wherein all activities and dates were recorded and closely monitored at each stage.

The dates were collected and information was populated in the respective Microsoft Excel®, 365, Worksheets. The differences between each activity were calculated for each product and median values were calculated for each, to obtain the time it takes for each activity within the registration process. Finalisation is the conclusion of an assessment by each respective Unit before registration. It should be noted that the finalisation timeline by the Pharmaceutical and Analytical (P&A) pre-registration Unit, is used as a tool for the direct comparison of the processes as the Unit is assessing the bulk of the information submitted by the applicant.

7.3 Results

7.3.1 Brief description of the MCC, BCP and RBA processes

The registration processes remain largely similar with deviations observed in certain steps as highlighted in Fig. 1. Upon receipt of the application, administrative screening was performed within 15 calendar days from the time of receipt. Applications were then routed to the relevant Units, where they are allocated to an evaluator to start the review process for the MCC process while for the other two processes technical screening was performed as illustrated in Fig 1. Queries raised from the technical screening were sent to the applicant and a response was requested within 10 working days. When all queries were addressed or the application is compliant the allocations for scientific assessments were initiated based on evaluator availability. Due to the limited number of evaluators, the application would wait in queue for an available evaluator before allocation. Once allocated in the P&A pre-registration Unit, the initial scientific assessments were conducted. The peer review stage differed in the three processes as shown in Fig. 1 in that detailed assessment reports prepared by the evaluators were peer-reviewed by the Chair or deputy Chair of the Committee in the MCC process. Thereafter these were made part of the agenda and shared with the Scientific Committee members for discussion during the meetings held every six weeks. In the BCP process, reports were peer-reviewed by an individual peer reviewer and thereafter quality assured by another assigned evaluator based on individual evaluator availability. In the RBA process, once the detailed assessment reports were received from the evaluators, the When Available poll [23] was used to determine the most suitable time for each weekly peer review session. The reports were compiled into meeting documents and uploaded on Google Docs [24] well in advance (5-7 days) to allow evaluators to provide their comments during peer review [22]. The peer review meeting sessions were then held and only specific points of discussion, highlighted by the peer review panel, were discussed.



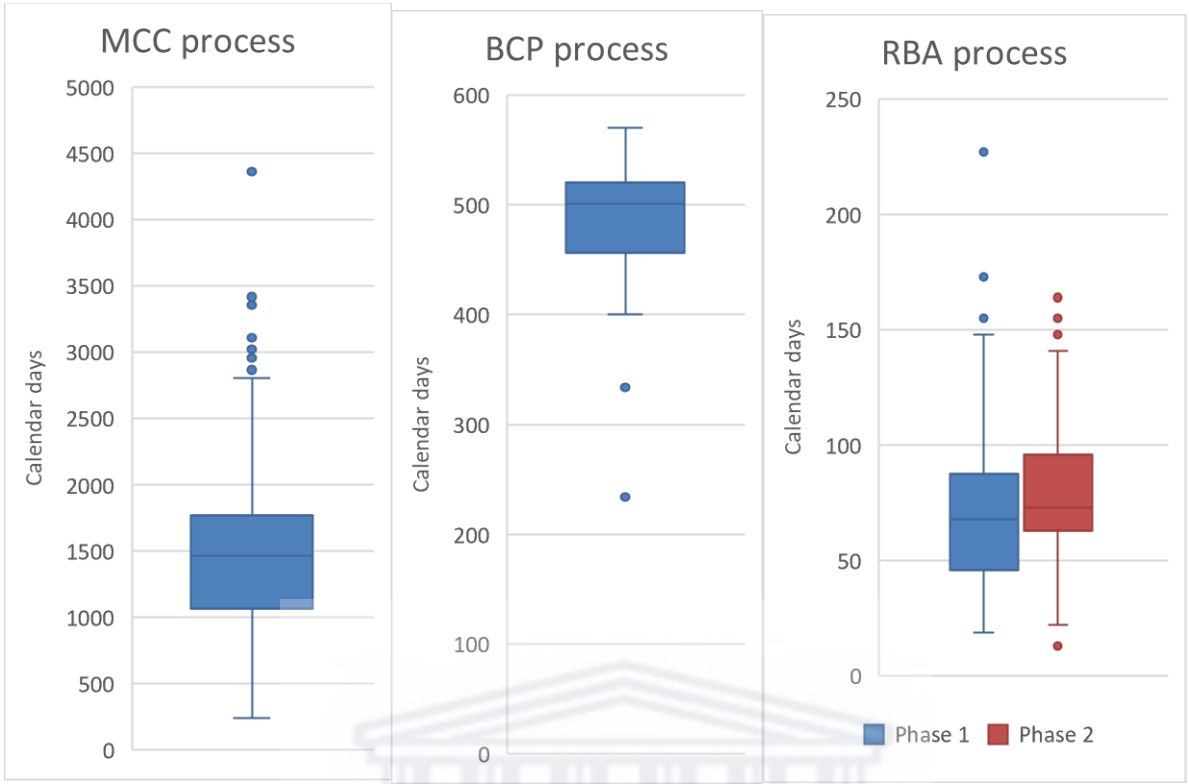
MCC = Blue, BCP = Green, RBA = Yellow.

Fig. 1: Depiction of the MCC, BCP and RBA processes utilised by SAHPRA between 2011 - 2022.

In the P&A pre-registration Unit, recommendations pertaining to quality and bioequivalence data were sent to the applicant and a response was expected within 90 calendar days for MCC process, 20 working days for BCP process and 15 working days for initial queries and 10 working days for response queries for the RBA process. The response would be reviewed by an evaluator and undertake the peer review process as described for each process. There were no limits to the number of response cycles between the applicant and the authority in the MCC process while this was restricted to only 2 response cycles for the BCP and RBA processes. Once the application is finalised by the P&A pre-registration Committee, the Clinical Committee, Good Manufacturing Practices (GMP) Committee and the Names and Scheduling Committee or their Units thereof, the medicine is considered for registration/approval by the authority at a Council meeting held every 60 calendar days in the MCC process or registration Committee meeting held weekly for the BCP and RBA processes.

7.3.2 Reported timelines for the three processes

The median values at each stage in the P&A pre-registration process were calculated and are depicted in Table 1 for all the different end-to-end registration processes. Fig. 2 illustrates the overall median finalisation time for the MCC, BCP and RBA processes as 1470, 501 and 68 calendar days. The second phase of the RBA pilot study was conducted in 2022 and the reported median finalisation time was 73 calendar days which is relatively similar to Phase 1. The results for RBA pilot study phase 1 and 2 as depicted in Table 1 confirm similarity for each timeframe.



n; MCC = 325, BCP = 129, RBA Phase 1= 59 (4 applications were withdrawn before finalisation), RBA Phase 2 = 156 (3 applications were withdrawn before finalisation).

Fig. 2: The graphical representation of finalisation timelines for the MCC, BCP and RBA processes with reported median values of 1470, 501 and 68 calendar days respectively.

Table 1: The identified activities within the three end-to-end registration processes employed by SAHPRA between 2011-2022 and the median timelines of the activities

	Median time in calendar days for registration activities for the MCC process (2011-2017)					
Cycle	Allocation timeframe	Preparation of assessment reports	Peer review process	Quality assurance	List of queries to the applicant	Applicant time
1	682	201	171	-	74 (0 finalised)	347
2	186		62	-	72 (168 finalised)	76
3	56		76	-	74 (116 finalised)	76
4	31		47	-	32 (35 finalised)	56

5	16		16	-	20 (6 finalised)	-
	Median Finalisation timeline			1470		
	Median Registration timeline			2092		
Cycle	**Median time in calendar days for registration activities for the BCP (2019-2022)**					
1	278	63	29	35	30 (0 finalised)	84
2	22	35	15	30	15 (30 finalised)	33
3	10	30	10	20	15 (58 finalised)	22
4	7	7	5	10	10 (25 finalised)	20
5	2	11	5	15	5 (13 finalised)	-
	Median Finalisation timeline			501		
	Median Registration timeline			591		
Cycle	**Median time in calendar days for registration activities for the RBA phase 1 pilot study (2021-2022)**					
1	431	5	8	-	2 (3 finalised & 2 withdrawn)	25
2	2	2	6	-	1 (44 finalised)	18
3	1	1	7	-	1 (6 finalised & 2 withdrawn)	10
4	1	1	7	-	1 (4 finalised)	-
	Median Finalisation timeline			68		
	Median Registration timeline			511		
Cycle	**Median time in calendar days for registration activities for the RBA phase 2 pilot study (2022)**					
1	~ 2 years	5	8	-	1 (6 finalised)	28
2	2	2	7	-	1 (102 finalised & 1 withdrawn)	15
3	1	1	7	-	1 (44 finalised & 2 withdrawn)	12
4	1	1	5	-	1 (7 finalised)	-
	Median Finalisation timeline			73		

	Median Registration timeline	-

In the MCC process, the first row of Table 1 represents cycle 1, where column 2 reflects the median time for the number of calendar days from the date the application was received to the time it was allocated for assessment as 682 calendar days. The time taken from the allocation of the application to the evaluator to the time the initial report was submitted is 201 days as indicated in column 3, the time taken from when the report was submitted to the initial peer-review meeting is 171 days, and from peer-review meeting to the time the query letter was sent to the applicant is 74 days. The last column indicates that it took the applicants 347 calendar days to respond to the initial queries, despite being granted only 90 calendar days to respond. This demonstrates how the applicants were also responsible for the delays. It emerged that some applicants would ask for extensions to provide the necessary data, which were granted, while others would exceed the response limit without asking for an extension. Due to the difficulty in obtaining the allocation dates of the responses for cycles 2 through 5 as depicted in Table 1, the time when responses were received to when report was submitted are merged. This is because the dates on which the responses were allocated to the evaluators were not recorded. The MCC process took up to five cycles before a product was finalised for the selected representative sample.

To assess the BCP process, the first row under the BCP median times in Table 1 represents cycle 1, which reflects the median time from the date of receipt to allocation for assessment as 278 calendar days. The time taken from allocation to submission of initial report is 63 days, the time taken from submission of report to the initial peer-review is 29 days, and from peer-review to quality assurance (QA), is another 35 days. The time taken from QA to sending the query letter is 30 days with the applicant taking 84 days to respond to the queries.

For the RBA process, the first row under the RBA median times in Table 1 represents cycle 1, which reflects the median time from the date of receipt to allocation for assessment as 431 calendar days while phase 2 denotes 523 days. The time taken from allocation to submission of initial report is five (5) days, the time taken from submission of report to the initial peer-review meeting is eight (8) days for both studies, and lastly, from peer-review meeting to communicating the query letter to the applicant is 1-2 days. Table 1 also outlines the number of applications finalised or withdrawn in each cycle in column 6. For example, in cycle 1 of the RBA process phase 1, three (3) applications were finalised and two (2) were withdrawn while 6 were finalised in RBA phase 2. Cycles were repeated four times depending on the queries and whether the response from the applicant was compliant or not.

7.4 Discussion

7.4.1 Alternative regulatory review models

Authorities use different regulatory review models to expedite access to medicines. These review models include the use of reliance strategy, whereby a regulatory authority in one country may consider and give significant weight to scientific assessments or inspection reports performed by another authority or trusted institution. Verification, abridged, and mutual recognition models are the reliance approaches that are used. Abridged review model is a selective assessment of market authorisation data, provided the product is registered by a reference national regulatory authority (NRA) [25]. This sort of study focuses on country-specific product quality requirements and clinical data for benefit-risk analysis. Verification model allows NRAs to rely on another NRA's regulatory decision by only comparing the submitted data which speeds up regulatory review [25]. SAHPRA implemented reliance models in 2019 and it was anticipated that using the verification and abridged review methods for most generic applications would reduce the backlog, however, this was not the case. SAHPRA considers the following countries as reference NRAs: USFDA, the European Medicines Agency (EMA), individual EU member states, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Swissmedic, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom, and the Australian Therapeutic Goods Administration (TGA) [16]. From this pool of authorities, full unredacted assessment reports are required to confirm the review. The limitations of this model include:

- In some circumstances primarily when European countries are NRAs, applicants have the reports and would share these with the authority, however, in most cases, these would not be available. The applicant must subsequently submit a letter confirming similarity to the reference country's application. The process of obtaining the reports from the NRAs takes months as they have other priorities. In other cases, the NRA requires the principal marketing authorisation holder to submit a declaration of access for the applicant in South Africa for authorisation of sharing the reports which would often take months before receipt of the reports. These result in delays in the registration timeframes
- From the reports shared, it is evident that the majority of the submissions had undergone numerous variations without amendments approval letters. The applications will then be subjected to full review and this will constitute more work as the information from the other regulatory authority required validation.
- Generic, well-known, pharmacopoeial applications registered in NRAs without unredacted reports will undergo a full review. Due to the absence of the reports from the NRA, a comprehensive review would be done even though these applications pose a negligible risk

based on the aforementioned characteristics. This approach wastes scarce resources for an organisation with significant resource constraints, necessitating the need for an alternative strategy for such applications.

As a result of the abovementioned drawbacks, approximately 20% of the applications were legible for the reliance pathway and the rest had to be subjected to full review. The RBA model is intended to deal with well-known generic applications that do not qualify for reliance review [22]. In-depth discussions are made for each stage of the registration process to identify obstacles and root causes of the backlog and how they were addressed by the RBA strategy to expedite the registration process.

7.4.2 Allocation timeframe

The median value from receipt of dossiers to allocation for assessment is 682 calendar days for the MCC products finalised between 2011 - 2017, this is considerably higher compared to ANVISA with 214 calendar days for applications approved between 2013-2016 [1]. Insufficient human resources resulted in time-lapse of approximately two years from receipt to allocation of the dossiers. Regular applications received in 2012 were only being allocated in 2016 [13]. This demonstrates that since the fast-tracked applications received priority for evaluation, the waiting period for the regular applications was four years in 2016 [14]. These delays had resulted in a backlog of 7902 applications in 2016. To eliminate the backlog, in 2019 SAHPRA started a project named the BCP as described in the section above [19]. Due to this, the date of receipt for applications in the BCP and RBA pilot study are the re-submitted date. These are reported as 278 and 431 days respectively. The difference in these times is attributed to the different times that were allocated for the various re-submission windows. For instance, RW1 was resubmitted between 01 August 2019 – 30 September 2019 while RW8 was resubmitted between 01 July 2020 to 30 July 2020 which is almost a year later [20] (See Additional file 1). Applications in earlier windows were assessed first while applications in later windows awaited the availability of evaluators. Although the median values of 278 and 431 days are quicker compared to that of the MCC timeline of 682 days, they remained to be higher than those of ANVISA with a timeline of 214 days. Apart from ANVISA there has been no other reports on timelines for each stage of the registration process by regulatory authorities. Even with the improved process and re-submissions SAHPRA implemented with the BCP, it was unable to reduce this timeline to a minimum which is what the authority would need to work on improving for reduced turnaround registration times.

7.4.3 Preparation of assessment reports

The time difference between the date the application was allocated for review to date when the report was received essentially determines the time it took to conduct the scientific assessments. Once the products were allocated for scientific review, the MCC process took approximately 201 calendar days

to evaluate the quality and bioequivalence aspects of the dossier. A number of factors resulted in this time difference. These are highlighted below:

- The sample selected is on non-sterile products which require the evaluation of both the quality and bioequivalence studies. The available evaluators either had expertise in either one of the areas or both, therefore allocation of these would in most cases be to two different evaluators. Due to the different rates and initiation times of evaluation, one evaluator would have completed a quality assessment while another would not have started the bioequivalence assessment, or vice versa, since the allocations were conducted in bulk and were not monitored.
- The authority had a lack of skilled staff to conduct the scientific reviews and largely used external evaluators. The PEM, P&A pre-registration Unit utilised 15-20 quality evaluators and only 8-10 bioequivalence evaluators. This also led to having more quality sections evaluated while the bioequivalence sections were outstanding in some cases, thus delaying the evaluation times further.
- Once applications were given to the evaluators, there was little to no supervision of them; Thus, an evaluator would work on an application for a long time without authority oversight. This led to the inability to track applications during the review process due to the lack of an efficient document management system.
- Since the external evaluators had primary work, they could only evaluate limited number of applications in their free time.

The time gap from first allocation to the time the report was received was substantially reduced from 201 to 63 calendar days for the BCP timeframes due to careful monitoring to achieve the project's aim of clearing the backlog in two years. This demonstrates how important it is to carefully oversee the registration process from beginning to end, especially in the P&A pre-registration Unit. This was also facilitated by the fact that there were more than thrice as many evaluators (63) employed to carry out the assessments as there were for the MCC process. The BCP also changed the assessment tools used which impacted on the review times. The timeline was further reduced to five (5) calendar days in the RBA phase 1 process utilising only 10 evaluators for the 63 applications and 17 evaluators for 159 applications in RBA phase 2. The five days were sufficient for the evaluators to submit their assessments owing to the strategic bulk allocation process that was used with identified similarities of applications. On average, 2 to 3 applications each week were allocated, and the evaluators would submit all the reports at once. RBA employed meticulous and thorough monitoring of each stage of the process as well as strategies to refine and reduce the review timelines. The implementation of the risk-based approach by SAHPRA is extensively reported on by Moeti and colleagues [22]. The report includes the evaluation timelines which are lower compared to the two processes detailed above.

A trend is observed with response cycles with the timelines becoming shorter as the cycles increase. For cycles 2 through 5, the MCC process had median values of 186, 56, 31 and 16 days from the time the response was received to the completion of the evaluation report, whereas cycles 2-4 for the RBA process saw a reduction with median values of 4, 2 and 2 days. The median evaluation time for the responses was also reduced to about three hours for initial responses. The RBA process evaluated the responses internally to effectively shorten the timelines compared to when external evaluators are assigned. The use of internal staff was, therefore, cost-saving.

7.4.4 Peer review process

The MCC process involved an additional individual peer review to be completed prior to the committee's peer review meeting, which contributed to 171 calendar days to the time taken to peer review the initial reports that were received. EMA reported on their target assessment time of up to 120 working days for initial reports which incorporates the review and peer review process while ANVISA reported 19 days for assessment and peer review [1, 26]. The combined timelines are much shorter compared to that of the MCC process. The reports from the MCC process were peer-reviewed after the evaluations were concluded by the Chair or deputy Chair of the Committee before being discussed at the Committee meeting. This meant that the peer reviewer would need to get the hard copy dossiers to conduct an in-depth review of all the applications. Upon completion, the meeting documents were compiled and couriered to the Committee members, who also reviewed the documents independently. The P&A Committee met every six weeks, which limited the number of meetings to six or seven per year, each lasting 3.5 days, and during which the product conclusions were made. As a result, there were delays as limited reports could be discussed for one peer-review meeting session.

Since the MCC process produced a median value of 171 calendar days which is over six months, it was necessary to modify it and employ a monitoring mechanism in order to shorten this timeline. The BCP process, therefore, amended the peer review process and included a one-person peer review as well as a one-person quality assurance approach. The Committee meeting setup which promoted collaborative scientific decision making was removed from the process. The median timeline was reported as 29 days from the period when the report was received to when it was allocated for peer review; 35 days from the period when the report was peer-reviewed to when it was assigned for quality assurance; and 30 days from the period when quality assurance was initiated and concluded. This is an overall median time of 94 calendar days for the peer review process employed in the BCP process. The refined BCP process suffers some drawbacks such as lengthy non-standardised queries to the applicant which resulted in requests of multiple extensions to respond to queries raised by the authority. In addition, significant inconsistencies in the queries were observed; applicants would receive different queries for

similar products as different reviewers were used and inappropriate peer review was conducted. This also led to significant delays in registration times.

The peer review meeting approach, which is also employed by the USFDA and EMA was reinstituted in the RBA process [26, 27]. Weekly peer reviews were held, allowing for a quicker flow of query letters to the applicants. The peer review meetings provided evaluator alignment in terms of the review criteria used. These sessions also played an important role in facilitating thorough scientific debate regarding the queries raised by the primary reviewer, based on the risk to the product in question. The approach required the peer reviewers to apply analytical thinking and research skills to determine the relevance of the initial queries based on the data provided and type of application, as well as its risk to the end user. Soliciting multiple experienced reviewers to provide peer reviewer input was effective, as it ensured thorough review of all critical quality attributes, which, in turn, offered assurance that only products of high quality, safety and efficacy were approved. The timeline was significantly decreased to 10 calendar days in the RBA process. Given the expertise of evaluators employed, the meetings acted as a platform for peer review and quality assurance. The When Available poll [23] was used to determine the most suitable time for each peer review session based on the evaluators' availability. The reports were then compiled into meeting documents and uploaded on Google Docs [24] well in advance (5-7 days) to allow evaluators to provide their comments [22]. The living document would then show all comments in real-time, allowing all evaluators to see each other's comments and refer to the electronic version of the dossier on the regulatory agency reviewing software, EURSNext, when required. This assisted in drastically reducing the meeting sessions as only specific points of discussion, highlighted by the peer review panel, were discussed. Most other aspects were collaboratively deliberated on during the real-time discussions via the Google Docs. This approach further minimises the risk as multiple assessors peer-review an application and can comment on the notes made by other peer reviewers which further facilitated review and reduces registration time considerably.

7.4.5 List of queries to the applicant

In the MCC process, a median value of 74 calendar days, which is significantly high, was observed between the time when the peer review is completed to when the query letter is issued. Without detailing the peer review process, ANVISA claimed a time difference of 19 calendar days for this stage [1]. Once the peer review meetings were concluded in the MCC process, query letters were created using the meeting minutes. Lack of oversight and control resulted in the P&A Unit exceeding the targeted 14 calendar days for this step.

Since the peer review meeting approach was not used for the BCP, this timeline is not provided; nonetheless, the determined median value from the date of receipt of the quality assured report

communicating the deficiencies observed was 30 calendar days, whereas the median timeline for the RBA process was two (2) days for this timeframe. This step required proper planning and preparation. The internal evaluators who coordinated the peer review meetings ensured that the query letters were prepared well in advance and amended as reviewers made comments in the live Google Docs. After the meeting, the letters are revised based on contentious issues, which takes a few hours before being forwarded to the Portfolio coordinator (PC). The applicant would then receive the query letters from the PC. A delay of one day is observed which can be improved to ensure that the PC shares the query letters immediately upon receipt.

7.4.6 Applicant time

The analysis revealed that the calculated median value was 347 calendar days instead of the 90 days that was requested for response to the query letters in the MCC process. Given that ANVISA claimed a median response time of 120 days [1], this is noticeably excessive. EMA also allocates a response time of 3-6 months to the applicant once the clock-stop is paused [26]. There were numerous extension requests and a lack of response monitoring tool to easily identify when the target time is exceeded. Therefore, in some instances, the applicant would surpass the time without requesting extensions which led to a significantly high median value. This demonstrates the criticality of an effective monitoring tool at each stage of the process. The PCs were, therefore, introduced in the BCP and RBA process, to monitor and identify when the target time is exceeded.

The response timeframe was shortened to the 20 working day target period in the BCP from the 90-day target of the MCC process, however, the median timeline of 84 calendar days was obtained. For the RBA process phase 1, the calculated median value for the initial response from the applicant was 25 calendar days, with a target response time of 15 working days. The difference in RBA response times for cycle 1 (25 days), cycle 2 (18 days), and cycle 3 (10 days) and a similar trend for phase 2 was attributed to the initial queries receiving a 15-working-day response window taking in cognisance, the magnitude of the queries raised, while subsequent queries received a 10-day response window. The applicant's response time largely depended on the type of queries recommended; if significant adjustments are suggested, they requested a longer extension which was granted, and this resulted in a longer approval time.

7.4.7 Response cycles and delaying queries

If the queries raised in the query letters are not addressed, the response cycles would repeat. The authority did not set a limit on the number of response rounds in the MCC process, which slowed down the finalisation timeframe. The average response cycles were five, and the maximum period for an

application to be approved was 4361 calendar days. Lack of monitoring and control allowed some applications to go unattended until the applicant inquired about the status of the application.

The other aspect which led to multiple response cycles is common deficiencies observed in the quality and bioequivalence study evaluations which resulted in back-and-forth communication with the applicant [13, 18, 19]. The deficiencies in the specification sections of the API and FPP were the most prevalent and included requests to tighten the proposed specifications of the product. In such cases, the applicant would provide a justification for retaining the proposed specification, but the authority would either decline or request additional supporting data, resulting in extended cycles. These were particularly common for tightening impurity limits, assay limits, and dissolution limits, when applicable. The applicant would offer the justification listed below for not tightening the proposed specifications:

- Request to gain further experience of the product and obtain data from future batches to be manufactured before tightening the specifications.
- Justifying retaining the limits based on the results observed in the stability data.
- Justifying retaining the assay limits based on the limits stated in the pharmacopoeia when the submitted results show that the percentage label claim of not less than 95.0% can be attained for the lower limit.
- Justification to use specifications that are wider than the bioequivalence batch results.

These were some of the justifications provided that were not accepted by the authority. The specifications are set and proposed based on the submitted data, any specifications wider would not be accepted since batch-to-batch consistency and reproducibility should be maintained throughout all future batches manufactured compared to the initial validation and bioequivalence batches.

The stability sections also had recurring deficiencies such as the request for further stability data to support the proposed retest or shelf life. These fell under the common deficiencies reported by SAHPRA and are discussed extensively in the recent publications [13, 18, 19]. The response cycles would be shortened as all requirements could be met with the approach of informing manufacturers of the common deficiencies identified.

7.4.8 Final adoption for registration

Once the product was finalised in the MCC process, it was sent to the administrative Unit to be collated with outcomes from the other Units before it can be registered. The median value for this stage was calculated as 482 days. This was attributed to the following:

- The initiation of evaluations was conducted at different times therefore finalisation within Units was not synchronised.
- Finalised product history packs were not sent to the administrative Units immediately upon finalisation.
- The inspections were undertaken after the P&A pre-registrations and Clinical evaluations Units completed their scientific assessments. Historically, the assessment process has been lengthy, and sites may not be GMP-compliant at the time of approval; hence, inspectors opted to perform inspections after assessments were complete. If the result was a negative GMP status, an inspection had to be rescheduled, which slowed registration, and in certain cases resulted in a rejection if the manufacturer did not meet the required GMP standards.

The following serve as potential solutions to obtain a reduced median registration time for this step:

- Sending queries simultaneously to applicants can reduce the number of unsynchronised finalisations. Units must therefore constantly discuss which applications to evaluate first. Having Units that are ahead of others in terms of evaluations would not result in registration; rather, additional personnel can be provided to the Units with the most work.
- With the synchronisation between Units executed, the finalisation of an application would be at similar times and properly monitored by the administrative Unit, now called the Health Product Authorisation (HPA) Unit.
- Inspections must be undertaken at the beginning of the process, and the status of the manufacturer must be established before scientific evaluations can be conducted.
- Increased frequency of registration meetings from six-weekly in the MCC process to weekly in the RBA process.

The last two solutions above were utilised in the BCP and RBA procedures, resulting in substantial improvements of the timeframes to 125 and 61 calendar days respectively. RBA Phase 2 study saw a reduced timeframe of 33 days since most of the applications were already finalised by the other Units.

7.4.9 Finalisation timeframe

Finalisation is the conclusion of an assessment by each respective Unit before registration. The finalisation timeline facilitates a comparison of the three processes utilised by SAHPRA between 2011 and 2022. The timeline was reported as 1470, 501, and 68 calendar days, for the MCC process, BCP process, and RBA phase 1 process respectively as depicted in Fig. 2. The median finalisation time of 73 calendar days was observed for the RBA phase 2 pilot study which consisted of a larger sample of

159 applications with a similar process as RBA phase 1. The finalisation time for the RBA process was drastically shortened, which is largely attributed to the strategic refinement, implementation of efficiencies, assessment style and ongoing monitoring of the registration process. The detailed examination of the MCC process enabled the authority to clearly identify the root causes inside the process; once these were discovered, the optimised and efficient RBA procedure was developed and piloted. The results clearly demonstrate that this procedure would reduce the backlog that has accumulated over time. It is crucial that each stage of the RBA process, as depicted in Table 1, has a precise deadline and monitoring mechanism to guarantee that these timelines are adhered to. The upscaling to 159 applications of the RBA procedure confirmed its repeatability and reproducibility with similar median timelines obtained. This robust procedure can therefore be utilised by other agencies who may have a backlog or want to optimise their registration process.

7.4.10 Registration/approval timeframe

It was determined that the median approval/registration time between 2011 and 2017 was 2092 calendar days. Relative to other regulatory authorities, such as TGA with 244 calendar days for 85 applications in 2021 and ANVISA with 795 days between 2013 and 2016, the calculated median time for the MCC process was exceptionally long. [1, 9] This approval time was recorded as 591 calendar days for the BCP but was reduced to 511 calendar days for the RBA process. The median approval time for the RBA is due to the substantial amount of time the application waited in the queue for allocation. These applications had already been resubmitted early to mid-year 2020 and were awaiting allocation until September 2021. Therefore, almost 18 months had lapsed. This was deduced from the observed calculation of the median finalisation timeline of 68 days, thus, the remaining 443 days were attributed to applications waiting in line for allocation.

7.5 Conclusion

This study identified the root causes which led to the formation of a backlog in the investigation of the MCC process. The factors were identified as inefficient processes employed, lack of monitoring and control, insufficient skilled staff for conducting the scientific assessments and limited review pathways employed. The most critical root cause was identified as the lack of monitoring and control by the authority in each step of the registration process which inevitably led to lengthy approval times. Comparison with the Brazilian authority also revealed that the claimed timeframes for the period 2011-2017 are much longer and must be substantially reduced to provide South African citizens with expedited access to medicine. The implementation of the BCP in 2019 introduced measures and resources that allowed for careful monitoring of the process. These contributed to reducing the reported

end-to-end registration timelines, but they continued to remain longer than those reported by other authorities, and the targeted timelines were not met. In addition, the authority continued to develop a backlog despite the implementation of the process; consequently, more optimisation and refinement was required to meet the reduced timelines. The RBA approach was then piloted in 2021 and 2022, and its findings were much better than those of the previous two processes. A finalisation timeline of 68 and 73 calendar days was reported for RBA Phase 1 and 2 pilot studies respectively, which is significantly shorter than the 1470 and 501 days indicated for the MCC and BCP processes. This rigorous RBA approach may also be used by regulatory agencies throughout the world to alleviate a backlog or to improve the efficiency of the existing process.

7.6 References

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CHAPTER 8

Conclusions and recommendations

The ultimate objective and current challenge for several regulatory authorities is providing expedited access to medicines for patients. The regulatory authorities' strides to safe, effective and quality-assured medicines suffer drawbacks due to a lack of built-in efficiencies during the evaluation of medicines as well as non-existing integrated systems to continuously track the status of the medicine through its life cycle (Preston C et al., 2020). Regulatory authorities are governed by basic principles such as transparency, accountability and science to facilitate access to medicine. This research study sought to explore this in two ways; the regulatory authorities promoting transparency with the relevant stakeholders in the pharmaceutical industry and developing a new regulatory pathway. Some of these concepts include the following:

- Publication of common regulatory deficiencies identified by regulatory authorities has been cited as one of the aspects that improve transparency and alert pharmaceutical companies and manufacturers to facilitate the submission of quality dossiers. This was executed based on the findings in the thesis as discussed in Chapters 2 to 5.
- Regulatory authorities have expressed an interest in exploring risk-based evaluation approaches as a strategy to be explored that can introduce a new review pathway for authorities to use (Keyter A, 2020). The results of this research as discussed in Chapter 6 support the development and implementation of the risk-based assessment (RBA) approach in scientific assessments.
- The South African Health Products Regulatory Authority (SAHPRA) reported an approval time as high as 2900 calendar days between 2014 and 2018 for New Chemical Entities and 1810 days for generics which displays slow performance for the authority. This resulted in delayed access to medicines for patients and a backlog of approximately 16 000 applications. The root causes of the formation of a backlog are clearly identified through analysis of the registration process between 2011-2022 and solutions to these are detailed in Chapter 7. This led to the development of an optimised end-to-end registration process, the RBA approach.

Promoting transparency

The regulatory review process involves the assessment of the scientific content recorded in the development process of a drug. Based on the deficiencies observed in the submission, the authority then generates queries to the applicant which should be adequately addressed. Often, the back-and-forth

communication between the authorities and the applicants is what results in delayed registration, either because the applicant did not adequately follow the guideline requirements, or the authority does not clearly communicate the queries raised. Publication of these deficiencies and clarifications for the queries, therefore, becomes paramount. The first part of this research successfully executed this fundamental principle of the regulatory authority. The common deficiencies from the regional, Active Pharmaceutical Ingredient (API), Finished Pharmaceutical Product (FPP) and Bioequivalence study sections of dossiers submitted to SAHPRA were qualitatively and quantitatively investigated and obtained. The results were published and will be of benefit to pharmaceutical companies, manufacturers and clinical research organisations when submitting dossiers to regulatory authorities. This will inevitably reduce the registration turnaround times.

New regulatory review pathway

The results obtained from the RBA approach include attaining and optimising the review and response targets for each stage of the registration process, which was not clearly outlined in the previous Medicine Control Council (MCC) process. To ensure that deadlines are respected by evaluators, these strict review and response targets would need to be adhered to and adequately monitored. In 2019, SAHPRA benchmarked approval times of 275 days for NCEs and 180 days for generics (SAHPRA, 2020; Low, 2018). However, this could not be achieved and a median approval time of 591 calendar days is reported between 2019-2021 in the Backlog Clearance Project (BCP). With the implementation of the RBA pathway, these targets would be achieved successfully since a finalisation time of only 68 calendar days and 73 calendar days was achieved from the two RBA pilot studies conducted in 2021 and 2022 respectively.

RECOMMENDATIONS

The following are further recommendations the authority could utilise to optimise efficiencies in the registration process.

The risk-based assessment approach

Chapter 6 provides an in-depth discussion on the development and piloting of the RBA approach within SAHPRA for adoption. Based on the reported results, it is recommended that the authority adopts this review pathway to alleviate the backlog that has already been created within the Business-as-usual (BAU) section within SAHPRA. The RBA approach can also be utilised by any regulatory agency experiencing a backlog and receiving a large influx of generic medicines for registration. It is critical for this review pathway to be adopted as an end-to-end registration process as proposed together with

the peer review mechanism utilised in the pilot studies for the reproducibility of the outcomes. The importance of the peer review mechanism is detailed below.

Peer review meetings

It should be noted that the peer review meetings were crucial to the RBA process and should be considered for implementation by SAHPRA. The meetings served as a cornerstone of the process, as this was the step where evaluator alignment in terms of the review criteria and methodology was fine-tuned. These sessions also played an important role in facilitating thorough scientific debate with regard to the queries raised or not raised by the primary reviewer, based on the risk-apportioning to the product in question. The approach required the peer reviewers to apply analytical thinking and research skills to determine the relevance of the initial queries based on the data provided and the type of application, as well as its risk to the end user. The scientific discussions conducted during peer review were essential; during these sessions, the evaluators performed an in-depth peer review by conducting further extensive research with respect to the relevance of the deficiencies raised by the primary reviewer. There was a benefit in soliciting multiple experienced reviewers to provide peer reviewer input, as it ensured a thorough review of all critical quality attributes, which, in turn, offered assurance that only products of quality, safety and efficacy were registered.

Creation of a centralised database

The evaluation of the quality and bioequivalence sections involves aspects of the API being submitted by an API manufacturer and aspects of the final product submitted by an FPP manufacturer and bioequivalence aspects submitted by a Clinical research organisation (CRO). It has been witnessed that different applications will consist of the same API manufacturer, FPP manufacturer and CRO. If this is not detected before evaluation or allocation, duplication is guaranteed. SAHPRA, therefore, needs a central database detailing amongst others the details mentioned above for each product (including registered products) so as to identify and avoid any duplication of efforts within the same or different Units in the organisation. All new, pending and registered (including variations) applications should be listed in the database. The database can be synchronised with the comprehensive tracker and continuously monitored and controlled by the administrative Unit, Health Products Authorisation (HPA), since all applications are received in the Unit. The use of an electronic system should be implemented by SAHPRA to further maximise efficiency. Lack of tracking or monitoring of applications remained one of the main root causes of the formation of the backlog. The application of management systems for tracking and monitoring applications will result in the monitoring of timelines and workflow for the end-to-end registration process.

Evaluator experience and qualification

The scientific data generated over numerous years during the development of the technology is provided to regulatory authorities for the approval of medicines and covers a variety of scientific areas. The expertise in those disciplines is therefore crucial for regulatory authorities to employ in order to ensure adequate assessment of the sections the experts specialise in. These evaluations necessitate individuals with research capabilities, analytical thinking skills, and quality control analysis skills to carry out the evaluation responsibilities. Committees are used by the European Medications Agency (EMA) to assess medicines. There are numerous Committees involved, including the Committee for medicinal products for Human use (CHMP) responsible for evaluating medicinal products. Members of the Committee are responsible for conducting scientific evaluations and upon completion of the assessments, the peer review meeting is performed, and all Committee members participate in the peer review process. A detailed analysis of curriculum vitae reveals that the members have advanced degrees in pharmaceutics, chemistry and medicine, including masters and doctoral degrees (EMA, 2022). The USFDA, Centre for Drug Evaluation (CDER) Department further indicates that it primarily recruits Chemists, Pharmacists, Epidemiologists, and Pharmacologists for assessment execution (USFDA, 2022) with the necessary experience and set skills as described above. In addition, research shows that the authors of the publications from various regulatory authorities reported in the study have the aforementioned degrees and therefore the required skills which confirm that most authorities have been employing this principle (Patel P et al., 2020; Stahl M et al., 2014; Sun CI et al., 2014; Borg JJ et al., 2009; Liberti L et al., 2020). With the above-recommended enhanced assessments and peer review procedure, research and analytical thinking skills, as well as considerable knowledge of scientific assessments, are essential. Therefore, it is imperative that SAHPRA consider employing evaluators with the same skill set in order to facilitate quality and enhanced evaluation.

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RESPONSE TO JOURNAL REVIEWERS

Chapter 2

Common deficiencies witnessed in Module 1 assessed by the Pharmaceutical Evaluation and Management (PEM) pre-registration Unit within the South African Health Products Regulatory Authority (SAHPRA)

Lerato Moeti[1,2], Madira Litedu[1], Jacques Joubert[2]

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Rebuttal letter to the South African Pharmaceutical Journal

1. **Response round 1**
2. **Response round 2**

Response round 1

Response to Reviewer B

Reviewer B:

Thank you for submitting the manuscript for review. The manuscript is interesting in that it highlights notable deficiencies in applications at SAHPRA during two time periods.

Response: Thank you for the commendation.

Language

Language editing can be done to help ensure ambiguity is avoided in the document, particularly when sentences become long or overloaded with a diversity of sectional information.

Response: We have reworked the manuscript considerably and improved the language. The flow has also been improved in order to improve the readability of the paper

Initial literature review

The initial review of document submissions provides good context, but becomes verbose and leads to a lower transition to the discussion of results.

Response: The whole manuscript has been proofread and refined to improve on the impact of the results, discussion and conclusion sections.

Methods

Some elaboration on how sub-sections of data collection was done and analysed, particularly since qualitative analyses was mentioned and thus infers combining of errors made during the application might be subject to researcher compilation.

Response: Please note that the following has been included in the methods section to expand on the question, included in line 100-102:

"The data collection involved extraction of the specific query from the letter and collating according to the section or sub-section in Microsoft Excel ® 2016 Worksheets."

Results and discussion

Contextualisation and discussion of the two different time periods, which may be confounded by the types of APIs that were within the selected samples. Inclusion of sample size of stratified errors will help contextualise the severity of these errors (apart from percentage).

Response: The Module 1 requirements are not dependent on the type of API of an application. The requirements are essentially the same for all products except for only one section, the labelling section, Module 1.3. The requirements differ slightly for sterile and non-sterile applications in accordance to the guidelines, scientific base and regulations to the medicines and related substance Act 101.

In the methods section, lines 93-94, it has been stated that a sample of 325 non-sterile applications were selected while a sample of 244 sterile applications were selected for the 2011-2017 study.

For the 2021 study, it was stated in lines 121-122 that 21 applications were sterile while 41 were non-sterile. This provides a direct proportionality of the two sets of samples with regard to the sterility percentage of the applications thus eliminating any error and bias in the comparison.

The author self-citations that may misrepresent the importance of individual articles, skew the calculation of journal impact factors and bias perceptions of the importance of a publication.

The reviewer's argument that self-citations may misrepresent the importance of individual articles, skew the calculation of journal impact factors, and bias perceptions of the importance of a publication is valid to some extent. However, there are several reasons why we believe that our self-citations are useful and legitimate.

Firstly, they provide context for our new publication by referencing our earlier work, which helps readers understand the development of our ideas over time. This will also attract the attention of readers to the first five papers in this series of six papers that build on one another. Secondly, our self-citations establish our credibility and expertise in the field, demonstrating our knowledge and experience. This is particularly important for us as early- to mid-career researchers who may not have many external citations yet. Lastly, our self-citations promote interdisciplinary research by connecting different fields and areas of study, building bridges between different research communities and fostering collaboration. While self-citations may potentially be used to skew impact factors, they can also be a legitimate and useful practice when used judiciously and appropriately, as we have done in our work.

Response to reviewer C

Reviewer C:

This manuscript claim to report common deficiencies in applications submitted to SAHPRA under the regional section of the CTD (Module 1). This falls within the scope of the SAPJ as to continuous professional development of pharmacists and related professions within the regulatory domain. Studies like these are pertinent to ensuring the quality of medicine applications to SAHPRA and ultimately accessibility to affordable medicines within the healthcare sector. The authors are commended for their massive undertaking, however the primary study report observations made between 2011-2017 on deficiencies under the former medicine regulatory authority the Medicines Control Council prior to the inception of SAHPRA in 2018. The applications evaluated during 2021 are relevant to common deficiencies currently experienced by the authority.

Response: The commendation is highly appreciated.

It should be noted that the 2011-2017 still hold significant relevance as the requirements have not changed in the Module 1 section since 2011 to date. The only change lies in the re-organisation of the Professional Information (PI) to align it with the European structure, the content, however, still

remains the same. Nonetheless, it was essential to conduct the 2021 study in order to ascertain and confirm that the assessment standards are still similar.

The authors could consider elaborating on the similarity of findings (using descriptive statistics) between the two authorities regardless of the new SAHPRA structure, legislative environment and published guidelines.

Response: The requirements on Module 1 from 2011 to date, have remained the same. This statement has been included in lines 125-126 and 249-250.

In addition, by the author's own report, the study investigated "common deficiencies identified in the assessments conducted by the PEM pre-registration Unit". The title of the article could therefore be misconstrued.

Response: This is well noted and correct since there are other Unit who also assess certain parts of Module 1. The title has been expanded to emphasise that the common deficiencies reported are from the PEM pre-registration Unit. The title of the manuscript has been revised to:

Common deficiencies witnessed in Module 1 assessed by the Pharmaceutical Evaluation and Management (PEM) within the South African Health Products Regulatory Authority (SAHPRA)

Key Issues that the authors should address include:

- In lines 10-12 the authors incorrectly state that SAHPRA "had formed a backlog of 16000 applications", whereas the new regulatory body inherited this backlog in 2018 (Keyter *et al.* 2018*)*.

Response: Well noted. This sentence has been amended accordingly to state that the backlog was inherited.

- Authors should clarify the reasoning behind their inclusion of information on previous submission formats under the MCC In lines 26-60 when the study aim is to provide information on the common deficiencies in module 1 of the CTD.

Response: The intent was to provide an overview and evolution of the previous formats utilised by the authority over the years. However, the comment is noted, comprehensive detailing of the formats previously used has been replaced with a few sentences, line 25 -28, to state that there were different formats used before the CTD.

- Caution should be exercised in referring to the MCC and SAHPRA interchangeably (Keyter *et al.* 2018*)*.

Response: Noted. To exercise this distinction, occurrence made before February 2018 are by MCC and those implemented after the date, SAHPRA, has been stated.

- In lines 17-19 the citation of reference 6 should be reconsidered or clarified as this FDA perspective reports common deficiencies in Abbreviated New Drug Applications: Drug

Substance, whereas the author's study report deficiencies in regional module 1 and it may not be pertinent to the matter under consideration.

Response: Noted, the specific referenced paper was the first of three series articles detailing common deficiencies in the dossier submissions by the USFDA. In the same article, although it reports on common deficiencies in the API, it specifically details on how transparency of sharing deficiencies with the pharmaceutical industry has improved in the overall quality of the submissions.

"Despite OGD's efforts, the number of amendments submitted in response to FDA's deficiency letters, have still been staggering. With this as prologue, a series of articles are forthcoming in an effort to be more transparent and to assist sponsors to submit applications with adequate justification for drug substance and drug product (DS and DP) specifications, in-process controls, choice of formulation, product design, and manufacturing processes. Our experience shows that having justification in the original submission reduces the number of deficiencies and provides assurance to the agency in the sponsors' ability to manufacture high quality drug products. These articles will attempt to clarify the intent and criticality of some of the common deficiencies cited throughout the Chemistry, Manufacturing, and Controls (CMC) portion of ANDA submissions."

The comment highlighted in blue is what is referred to in the manuscript, it is stated that based on the authority's experience, transparency of common deficiencies reduces the number of deficiencies from the original submission. It should be noted that there have been no reports on common deficiencies reported by other regulatory authorities on the regional section, Module 1, which makes this study novel hence no similar reference on specifically Module 1 of the CTD.

Minor Issues include

- In lines 3-5 the authors cite reference 2 that speaks to small states not applicable to South African healthcare economics as a developing country.

Response: Noted, by definition, South Africa does not fall under small states in terms of the definition provided by population quantity, however, the large array of challenges faced in those states are identical to what South Africa and most third world countries are currently experiencing in their regulatory systems. The sentence has therefore been rephrased accordingly in line 5.

Comments in the manuscript as track changes:

Under which formats were these captured to organise them? Quantitatively?

The experienced technical assessors who have a thorough knowledge of scientific assessments and the layout of Module 1 of the CTD manually compiled and quantified the deficiencies from the 569 query letters. The procedure involved extracting a particular query and placing it in the appropriate section or sub-section in Microsoft Excel ® 2016 Worksheets. The frequency value is then increased as the identical query is observed in other query letters.

From a data visualisation perspective, avoid three-dimensional transformations as it compromises readability.

How were individual groupings determined?

Figure 1 and 2 have been revised to remove three-dimensional transformations.

The grouping was based on prevalent sub-sections as shown in Table 1. The module 1 format is already grouped according to sections and sub-sections as illustrated in Table 1.

Is it possible difference arise due to API identity?

Please see the response below which is also included in above to respond to reviewer B:

The Module 1 requirements are not dependent on the type of API of an application. The requirements are essentially the same for all products except for only one section, the labelling section, Module 1.3. The requirements differ slightly for sterile and non-sterile applications in accordance to the guidelines, scientific base and regulations to the medicines and related substance Act 101.

In the methods section, lines 93-94, it has been stated that a sample of 325 non-sterile applications were selected while a sample of 244 sterile applications were selected for the 2011-2017 study.

For the 2021 study, it was stated in lines 121-122 that 21 applications were sterile while 41 were non-sterile. This provides a direct proportionality of the two sets of samples with regard to the sterility percentage of the applications thus eliminating any error and bias in the comparison.

Please include total number for the number of dockets analysed.

This is included in line 119-120 as 52 applications.

Structure of sentence, line 163

The sentence has been revised as follows:

The highest prevalent deficiency across the 2011–2017 study, the temperature for the storage condition, is crucial and should be correctly stated for the end-user in accordance with the stability data submitted. Located in line 163-165

Context needed here, line 197

When applicants respond to query, an amendment schedule is utilised as a comparison template of the information originally submitted and the changes effected after queries have been sent by the authority. When applicants respond to these queries using the amendment schedule, they would indicate that information has been submitted in the relevant section of the dossier, however, upon assessment, the required documentation would not be located in the dossier as stated by the applicant, this results in queries being sent to the applicant which delays the finalisation process further. The sentence has therefore been rephrased as follows:

The other 62% and 32% respectively for both studies were on applicants indicating that the information has been included in the amendment schedule. However, the documentation as stated in the amendment schedule could not be located in the dossier upon evaluation. This prompted another round of queries, which ultimately caused the product's finalisation to be further delayed. Located in lines 196-200.

Response round 2

Response to second review by reviewer B:

Align with amended title and method section

Amended the title accordingly by including the word “pre-registration” to align with the method section as well.

SAHPRA prefers the word medicine

Agree. Change accepted on line 31.

As per previous recommendation clarify sections assessed for common deficiencies

The amendment made by the reviewer is accepted. The sentence on line 52-54 now reads as:

“The current study focuses mostly on the common deficiencies found by SAHPRA in specific sections of Module 1 of the regional section as assessed by the PEM Pre-registration Unit.”

As per previous recommendation to distinguish between the two judicially different medicine regulatory authorities in line with Amendment of the Act published.

The amendment made by the reviewer is accepted. The sentence on line 55-57 is revised to:

“From its inception in 1964 until the year 2002, South African authority (previously known as the Medicines Control Council (MCC))…”

Align methods with the study aim and what is in the previous section

Agree with the amendment. The sentence on line 126-127 is revised to:

“The common deficiencies observed in specific sections of Module 1, as assessed by the PEM pre-registration Unit, were collected from applications finalised between 2011-2017.”

In addition, check that both figures uploaded onto the journal page is formatted the same.

Noted, the figures have been formatted the same.

Kindly reword for eligibility and better syntax

Sentence 256-259 revised as follows:

With the reliance approach adopted by SAHPRA since 2019, no assessments are necessary; only verification with reports from the other regulatory bodies that SAHPRA is aligned with is required to establish that the dossiers/products are the same.

RESPONSE TO JOURNAL REVIEWERS

Chapter 3

Common deficiencies found in the Active Pharmaceutical Ingredient (API) section of non-sterile generic products submitted for registration by SAHPRA

Lerato Moeti[1,2], Madira Litedu[1], Jacques Joubert[2]

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[2] *School of Pharmacy, University of the Western Cape, Cape Town, South Africa.*

Rebuttal letter to the Journal of Therapeutic Innovation and Regulatory Science

Response to Reviewers and Editor

Reviewer #2:

The title of the paper is not appropriate. Job of the regulators is to identify the deficiencies in the submission and communicate the same to sponsors. Why should and will have any perspective on deficiencies?

We have amended the title as per the suggestion of the reviewer.

The objective of the paper is good, but everything else is bad. The language is poor and confusing.

We have reworked the manuscript considerably and improved the language. The flow has also been improved in order to improve the readability of the paper.

Some very basic questions on the manuscript are:

1. What is the sampling methodology used and why?

A detailed description regarding the sampling methodology has now been included in the Methods section.

2. Why were the applications finalised in 2011-2017 were evaluated from Jan - May 2020? Were they finalised with deficiencies?

The evaluations from Jan to May 2020 were those of new applications containing information of the restricted part of the dossier. These new applications were evaluated in order to observe if there was any correlation between the applications evaluated and finalised between 2011 to 2017 with those observed in the submissions containing the restricted part in 2020. Similarities were observed and discussed in the manuscript.

3. How can increasing the turnaround time for registration be good as mentioned on last but one line of page1/29?

Corrected to “decreasing” the turn-around time. Thank you for observing this error.

Editor

I have read the paper and tend to agree in principle with the 2nd reviewer. the 1st reviewer declined to comment while recommending acceptance of the paper. i would like to suggest that you revise the paper if you would like to resubmit. you may wish to put the equations that define how you selected subjects into an appendix since this kind of material exists in statistics books devoted to sampling. the main body of the paper should provide intuition regarding the sampling strategy used.

The equations have been included in the supplementary information file and the main body of the paper has been revised to provide intuition regarding the sampling strategy used.

RESPONSE TO JOURNAL REVIEWERS

Chapter 4

Common deficiencies found in generic Finished Pharmaceutical Products (FPPs) applications submitted for registration by the South African Health Products Regulatory Authority (SAHPRA)

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Response to the Journal of Pharmaceutical Policy and Practice

1. **Response round 1**
2. **Response round 2**

Response round 1

Reviewer #1 Comments

ABSTRACT

Comment 1

The sampling error that was used in this case is not presented. There is no guided by the selection of a particular drug that fell into the sample within the therapeutic group (random or some inclusion/exclusion criteria were used).

Response to reviewer:

The sampling error that was used has been included in the abstract. A 95 % confidence level was used resulting in a ±5% sampling error which is highly used in a number of statistical calculations and found acceptable.

The selection process has now been described in the abstract. The selection of the products were according to the therapeutic category using the multi-stage sampling method called stratified-systematic sampling. Stratified sampling involves dividing the population according to one variable which in this case was the therapeutic category. Within the different strata, systematic sampling is employed ensuring that each group is well represented. Systematic samples provide each element with an equal chance of being selected within the strata hence the calculation of the k^{th} term which is attained from dividing the population size with the calculated sample size.

This resulted in the selection of 325 applications for non-sterile products and 244 applications for sterile products

Comment 2

Reference to specific modules in the table - if the reader is limited only to abstract data, then the numbers of the modules only interfere with the perception of information, it is better to leave only characteristics.

Response to reviewer:

Well noted. The modules of the Common Technical Document (CTD) have been omitted in the abstract and the characteristics of section or subsection used.

BACKGROUND

Comment 1

For a full-fledged picture, there is not enough information about the number of approved files/requiring revision/rejected until the moment of study, e. That is, the real need for systematizing data. Unless, of course, they are in thematic literature.

Response to reviewer:

SAHPRA receiving approximately 1200 applications annually, by 2016, a backlog of 7902 applications was accumulated. Within the period 2010-2015 only 3779 application were registered or rejected. From the backlog of applications, 4397 applications had not yet been allocated for evaluation while 3505

were in-process in the pre-registration phase. This shows the urgent need to employ measures such as collecting and analysing the quality review issues, which will serve as a reference and a communication medium for applicants to understand the regulatory requirements, thereby accelerating approval process by the authority.

In order to identify general trends in the quality deficiencies for SAHPRA, we analysed all deficiencies from products finalised during the P&A Committee meetings over a 7-year period (2011-2017). The 3148 applications finalised were considered a large sample to use for the study therefore a statistical sampling approach was employed to obtain a representative sample.

METHOD

Comment 1

The principle of combining into homogeneous groups - "starts" is not specified. Therefore, this section is better to transfer here from the results section

Response to reviewer:

The comment is noted. The discussion on sample selection has been moved the methods section as proposed.

RESULTS (non-sterile)

Comment 1 (now moved to methods as per comment 1 above)

Equation 4 with N as the population size and n as the calculated sample size. - it is need to paraphrase.

Response to reviewer:

The definition of Equation 4 has been expanded in order to provide clarity. The kth term serves as a constant value used for systematic sampling and is calculated as illustrated in Equation 4 with N* as the population size and n* as the calculated sample size. A systematic sampling method would select the first term and thereafter the kth term on the list afterwards until the required sample has been selected in the whole population. The interval between the selected elements would then be the population size/ calculated sample size. The calculated k^{th} term therefore gave the value 2.73. This therefore makes the value three the k^{th} term for the systematic sampling i.e. in all strata.

Comment 2

When listing non-sterile dosage forms, only oral preparations are indicated. Were the soft and liquid dosage forms (creams, gels, suppositories, solutions) analyzed? If not analyzed, this should be described.

Response to reviewer:

These dosage forms were analyzed but fall under the “other” category since the amounts were small on the sample. This has been expanded and all the non-sterile dosage forms have been included. The dosage forms which fall under the “other” category included oral solutions, creams, nasal spray, immediate release granules, gels, implants, ointments, suppositories, lozenges and nose drops.

Comment 3

The study did not analyze all sterile dosage forms. Or do the authors attribute the remaining ones to "minority of other comprising of the remaining"? You must add an explanation. It is better to transfer the paragraph listing dosage forms before the Table 4.

Response to reviewer:

Yes the other dosage forms were listed were a minority and listed as other. This explanation has been included in the manuscript as advised. These dosage forms were sterile suspensions and chelating agents.

Regarding the transfer of the paragraph, this is noted. The paragraph on the description of dosage forms present in the sample has been moved to the proposed section.

Comment 4

Figure 2, 3, 4 - sign full names, not codes, at least for the most common ones. Otherwise, you must constantly return to the table and text, which is not convenient for the reader.

Response to reviewer:

Well noted. The descriptions have been added in the figure for figure 2 and included as footnotes for Figures 3 and 4 to avoid the figures being overpopulated with information.

Comment 5

The tables contain many abbreviations without decryption.

Response to reviewer:

This is noted and has been amended accordingly. Each abbreviation has been worded if used for the first time in the text.

RESULTS (sterile)

Comment 1

Equation 4 with N as the population size and n as the calculated sample size. -it is need to paraphrase.

Response to reviewer:

The definition of Equation 4 has been expanded in order to provide clarity. The kth term serves as a constant value used for systematic sampling and is calculated as illustrated in Equation 4 with N* as the population size and n* as the calculated sample size. A systematic sampling method would select the first term and thereafter the kth term on the list afterwards until the required sample has been selected in the whole population. The interval between the selected elements would then be the population size/ calculated sample size. The calculated kth term therefore gave the value 2.73. This therefore makes the value three the kth term for the systematic sampling i.e. in all strata.

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Figure 2, 3, 4 - sign full names, not codes, at least for the most common ones. Otherwise, you must constantly return to the table and text, which is not convenient for the reader.

Response to reviewer:

Well noted. The descriptions have been added in the figure for figure 2 and as footnotes of the Figure for Figures 3 and 4 to avoid the figures being overpopulated with information.

Comment 5

The tables contain many abbreviations without decryption.

Response to reviewer:

This is noted and has been amended accordingly. Each abbreviation has been worded if used for the first time in the text.

Response round 2

Comments from Reviewer #2:

Overview:

An interesting and important study. Entire paper needs to refocus on section 3.2.P, not whole CTD. And it is hard when everything is referred by a module number. To improve clarity, use module numbers along with titles of those modules, not any one in isolation.

Response: This is well noted. The paper covers the FPP section of the CTD and not the entire CTD, therefore this has been made explicit in the abstract and relevant sections by stating that the deficiencies are for the FPP section of the CTD.

The manuscript has also been modified in areas where the module number is indicated to be expanded to include the description of the module, section or subsection. This could not be attained in the tables, however a footnote has been included to provide the descriptions.

Abstract:

1. The manuscripts' abstract is well written. But can be modified further avoiding some detailed descriptions which could be given in background and method sections.

Response: The abstract has been modified with certain aspects that could be included in the methods and background removed and stated in those sections. Some aspects were already repeated in the background and methods sections therefore they were only omitted in the abstract.

Title - 2. Suggested to include the word Documents OR applications in the title.

Response: We would like to thank the reviewer for the valuable recommendation, the title has been expanded to include the word “applications” for better clarity.

Background

3. Some abbreviated terms have not been defined at the first encounter. (Eg. WHOPQTm)

Response: This is well noted. The whole manuscript was carefully perused to define all abbreviations indicated at first encounter.

4. This study is exclusive to section 3.2.P. of CTD. Better to modify the last paragraph of Background section to mention the reasons as to why your study is focused to section 3.2.P. of CTD.

Response: The last paragraph has been expanded to include reasons why the investigation on the common deficiencies of the FPP section is conducted. Please see the amended last paragraph of the background section.

Method

5. Equation 2, please define n.

Response: The variable n, has been defined in the manuscript. n is defined as the adjusted sample size calculated for population sizes that are less than 3000 in order to adjust the sample size slightly.

6. Table 2 is given before Table 1. When this is corrected, please check the whole manuscript to alter the places referring these two tables

Response: We would like to apologise for this oversight, Table 2 has been amended accordingly as Table 1 and Table 1 as table 2. Thereafter, the entire manuscript was revised to ensure the correct references are made to the respective tables.

7. In the table 2 different strata are tabulate with a number in the first column. From where are these numbers coming? It is better to include numbers separately as the first column.

Response: The strata are arranged in terms of therapeutic category of the applications. Thus, the numbers in the first column of the new Table 1 are the number of finalised applications within that therapeutic category for sterile products. For example, there were 138 applications finalised with a pharmacological classification, **Central nervous system depressants.** The first and second rows of the table has been amended accordingly for better understanding. This statement has also been incorporated in the manuscript. We hope this provides the required clarity.

8. Page 12 of PDF line 26-31 says about the parts of section of 3.2.P and followed by table 1. Is this classification of section of 3.2.P is common to both sterile and non-sterile products? If so better to mention it. Because later the results and discussion links with this table.

Response: Well noted. A sentence has been included before the new Table 2 to indicate that the table is applicable for all medicines including those that underwent sterile manufacture and those that did not.

Results

9. PDF Page 14, line 16 figure 2 description should be better to reword and focus to section 3.2.P. of the CTD.

Response: The recommendation is noted. The description of figure 2 was amended to state that the deficiencies are based on the FPP section of the CTD.

10. Figure 2 caption should also need to be focused to section 3.2.P. The present way of writing refers to the whole CTD.

Response: The caption for figure 2 has been modified accordingly to state that the deficiencies are for the FPP section.

11. Figure 2 better to mention module numbers of each section within brackets to facilitate easy reading.

Response: Figure 2 has been amended as per the recommendations, the module numbers have been included within brackets to facilitate easy reading.

12. PDF Page 14, line 25, explains the details about table 3, this is not clear. First, refocus this to section 3.2.P sections and subsections of CTD not the whole CTD. Second, table 3 is giving 2 percentages. What is referred to Overall % here. (better to arrange this as given in table 4)

Response: The sentence has been amended accordingly as per the recommendation, the Table 3 has been modified to be presented similar to Table 4 with only one column on percentage per section. The description has also been expanded to include an example statement for further clarity in the sentence described above.

The Overall % was the percentage of each deficiency per overall 3.2.P sections, however that column has now been removed.

13. It is suggested to subdivide Table 3 according to main sections of CTD 3.2.P. And name the subdivisions with module number as well as the title of its content to enhance the clarity.

Response: Noted. Table 3 has been amended as prescribed in order to enhance the clarity of the data. The main sections and subsection titles have been included.

14. There is a note under the Table 3. It has no reference made to the table.

Response: The note has been removed.

15. PDF Page 19, line 24-33, how these percentages are coming from table 3 is not clear.

Response: Table 3 has been amended to include the percentages prescribed in figure 3 in order to provide the link. The percentages and figure 3 have been amended where necessary in order to correlate with Table 3.

16. Figure 3, bar chart - It is not clear how the % of deficiencies are taken from Table 3. Table 3 should be formatted to show these values.

Response: Figure 3 and Table 3 have been amended accordingly as recommended.

17. Figure 3 caption too should be reword to focus on CTD section 3.2.P.

Response: Noted, the caption has been amended accordingly to include the focus on the 3.2.P. section.

18. Footnote of figure 3 defines module numbers in a random order. Any special reason. Better to start from 3.2.P.1

Response: The footnotes have been amended to show the module numbers and descriptions in chronological order as per the recommendation

19. PDF Page 20, line 30-32, "Therefore, the deficiencies for sterile products are over and above those listed under Table 2 for non-sterile products depending on their applicability to the dosage form" what does this mean? Better to write in a meaningful manner.

Response: To provide clarity on what the statement means, a few examples are provided, for instance, The deficiency in 3.2.P.1 in Table 4 is only applicable for sterile products but not non-sterile products, the same is true for all the deficiencies in Table 4. However, some of the deficiencies outlined in Table 3 would be applicable for sterile products as well, over and above those in table 4 but these were not qualitatively described in the table to avoid duplication but quantitatively included as “other” due to the low frequency observed.

The statement is to therefore alert the manufacturers that depending on the dosage form, other deficiencies listed under non-steriles tables that would be applicable for sterile products as a requirement to the 3.2.P section according to ICH would be applicable. For example the query “state the polymorphic form of the API(s) used” would also be a requirement for a sterile product if not included in the sterile application.

20. Table 4 title should focus on section 3.2.P not the whole CTD

21. Suggested to modify as recommended for Table 3.

Response: The recommendation as stipulated for Table 3 have been incorporated in Table 4 which includes the title, the inclusion of module titles and subsection titles.

22. Table 4, foot note says; "Note that there are other deficiencies applicable to sterile products already included in Table 3, these were not included in this table to avoid duplication." But table 3 is for non-sterile products. How did you include sterile product documentation deficiencies in Table 3.

Response: This query is similar to comment 19 above and a detailed has response has been provided to give clarity.

23. If you analyzed only sterile product specific details for sterile product, generalization made in PDF page 23 line 42-47 may not be true.

Response: As per the clarification provided above, the generalization would be true as the study was on all the deficiencies obtained from the sampled applications for sterile products, the deficiencies common to non-steriles were quantified, however under other due to the low frequency. We note where the confusion arises and have therefore amended the statements adequately. The intent was to alert manufacturers of sterile applications to not only focus on Table 4 as they may be relevant deficiencies in Table 3, however with a lower deficiency frequency.

24. Figure 4 footnote, in random order. Change as suggested for Figure 3

Response: The footnotes are in a sequence of the sections and subsections with the highest deficiencies to the lowest deficiencies. Only the highest eight were included in the footnote.

Discussion:

25. Subsections in the discussion-it will enhance the clarity if the titles of the sections can be put together with the module numbers.

Response: Noted, all the module numbers have been expanded to state the title of the section or subsection to enhance clarity.

26. PDF page 24, line 44-50 better to mention the section titles with module numbers. Suggested to modify the whole discussion to improve easy reading.

Response: This suggestion has been applied onto the whole manuscript to improve easy reading for the reader.

27. Table 6, foot note asked to see figure 4. Seems like it is not necessary

Response: Noted, reference made to figure 4 has been removed.

Additional

28. Suggest adding limitations of the study and future directions

Response: These have been included as a section after the conclusions.

Conclusion

29. The last sentence of the conclusion does not match with the aims of the study. Reword the focus to show that the deficiencies identified in documentation among these authorities.

Response: Noted, the last sentence has been re-worded accordingly, the intent is to highlight that the comparison of scientific assessments by SAHPRA is similar to those of other international regulatory authorities confirming that the quality and safety of medicines is not compromised.

Citations:

30. Citations were added after finishing the sentence. It should come before the full stop.

Response: Noted and thank you. This has been amended accordingly in the whole manuscript.

Suggested to recheck the whole paper before publishing. Further citation style is different to that of the journal style.

Response: Noted, this has been corrected on the whole manuscript. The citation style has also been corrected to the required journal style.

RESPONSE TO JOURNAL REVIEWERS

Chapter 5

Bioequivalence common deficiencies in generic products submitted for registration to the South African Health Products Regulatory Authority (SAHPRA)

Lerato Moeti[1,2], Madira Litedu[1], Jacques Joubert[2]

[1] South African Health Products Regulatory Authority (SAHPRA), Pretoria, South Africa

[2] School of Pharmacy, University of the Western Cape, Cape Town, South Africa.

Response to the Journal of Pharmaceutical Policy and Practice

3. **Response round 1**
4. **Response round 2**

Response round 1

Response to comments by Reviewer #1 and Reviewer #2

Reviewer #1

1. The title gives a short but accurate description of the research project and conveys the core focus of the study to the reader

Merits of the manuscript:

1. This is a very relevant project and will make a huge contribution to the health of the people in SA . The results will allow accelerated access to medicines for patients, will assist assessors to improve on their bioequivalence assessments and will reduce the turnaround product registration timelines for SAHPRA

2. The authors revealed a sound understanding of the nature and purpose of their proposed investigation and their reasons for choosing it are clearly and precisely laid out.

3. The methodology is explained in a clear and logical way.

Well noted, this is greatly appreciated.

2. Technical presentation

There are a number of typographical and grammatical errors which need to be corrected. There are some inconsistencies wrt spelling, the format of references etc. that need to be addressed.

Recommendations

P 2 line 35 325 (Fig 2a) , 300 masters applications (Fig 2b) (For clarity figure 2 should be divided into Fig 2a and Fig 2b)

Well noted, this has been amended as promised and reference to Figure 2a and 2b made on the text.

P2 line 47 analysis (10 %) (Fig 3)

Noted, the reference to Figure 3 has been included.

P 3 line 56 please clarify if it is one or two separate units.

This would be one Unit, the P&A pre-registration Unit.

P 4 line 18 required

The word "d" has been included as proposed.

P 4 line 35 please clarify the following: "The international Council or Conference (see reference 11)

The term has been corrected accordingly under references, ICH stands for The international Council for Harmonisation.

P 4 line 57 prequalification vs pre-qualification See references 15 and 32. Consistency is needed wrt spelling.
Well noted. The term “pre-qualification” has been amended accordingly in reference 32.

P 5 6 line 49, 57 non- sterile vs non sterile fig 2b and table 1

Figure 2a has been included for reference to 325 non-sterile applications in lines 49 and 57. The reference to Figure 2b was also been included in line 61.

P 6 line 2 325 non-sterile (Fig 2a) Consistency is needed wrt spelling.

Corrected as requested.

P 6 line 7 0ne, two and five (300) (Fig 2b)

Corrected as proposed.

P 6 line 45 are illustrated in Figure 1 ???? Figure 3. Please ensure that all data discussed in the text concur with the figures and tables (Numbers , percentages etc).

Noted, this sentence has been expanded to include Fig 3 as well, however reference to Fig 1 is correct as it also highlights the nine categories investigated

P 7 line 7 immediate-release, line 8 extended-release , line 16/17 immediate release, line 19 extended release-tablets. Consistency is needed wrt spelling

Well noted, the words have been corrected to ensure consistency

P 7 line 58 *in vivo* Words and abbreviations derived from Latin should be in italics

Noted and corrected as proposed. Thank you

P 9 Line 7 while III and IV have low permeability.
The sentence has been amended to include low permeability.

P 9 line 28 single dose vs line 42 single-dose. Consistency is needed wrt spelling

Corrected as requested for consistency.

P 11 line 33 remove comma after steep dose

Noted this has been removed.

Page 11 line 51 leave a space between laboratories, and all data

Noted, this has been amended.

P 11 line 54 42 % ???? 44 % Please ensure that all data discussed in the text concur with the figures and tables (Numbers , percentages etc).

Agreed, the corrected percentage has been included as 44 % and all numbers, figures and percentages checked to confirm accuracy.

P 12 line 55 impact on the quality

Noted, the sentence has been amended as requested.

P 13 line 33 the two most common deficiencies related to dissolution are ----

The sentence has been amended as proposed.

P 13 line 38 The USFDA

The sentence has been amended as proposed.

Page 13 line 42 *in vitro* Words and abbreviations derived from Latin should be in italics

Noted, this has been corrected throughout the manuscript.

P 14 line 7 the USFDA

The sentence has been amended accordingly.

P 14 line 18 and an unacceptable

The sentence has been amended to include the proposed word.

References

The manuscript is full of inconsistencies mainly with regard to the way in which the names of authors and journal titles are presented.

No 4. Accessed 16 June 2021

The word Accessed has been included

No 13. U.S is abbreviated but that is not the case for references no 6 and no 12

Reference 13 has been corrected.

No 8, 22 *In vivo* Words and abbreviations derived from Latin should be in italics

Noted these have been corrected throughout the manuscript.

No 15 Who prequalification vs no 32 Who Pre-qualification. Be consistent

Reference number 32 has been corrected for consistency.

There is an inconsistency wrt the names of the authors. In some cases the names of all the authors are given, other times one name only (no 26) or 3 names (no 22; 29) followed by *et al. respectively). Consistency is needed*

Sometimes a comma followed the name of the second last author (no's 20, 24) , other times the word ***and*** *was used (no 19, 18,). Consistency is needed*

In some cases there was a comma after the name of the journal (no 15, 18); some cases a full stop (no 24) other cases no full stop or comma (no 22)

Well noted. The list of references has been carefully revised to ensure consistency is maintained and that the requirements of the journal are met on the required reference style.

Figures

For clarity Change Fig 2 should be divided into Fig 2a and Fig 2b

Agreed, this has been corrected as proposed

Ensure that all the data provided in the tables and figures concur with the data discussed in the text

Table 1 ***The illustration/depiction*** *of application****s***

Well noted. These have been checked to ensure that the references are accurate.

Common deficiencies

Please rephrase the following deficiencies/issues. It is not very clear

Table 3. 9.1 Define SmPC = summary of product characteristics

The acronym has been expanded to include the full name.

Table 3: study design deficiency 9.2

Study design 9.7.2 Ensure that the number -------

The sentence has been revised as follows:

"Ensure that the number of additional subjects added to the sample size to compensate for potential dropouts or withdrawals are realistic and consistent with the study design."

This query requires the applicant to ensure that the additional subjects used to compensate for dropouts and withdrawals are realistic and not too high.

Sample analysis 9.54 Calibration data ---------May be provide?

Noted. The statement did not include "should be provided" which has now been included.

Statistical analysis 11.4.1 the criteria for ---

The statement has been expanded to include what is required from the applicant.

11.4.1 Address the high point -------

It is desirable for the point estimates to be consistent in the results observed, in these instances, higher point estimates were observed. The deficiency has been expanded to clearly indicate what is required.

Table 6 Bring the final ---- Last sentence needed to be addressed

The last sentence has been amended to include the following:

"A specific specification is proposed based on the results observed."

Based on the results of the profiles observed, a specific specification is proposed to the applicant.

Table 6 The incorrect comparison -----. Last sentence – can therefore **not** be confirmed

Well noted, the statement has been amended accordingly.

Reviewer #2

This is a good attempt and useful data. A comprehensive table of all published results from USFDA, WHO and values obtained in this study will help reader as ready reckoner. Data from 2011-18 and 20-21 can be mentioned in single table with an additional column instead of separate table."

Noted. The work by other authorities has been helpful in the study as it allowed for comparison and confirmation of similarity in the deficiencies observed. This data has been reported in the referenced articles and documents included in this manuscript. We would prefer not to include this information in a separate column as it would not add any significant value to the manuscript.

Response round 2

Reviewer #1:

Bioequivalence common deficiencies in generic products submitted for registration to the South African Health Products Regulatory Authority (SAHPRA)

TIRS-D_22_00085R1

Dear Editors,

Most of the recommendations **were adhered to**. There are however still some minor corrections that need attention: There are still inconsistencies wrt the spelling of *in vitro* vs *in-vitro (italics)* . See page 2 line 40, page 4 line 32, page 7 line 39, page 8 line 7, page 13 line 44, page 16 reference 8, page 17 reference 22, Fig 4, table 2, table 6. (consistency needed)

We apologise for the inconsistencies in the word *in vitro*, this has been revised accordingly throughout the manuscript.

Page 5 line 42, 44, 50, page 6 line 9, Page 7 line 9, 10 **Non-sterile vs non sterile** Table 1 , Table 3. Consistency needed.

We apologise for the inconsistencies in the word non-sterile, this has been revised accordingly throughout the manuscript.

Page 4 line 27 please indicate the **category for RW5.**

The therapeutic categories for applications submitted in RW5 have been included. These are medicines targeting Diabetes, Malaria, maternal and newborn health as well as all the SAHPRA priority APIs.

Page 8 line 38 provide a breakdown of the 15 % (in brackets) as indicated in the relevant table (for clarity)

The breakdown of the deficiencies which constitute 15 % has been described in the manuscript as detailed in Table 2. The statement was used as a standard in cases where the dissolution studies were not submitted accordingly.

Page 10 line 22 provide a breakdown of the 12 % (in brackets) as indicated in the relevant table

The sentence has been expanded to stipulate the breakdown of the resultant 12% from section 14.1. Please note that the deficiencies under 14.1 of the ICH E3 guideline under study design section have been combined to result in the 12% as these relate to the demographic details of the subjects.

Sentence is expanded revised as follows:

The details on the study design also did not include critical aspects such as demographic details of the subjects i.e. age, race, ethnicity, body mass and description of the gender of subjects used in the study (12%),

Page 10 line 42- 45 add to the last part of the sentence were not provided

The statement, “were not provided” has been included in the last part of the sentence.

Page 12 line 46 and 51 provide a breakdown of the 31 % and 42 % respectively (in brackets) (for clarity)

For the 31%, the breakdown has been included in the manuscript with the deficiencies quantified as stated in Table 4.

For the breakdown on the 42%, the recommendation was posed as a standard query therefore the expansion on the description of the deficiencies has been included.

The sentence is expanded as follows:

“The data requirements are confirmation of the following to ensure no significant changes occurred: unit formulation, manufacturing procedure and equipment, site of manufacture of final product and manufacturer of the API and overall product specifications.”

Page 12 line 7 ---- if the submission received was older than five years

The statement has been corrected as recommended.

Page 13 line 48 –include a lack of SOPs

The inclusion has been made as recommended.

Table 3 5.1 –Approval letter **by** the Ethics----

The sentence has been corrected as recommended.

Table 3 9.2 delete **should**

The word “should” has been deleted as recommended.

Kindly note that Table 6 has been removed and deficiencies incorporated into Tables 2-5 as per the recommendation by reviewer#2 to reduce on the number of pages and avoid duplication.

Table 6; Biowaiver: correct the spelling of pharmacopoeial

The spelling of the word pharmacopoeial has been corrected. Since Table 6 has been removed, the deficiency has been relocated to Table 2 under the biowaiver section, row 3, first sentence.

Table 6; Study design: 16.1.2 . The third 16.1.2 is a duplicate of the first one

Well noted. The third deficiency of 16.1.2 under study design section has been deleted as it is a duplication. Since Table 6 has been removed, this deficiency is now located in Table 3 under study design section as the second query in 16.1.2.

Table 6; study design: second 9.1 cross-over vs crossover page 9 line 34, 44,46, (consistency needed)

Noted. The word crossover has been corrected throughout the manuscript. The deficiency is now located in Table 3 under study design, the last deficiency of 9.1, this has been aligned with the rest of the "crossover" words in the Tables.

Table 6 ; study design: 12.2 re-analysis vs reanalysed vs re-analysed (consistency needed)

The words reanalysed and reanalysis have been corrected in all the Tables for consistency.

The changes for reanalysed and reanalysis are located below:

In Table 3 under sample analysis, the second row of 12.2,

Table 3 under statistical analysis in the third row.

Table 6; Statistical analysis: 14.2 International Council. Also table 6 Council of Harmonisation vs reference 11 Council for Harmonisation. Please clarify and correct the error

Noted. The errors have been corrected. The missing letter has now been included in the word Council. In addition, the word "for" is included so as to read as Council for Harmonisation. Since Table 6 has been removed, this deficiency is now located in Table 3 under statistical analysis, the second deficiency on 14.2.

Table 6; details of the test and reference product and inspections: --batch number and expiry date were visible ----

The query is now located in Table 4 as the nineth deficiency under details of the test and reference product (row 9). This was already worded differently from the deficiencies identified in 2011-2017. The query has therefore only been expanded to include the label with visible name of the product, name and address of the applicant, batch number, and expiry date.

Table 6; provide justification for the use of a foreign reference product

The sentence has been improved as recommended. The query is now located in Table 4 as the first deficiency under details of the test and reference product. This was already worded differently from the deficiencies identified in 2011-2017.

There are still inconsistencies wrt references:

et al. Words and abbreviations derived from Latin should be in italics

Note that the word et al. has not been italised since the author guide for the Journal does not specify italising of the word. Comparison with other published articles from the Journal also confirms that the word is not to be italised.

Please see the below extract from author guide:

“Lender D Jr, Arauz-Pacheco C, Breen LM III, et al. A double blind comparison: the effects of amlodipine and enalapril on insulin sensitivity in hypertensive patients. Am J Hypertens. 1999;12:252–298.”

Reference 4. Guideline on the investigation of bioequivalence by Committee for medicinal products for human use vs reference 25 Committee for medicinal Products for Human use vs reference 27 Committee for Medicinal Products for Human use (lower case) vs upper case . Consistency needed

The references have been harmonised in accordance to how the name is stipulated on the European Medicine Agency website which is: Committee for Medicinal Products for Human use.

Sometimes the abbreviated name of the journal is followed by a full stop, see reference 9 - Front. Pharmacol. , other times only a comma is used for example AAPS Journal, . Also see reference 26

The full stop has been included after the abbreviated Journal name.

Please ensure that reference 19 and 14 concur wrt abbreviated name of the journal AAPS Journal vs AAPS J

The abbreviation for the Journal has been corrected accordingly.

Reference 18 delete and after Litedu M,

Noted. The word “and” has been removed after the surname.

Most journals have a comma after the name of the journal, followed by the date using ; and then the volume : followed by the page numbers for example reference 18- Ther Innov Regul Sci, 2022;56:276-290. Please correct reference 22, and 24 etc.

Well noted. The referencing has been corrected accordingly in the references to be in line with the author guide.

Reference 29 remove the comma after the surname of the first author

The comma has been removed after the first author of reference 29.

Most journals have the names of 3 authors followed by ***et al.*** ***For*** reference 14 there were 4 names provided. Please correct.

Noted, the fourth author has been removed in reference 14.

Reviewer #2:

I am still not convinced about having TWO tables for TWO study periods. This will only increase the number of pages.

This is well noted, the proposal is appreciated and welcomed. The results of the deficiencies witnessed in 2020-2021 have been incorporated into Tables 2-5 since there is a high degree of commonality in deficiencies observed. All the deficiencies that were not common have also been added to the Tables. Overall combination of these has drastically reduced the number of pages and eliminated the duplication of reported deficiencies.

RESPONSE TO JOURNAL REVIEWERS

Chapter 6

The implementation of a risk-based assessment approach by the South African Health Products Authority (SAHPRA)

Lerato Moeti[1,2], Madira Litedu[1], Jacques Joubert[2]

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Response to the Journal of Pharmaceutical Medicine

1. Response round 1
2. Supporting amendment table

Response to comments by Reviewer #1, Reviewer #2, Reviewer #4 and Editor.

Kindly note that based on the recommendations from the reviewers, some information has been moved from one section to another. Extensive rearrangement was conducted to also allow for adequate flow of the information in the manuscript. A description of the changes has been made for each section in the letter as well as an additional document titled *the amendment table to the manuscript*. This document clearly shows where the changes were made on the original manuscript for each section compared to the revised version. The second column of this depicts the information that was originally submitted, the third column shows the changes or amendments, and the last column contains the information pertaining to the rationale for the effected changes. Additions or omissions to the original information are in red text.

Reviewer #1

Excellent article that provides a good example for NRA to adopt.

Thank you very much, our hope is for this to be a great tool for NRAs to use with the intent to promote accelerated access to medicines for patients.

Reviewer #2

The conclusions in the Abstract as well as in the body of the manuscript (page 28) do not succinctly state the outcome of the study. The recommendation would be to compare the median finalization times between the existing process (even if it is an estimation), and the observed median finalization time for the risk-based approach. Declare the superiority of the risked-based approach, clearly state the impact of the latter on the backlog and hence recommend for adoption.

The comment by the reviewer is well noted. A study has been concluded wherein the timeline of the risk-based assessment and the current process are compared and the results of the study show that the current process yields a median finalisation time of 501 calendar days. The conclusion in the abstract and in the body of the manuscript have therefore been expanded to include this comparison.'

The abstract remains on page 2 of the revised manuscript and the conclusions is on section 5, page 15.

Table 1 (page 3): For clarity, insert a column labeled 'Country/Region' after the 'Authority' column, as not all readers know the names and affiliations of the medicine regulatory authorities listed.

Noted. An additional column has been included in Table 1 which states the country in which the authority is affiliated with. This is now located at the bottom of the manuscript after the reference list in line with journal styling guide. Table 1 is now located on page 21 of the revised manuscript.

The definition of 'Risk' on page 7 should have come much earlier. Recommendation is to move that paragraph to page 6, under the header '1.2 Risk-based assessments.'

This is well noted. The paragraph on the definition of risk has been moved to section 1.2 as requested.

This paragraph is now on page 4, second paragraph of the revised manuscript.

The statement on page 7, paragraph 2: 'Often risk assessment focuses more on the disease…and less attention…in the development and manufacture...' is simply inaccurate. Risk assessment is a cardinal

feature and pillar in pharmaceutical R&D and in manufacturing. Risk assessment is mandatory in the development of quality systems associated with Good Manufacturing Practices.

This is well noted. The sentence has been modified to support the statement made by the reviewer. It has been amended to state: “Risk assessment is applied on the diseases to be treated as well as in the technology involved in the development and manufacture of the pharmaceuticals.”

This is now on page 4, second paragraph due to the revision of the manuscript.

In the last paragraph on page 8, the authors identify a lack of unit alignment as an issue in the review and registration process at SAHPRA. A question that this calls for is: Could an alignment of unit process alone reduce the backlog? Or would the risk-based approach be even more impactful if unit alignment were achieved?

The suitable place to expand on this was in the discussion section 4.2 which provides a discussion on the current process employed. The paragraph that has been expanded in on page 10 of the revised manuscript.

The Unit misalignment was one of the many reasons that resulted in the backlog. In 2019 when the backlog clearance programme was initiated, the business-as-usual (BAU) section were provided the opportunity to start on a clean slate while the backlog clearance programme dealt with all the ~8220 applications.

To date, SAHPRA has now created another backlog within the BAU section of more than ~2000 applications.

The investigation of the root cause of the backlog shows that it is not only one factor that resulted in its formation, therefore solving the misalignment alone would not be the solution to alleviating backlog. Some of the reasons for the backlog are discussed throughout the manuscript and include the following:

- Human resource constraints of skilled evaluators to conduct the assessments
- The uncontrolled influx of applications submitted with no restrictions on duplicated APIs in the market.
- The misalignment of work within the Units
- The fact the PEM, pre-registration covers a larger portion of the scientific assessments than other Units, therefore, the evaluation times are longer
- The end-to-end registration process that was employed
- The peer review process that was employed
- The response time of 90 days for applicants to respond

Agreed, the risk-based assessment approach was more impactful as it was designed to improve the process by resolving the issues outlined above. It should be noted that the risk-based assessment approach is designed as a collective process which should be adopted from end to end if the intent is to alleviate the backlog.

Section 4.2, page 10, has been expanded to incorporate the above as follows:

“In 2019 when the backlog clearance programme was initiated, the business-as-usual (BAU) section was provided the opportunity to start on a clean slate while the backlog clearance programme dealt with all the ~8220 applications. In the period 2019 and 2022, SAHPRA amended its processes and put systems in place such as the inclusion of a tracker that allows all Units to monitor each other, however, even with that, a backlog has formed within the BAU section of SAHPRA. The tracker was aimed at providing transparency and synchronisation within the Units, however, this did not correct the

misalignment as Units could still allocate the same applications at different times and communicate the queries at different times. The solution to this would have been to have one set of queries from the different Units communicated at the same time by the PC, as conducted in the 2015 study to ensure alignment within Units at all times. This meant some Units would finalise applications before others which leads to the misalignment. It should be noted that the root cause of the backlog is not as a result of one factor such as the misalignment of Units only, there is a number of reasons which are detailed in the study which is why the risk-based assessment approach was developed as an end-to-end registration process providing corrective or preventative measures or solutions to prevent the root causes from occurring in future."

Minor omissions and typos: On page 4, the abbreviation 'NCE' is used for the first time without definition - presumably this refers to new chemical entities (NCE)

Noted, it was noticed that the first time the word New Chemical Entity is used is in page 3 on the first paragraph, the acronym has been expanded there.

| Page 9, line 1 first 'served' not serve.

The word serve has been corrected to "served" as indicated. Thank you.

This is now on section 2.2, page 6 of the revised manuscript.

Reviewer #4

This is an interesting manuscript, highly informative for peers and in particular for less advanced NRAs in other countries. I have some suggestions and recommendations for improvement.

The words from the reviewer are highly appreciated and recommendations welcomed.

a. As the lack of coordination across units have historically been a cause of backlogs, it would be interesting to know if the processes have been now informatized (or if there are plans to do so), so that all units would have access at the same information at the same time, and could easier fine-tune their activities.

Section 4.2, page 10, has been expanded to provide an explanation for this question.

"In 2019 when the backlog clearance programme was initiated, the business-as-usual (BAU) section was provided the opportunity to start on a clean slate while the backlog clearance programme dealt with all the ~8220 applications. In the period 2019 and 2022, SAHPRA amended its processes and put systems in place such as the inclusion of a tracker that allows all Units to monitor each other, however, even with that, a backlog has formed within the BAU section of SAHPRA. The tracker was aimed at providing transparency and synchronisation within the Units, however, this did not correct the misalignment as Units could still allocate the same applications at different times and communicate the

queries at different times. The solution to this would have been to have one set of queries from the different Units communicated at the same time by the PC, as conducted in the 2015 study to ensure alignment within Units at all times. This meant some Units would finalise applications before others which leads to the misalignment. It should be noted that the root cause of the backlog is not as a result of one factor such as the misalignment of Units only, there is a number of reasons which are detailed in the study which is why the risk-based assessment approach was developed as an end-to-end registration process providing corrective or preventative measures or solutions to prevent the root causes from occurring in future."

The other reasons for the formation of the backlog are listed below:

- Human resource constraints of skilled evaluators to conduct the assessments
- The uncontrolled influx of applications submitted with no restrictions on duplicated APIs in the market.
- The misalignment of work within the Units
- The fact the PEM, pre-registration covers a larger portion of the scientific assessments than other Units, therefore, the evaluation times are longer
- The end-to-end registration process that was employed
- The peer review process that was employed
- The response time of 90 days for applicants to respond

Furthermore, resource constraints have also been stated as one of the reasons for formation of the backlog, however, increase on human resource alone would not be the solution to alleviate the backlog as observed from the backlog clearance project where 56 international assessors were employed, however, the backlog is still not yet cleared. (See section 4.2) It should be noted that the root cause of the backlog is not as a result of one factor such as the misalignment of Units only or insufficient human resource only, there is a number of reasons which are detailed in the study and some above which is why the risk-based assessment approach was developed as an end-to-end registration process aimed to alleviate the backlog.

b. It would be interesting to elaborate on whether the new risk-based approach, developed for correcting the backlog, will also be applicable in future, in particular for accelerating the review of products that have a particular value to public health, such as new products of an essential medicine for which there are not enough generics on the market.

It was decided before the initiation of the second risk-based approach pilot study in 2021, to apply this pathway on generic products only, with NCEs and biologicals assessed under full review. Other medicines which fall under the essential medicines list but not NCEs or biologicals would follow the risk-based approach pathway and be likely to be classified as high risk as that also involves a high level of assessment compared to low-risk applications. Using the developed risk classification template, those medicines would likely not be pharmacopoeial and be used as chronic medicines, hence overall classification as high risk.

This has been included in section 3.2.2 of the results, page 7.

c. It would also be important to indicate whether products registered under the risk-based approach would be subject to any closer follow-up, or targeted post-marketing surveillance.

The following were proposed and will be conducted on applications that undergo the risk-based assessment approach:

- The applicant requested to give the Post-Registration Reports on a yearly basis to Pharmacovigilance and annual product review to the Inspectorate. Depending on the information submitted on the reports, the Inspectorate could perform inspections of the non-compliant manufacturer/applicant.
- Post-marketing surveillance by the Inspectorate Unit
- Re-evaluation of the information (dossiers) after 5 years (Applicable for all applications)

This information has been included in Section 4.3.6 under discussion, page 15.

d. External reliance clearly plays an important role in this procedure, and its use is in line with international guidelines and WHO guidance. However, it would be important to indicate which regulatory bodies are considered by SAHPRA for reliance, and/or based on which principles.

There are a number of countries SAHPRA aligns itself with and uses the unredacted reports of in order to apply reliance as indicated in the first part of the developed risk assessment template. These countries are:

• European Medicines Agency

• Health Canada
• Medicines and Health Products Regulatory Agency (MHRA), UK

• Ministry of Health, Labour and Welfare (MHLW), Japan

• Swiss Agency for Therapeutic Products (Swissmedic)

• Therapeutic Goods Administration (TGA), Australia

• US Food and Drug Administration (US FDA)

This is detailed under discussion, section 4.3.2, page 11.

e. On a minor note, it reads in p. 4 that "The large influx of medicines from pharmaceutical companies due to the emerging pharmaceutical market as a result of the increasing disease burden, has made access to medicines a challenge to regulatory authorities in low to middle-income countries": however, the increasing disease burden is likely not to be the only reason for having more applications for MA. Other reasons may be related to the proliferation of me-too drugs, the growth of the national and international generic sector, and (as mentioned in p. 5) the fact that there is not a "ceiling" to the number of products that should be registered for multi-source medicines.

Well noted and agree, the other reason which is the growth in the generic pharmaceutical sector has been expanded as stated as well as a reference to support this. (Page 3) This paragraph is then followed by the one which discusses “dossier farming” on not having a “ceiling” for the number of products on the market. This links the two and avoids repetition. This information is now located on page 3 as well, of the revised manuscript.

f. Also on a minor note, it reads in p. 5 that "Regulatory authorities in developing countries such as SAHPRA face a number of resource constraints…."; it could be interesting to briefly discuss on

SAHPRA initiatives to upgrade their capacity, and in particular on any plan to undergo the WHO benchmarking.

Note than in 2019, the BAU section of SAHPRA was provided a clean slate with new operational processes while the backlog clearance programme operated as a separate entity and the human resources has gradually increased with the intention to increase this to more than 450 personnel to complete the fit-for-purpose structure. However, as it stands, SAHPRA has formed another backlog within the BAU Unit of approximately 2000 applications.

It should be noted that the root cause of the backlog is not as a result of one factor such as the misalignment of Units only or insufficient human resource only, there is a number of reasons which are detailed in the study and some above, which is why the risk-based assessment approach was developed as an end-to-end registration process aimed to alleviate the backlog.

In summary this is to say, the initiatives that have been solely adapted without the assessing all the root causes have not contributed to alleviating the backlog, but instead created a new backlog, therefore we would propose not to include this minor note.

g. The abstract should be adapted, in line with changes in the main manuscript as needed.

Noted, the abstract has been amended accordingly.

Based on the revision of the manuscript which involved the rearrangement of information from one section to another within the manuscript, the abstract has been amended accordingly to incorporate this. The changes are as follows:

The background previously included information which is considered part of the study findings and this has been modified to include the findings before the study began and need for the study.

The objectives now strictly include focused information on the intent of the study, what the research aims to achieve.

The methods section previously included information that is part of the results of the study, this has now been modified to include the description of how the study was conducted and how the required data was obtained.

The results section now includes a summary of the results obtained in the study.

The conclusion section also includes the overall conclusions of the findings of the study.

Comments from the Editor:

General comments

Please download the journal styling guidance, which is available as an attachment in Editorial Manager, and submit the checklist with your revised manuscript as an 'other' file. We are trialling this new document so any feedback you have about whether it is easy to find, understand and complete, would be useful.

The journal styling guidance checklist has been completed and is accompanying the manuscript and supporting documents.

The manuscript will need extensive revision to ensure that your findings are presented in a clear way. Original research articles follow a standard format with separate sections for Background (that also describes study objectives as the last paragraph or this can be a separate Objectives section if you prefer), Methods, Results, Discussion, and Conclusions. At present this information is jumbled together so it's not clear to me exactly what was part of this study and what was not.

Well noted the manuscript has been revised to adequately distinguish on information that should be included under the methods, results, discussion and conclusions as recommended below. The description of the changes is highlighted below.

The Background needs to be shortened to focus on the need for this study, and what was already known before it began. This is the 'why' part of your study. Please avoid giving study results in this section.

This is well noted and appreciated. The background has been amended to include what was known before the study began, the quantification of the backlog has been moved to the results section as it includes data on 2015 as well which is the same year as when the study was initiated. The flow of the introduction is more focused and is structured as follows:

- Report on approval times by other regulatory authorities with the intent to introduce the comparison of the high approval times by SAHPRA,
- A brief description on SAHPRA's organisational structure
- Introduction on risk-based assessments then
- Objectives.

Other changes made in the introduction in the revised manuscript:

- Figure 1 and 2 and its related paragraph has been removed from the introduction section and placed in the results section since this data serves as quantification of the backlog over the years which forms part of the objective of the study. The journal styling guide requires the figures to be submitted as separate files, therefore these and all other figures have removed in the main body of the manuscript.

- Based on the recommendation by reviewer #4, point e, regarding the other reasons that resulted in the formation of a backlog, the paragraph which details the reported reasons on the formation of the backlog was moved to that section for better flow of information.

- The following addition was included at the end of section 1.1, page 4 to link it with section 1.2 on the risk-based assessments:
  "The PEM, P&A pre-registration Unit has proven to be the rate-limiting part of the registration process since the bulk of the evaluations which include quality and bioequivalence assessments are conducted in the Unit. The growing application backlog in SAHPRA demonstrates the need for mechanistic interventions such as the risk-based assessment approach to alleviate the backlog by reducing the scientific evaluation timelines."

We hope the amended structure of the background section is found acceptable.

The Methods needs to describe 'what' was done for the study and 'when' and 'how' it was achieved. For example, did the study begin with the 2015 Pilot or was this already complete and used as a background piece of information? The risk-based assessment process is obviously a key feature of this work – but was this developed to facilitate the study (i.e. Methods) or developed as an outcome of the study (i.e. Results)?

The study began with the 2015 pilot and the intent is to report on the results of the 2015 pilot and not include it as background information. We apologise for not making this distinction in the manuscript. To provide a bit of background, the results from the 2015 pilot only was going to be used for the manuscript, then recommendations made to the authority to adopt the review process, however, the approval to conduct another pilot was given in 2021, therefore the results is also incorporated in this study which then provides a good comparison and up-do-date data of the risk-based approach.

The risk-based assessment approach is developed as an outcome of the study. Relevant information has therefore been moved to the results section. Thank you.

The methods section has now been improved to detail how and when the data which allowed for the implementation of the projects was obtained while eliminating report of any results to the study.

There is no new information in the methods section.

The Results should just describe the study findings. The Discussion should describe the implications of the study findings and the Conclusions should describe the findings as they align with the stated study objectives and outline any future areas of research.

This is well noted and has been corrected accordingly. The results and discussion section were combined and these have been separated to also follow the journal styling guideline.

Information pertaining to the results of the study has been included in the results section. The flow of the results section is now as follows:

- Report on the quantity of SAHPRAs backlog over the years and how it formed annually between 2006-2016.

- Report on the results of the initial phase of the 2015 backlog project.

- Report on the results obtained from the risk-based assessment approach from the developed registration process, to how the risk classification was conducted, to the summary of results of the complete approach for the two pilots.

Other changes:

- The footnotes on Table 2 have been revised to align with the journal style guidance. Note that the tables have now been placed at the end of the manuscript, after the reference list.

- Table 4 in the revised manuscript has been expanded to include the time in which application were on queue awaiting allocation before the two pilot studies were initiated. A footnote has also been included to explain the calculation of the approval time in the table.

- Table 4 and 5 were swapped from the original manuscript to the revised manuscript for better flow of information in the manuscript.

Information that should be in the discussion section has been placed in the relevant section. The flow of the discussion section is similar to that of the results and is as follows:

- Discussion of the results of the 2015 backlog project, initial phase
- Discussion of the second phase, preparation of the risk-based assessment pilot studies
- Discussion of the developed risk-based assessment approach end-to-end registration process
- How the risk classification was developed and conducted
- The identified critical areas for scientific assessments for the different classifications

- Discussion on the actual reported results of the risk-based assessment approach which includes discussion on the reduced evaluation times.

Most of the information stated above was already included in the original manuscript, the information has only been rearrange for adequate flow of information in the manuscript. The following are new information that has been included due to recommendations raised by the reviewers:

- Section 4.2 has been expanded to address recommendations raised by reviewer #2 and #4. The expanded section is the last paragraph on section 4.2, page 10 which has been discussed above.
- Section 4.3.2 has been expanded to define the reliance aspect as recommended in point d above by reviewer #4.
- Section 4.3.6 has been expanded to include measures to be taken to monitor the application post-registration. This has been included based on the recommendation by reviewer #4, point c as indicated above.

The abstract will also need to be rewritten to follow this same presentation and provide a concise summary of the key information, with sections for Background, Objectives, Methods, Results and Conclusions.

Based on the revision of the manuscript made which involved the rearrangement of information from one section to another within the manuscript, the abstract has been amended accordingly to incorporate this. The changes are as follows:

The background previously included information which is considered part of the study findings and this has been modified to include the findings before the study began and need for the study.

The objectives now strictly includes focused information on the intent of the study, what the research aims to achieve.

The methods section previously included information that is part of the results of the study, this has now been modified to include the description of how the study was conducted and how the required data was obtained.

The results section now includes a summary of the results obtained in the study.

The conclusion section also includes the overall conclusions of the findings of the study.

The background section needs to describe the need for the study. It should not describe the study findings (in terms of number of applications in the backlog) nor the study objectives.

Noted, this has been modified as indicated above.

Example articles can be viewed here:

https://link.springer.com/article/10.1007/s40290-022-00432-0

https://link.springer.com/article/10.1007/s40290-016-0172-4

The alternative would be change the article type to a review style 'leading article' and offer your insights in a more educational way that avoids the need for a Methods/Results format. See this article for recent example: https://link.springer.com/article/10.1007/s40290-020-00349-6

The amendments as proposed have been made in order to align with requirements for an original research article.

Once the revisions are complete, please carefully review the language used to ensure accuracy. For example, the Introduction text implies that median is the same as average (see below). Also FDA = Food and Drug Administration and the Institute for Regulatory Science is now known as the 'Centre for Innovation in Regulatory Science'

Noted the accuracy of the language has been carefully reviewed throughout the manuscript.

The United States Food and Drug Administration has been corrected in page 3, paragraph 1.

The Centre for Innovation in Regulatory Science has been corrected and is located in page 4, paragraph 3.

No other language errors were identified.

Specific comments:

Recommend rewriting the text that currently reads "The median approval times by several regulatory authorities are outlined in Table 1 for the period of 2015-2019 to illustrate the average approval times for access to medicines [3-6]. The table illustrates the median approval times reported with the lowest as 247 calendar days for 48 applications by the United States Federal Drug Administration (USFDA) [3], and the highest with a median approval time of 1622 calendar days for 121 NCE applications by the South African Health Products Regulatory Authority (SAHPRA) [6]." Because median and average are not the same and also to reduce duplication. You could potentially delete the text that reads "to illustrate the average approval times for access to medicines [3-6]. The table illustrates the median approval times reported"

Noted, the sentence "to illustrate the average approval times for access to medicines [3-6]" has been deleted. This information is still located on page 3 of the revised manuscript.

Pg 22: is PI 'professional information' or should it be 'product information'?

Due to the revision of the manuscript, the information that was located on page 22 has now moved to page 12. Kindly refer to this page to assess this recommendation.

The correct term for PI is Professional Information.

Figures and tables – please conduct a final review to ensure consistent formatting and use of capital letters etc.

A review of all the figures and tables has been conducted to ensure they are in line with the journal style. The style guide indicates that figures should be stated as Fig. X, note that all figures were amended accordingly and separate files created for these.

Figures 3 and 4 do not add additional information over and above the text – recommend to delete.

Noted, the two figures have been deleted.

Due to the deletion of these figures note that the numbering of the figures is revised.

Figure 5 needs a more descriptive title as it's not clear what "The grouping of the different statuses of the pending products" means

Note that due to the deletion of Figure 3 and 4 as advised above, the figure numbers in the whole manuscript has been revised. Figure 5 is now Figure 3.

The description of figure 3 has been changed to provide clarity. The figure is now titled as "Status classification and quantification of the in-process applications once phase 1 of 2015 project was concluded." A separate file titled Fig3 is submitted.

Before this exercise was conducted, the authority did not accurately know the status of all the 3505 applications for all the different Units especially the PEM pre-registration Unit. Without this information there would be further delays in the approvals.

Table 2: recommend to delete the score column since this is blank. You could simply add a footnote to say that scores are combined at the end of the evaluation, or similar.

The score column has been deleted and a footnote included as per the journal style description. This table is now located on page 21 of the revised manuscript.

Please note that journal style is to use superscripted lower-case letters for footnotes (e.g. a, b, c etc)

Noted. The footnotes have been amended accordingly to be in line with the journal style.

References

Due to the revision of the manuscript, note that the references were also amended throughout the manuscript.

Please review references to ensure all the necessary information s provided. Examples of reference formatting are available in our Instructions for Authors on the journal website.

Ref 1 – should this be two different references?

This reference has been corrected and a URL included.

This is now located on page 16 of the revised manuscript.

Refs 28, 29 should be deleted

The two references have been deleted

Ref 37 – what is this ref? Any more information available?

The reference is a dissertation of research work conducted at the University of Malta. The URL has been included.

Reference 37 is now reference 36 due to the deletion of 2 references and addition of one other reference. This is now located on page 19 of the revised manuscript.

Ref 44 – add URL?

The URL has been included.

This reference is now reference 43. This is now located on page 19 of the manuscript.

Ref 46 – add author, URL?

The URL has been included. This is a guidance document by the Pharmaceutical inspection convention (PIC/S). This has been amended accordingly.

This reference is now reference 45. This is now located on page 20 of the manuscript.

Page/ section	Existing	Amended	Reason for amendment
All	Size 11, Times New Roman	Size 10, Times New Roman	In line with the author guide checklist document.
		Due to the revision and rearrangement of the manuscript, most references were renumbered.	
1	**The implementation of a risk-based assessment approach by the South African Health Products Authority (SAHPRA)** **Lerato Moeti[1,2], Madira Litedu[1], Jacques Joubert[2]** [1]South African Health Products Regulatory Authority (SAHPRA), Kirkness Street, Arcadia, Pretoria, 0007, South Africa. [2]School of Pharmacy, University of the Western Cape, Robert Sobukwe Road, Bellville 7535, Cape Town, South Africa. **Keywords**:	**The implementation of a risk-based assessment approach by the South African Health Products Authority (SAHPRA)** **Lerato Moeti[1,2], Madira Litedu[1], Jacques Joubert[2]** [1]South African Health Products Regulatory Authority (SAHPRA), Pretoria, South Africa. [2]University of the Western Cape, School of Pharmacy, Cape Town, South Africa. Corresponding Author: jjoubert@uwc.ac.za School of Pharmacy, University of the Western Cape, Robert Sobukwe Road, Bellville 7535, Cape Town, South Africa.	The affiliations have been amended to be in line with the author guide checklist and include the following format: institution name, department, city [state], country. The street name, area and postal code have been deleted. The details of the Corresponding Author have been included as per the author guide

	South African Health Products Regulatory Authority (SAHPRA), registration, approval times, turnaround times, backlog, risk-based assessment		checklist. This includes the email address and the full postal address for the author. The keywords have been deleted as prescribed on the author guide checklist.
2	**Abstract** **Background** This research study aims at assessing the registration process within SAHPRA in the effort to refine and promote efficiency for accelerated access to medicines. In 2016, SAHPRA had accumulated a backlog of 7902 medicinal product applications in the system and by 2018, this had escalated to 8 220. **Objectives** To alleviate the backlog, the use of a risk-based review on the scientific quality and bioequivalence assessments was explored aimed at assessing the critical quality attributes without compromising on quality, safety and efficacy of medicinal products. The risk-based review approach employed provides a prototype solution to counteract the influx of medicinal product applications received by the regulatory authorities. The developed tool and approach were conducted in 2016	**Abstract** **Background** An extensive backlog of pending regulatory decisions is one of the major historical challenges that the South African Health Products Regulatory Authority (SAHPRA) inherited from the Medicine Control Council (MCC). Revising and implementing new regulatory pathways is one of the strategic mechanisms that SAHPRA employs to circumvent this problem. **Objectives** To alleviate the backlog, the use of a new review pathway termed the risk-based review on the scientific quality and bioequivalence assessments was explored. The objective of the study is to articulate the risk-based assessment (RBA) pathway, to determine robust criteria for the classification of the levels of risk for medicines and to	The background was amended due to the revision of the manuscript. The information included on the backlog numbers serve as part of the reported results. The objective was amended to be in line with what has been stated as the objectives of the study. The data previously included contained details that

	and further piloted in 2021 using the knowledge gained from the 2016 study for optimisation of efficiency. **Methods** In 2015, an extensive exercise was conducted by SAHPRA to identify the unknown status of all products in the pre-registration phase. In 2016 the risk-based review pilot project commenced with 99 master applications received in 2011-2012. Further to that, for efficiency enhancement, a similar pilot study was conducted in 2021 with 63 master applications. **Results** The 2015 project entailed two phases. The initial phase was conducted to identify the status of 3505 in-process applications, which resulted in the registration of 198 applications. The second phase commenced in 2016 on 4397 applications not yet reviewed and the risk-based assessment was piloted. The pilot resulted in a finalisation time with a median value of 90 calendar days and a median approval time of 109 calendar days. The throughput of the risk-based assessment pilot study conducted in 2021 was 68 calendar days finalisation time. Both the 2016 and 2021 studies had similar approval times. The reported evaluation timelines for both studies were within 6-7 hours for a low-risk quality assessment, 9-10 hours for a high-risk quality assessment, 7-8 hours for a bioequivalence assessment and 2-3 hours for a biowaiver and initial response assessment.	define the improved process to be followed in the assessment and approval of medicines. **Methods** In 2015, an extensive exercise was conducted by SAHPRA to identify the unknown status of in-process applications. The RBA pilot project commenced in 2016 and further piloted in 2021 using the knowledge gained from the 2016 study for optimisation of efficiency. **Results** By 2015 the backlog was quantified as 7902 applications in the pre-registration phase. The 2015 project entailed two phases, the initial phase was conducted to identify the status of 3505 in-process applications, which resulted in the registration of 198 applications. The second phase commenced in 2016 on 4397 applications not yet reviewed whereby RBA approach was explored. With the developed criteria for risk classification and refined end-to-end registration process, the pilot resulted in a finalisation time with a median value of 90 calendar days and a median approval time of 109 calendar days. The throughput of the RBA pilot study conducted in 2021 was 68 calendar days finalisation time for the 63 applications used. These	should be on the methods section, on when the study was initiated. The methods section is now amended to only include the description of when and how the study was initiated without inclusion of the results to the study. The summary of the results section has been amended to include outcomes of the study that are inline with the objectives identified. The results of the quantification of the backlog have now been included in this section. The quantities of the applications used at initiation of the 2016 and 2021 pilot studies have now been included in this section since they form part of the results.

	Conclusions The refined processes used in the risk-based pilot studies to alleviate the SAHPRA backlog are described in detail. This approach, therefore, aims to reduce the approval times for quality and bioequivalence assessments for regulatory authorities without compromising on the quality, safety and efficacy of the medicinal products. Implementation of this approach by other regulatory authorities could assist in the reduction of the backlog of applications created due to resource constraints.	finalisation times are lower in comparison to the 501 calendar days for the current process employed by SAHPRA for the backlog clearance programme initiated in 2019. Both the 2016 and 2021 studies had similar approval times calculated from the date of allocation of scientific assessments. The reported evaluation timelines for both studies were within 6-7 hours for a low-risk quality assessment, 9-10 hours for a high-risk quality assessment, 7-8 hours for a bioequivalence assessment and 2-3 hours for a biowaiver and initial response assessment. **Conclusions** The refined processes used in the risk-based pilot studies to alleviate the SAHPRA backlog are described in detail. The process managed a reduction of the finalisation time to 68 calendar days in comparison to 501 calendar days for the current backlog clearance programme initiated in 2019. The RBA approach, therefore, reduces the finalisation and approval times for quality and bioequivalence assessments for regulatory authorities without compromising on the quality, safety and efficacy of the medicinal products. In addition, the approach provides a prototype solution to counteract the influx of medicinal product applications received by the regulatory authorities. Key Points:	As advised by reviewer #2, the reported finalisation times are compared to those of the current process employed. This is also stipulated under conclusions. The conclusion provides a summary of the study based on the results reported. This section then clearly state the impact of the RBA on the backlog and hence recommends for adoption by other regulatory authorities. This is as per

		The South African Health Products Regulatory authority (SAHPRA) had accumulated a backlog of 7902 medicinal product applications in the system in 2016 and by 2018, this had escalated to 8 220. In addition, a median approval time of 1622 was reported between 2015-2018. The growing application backlog in SAHPRA demonstrates the need for drastic interventions; hence the development of the risk-based assessment approach aimed at alleviating the current and continuously forming backlog by reducing overall approval timelines. The risk-based assessment approach is a robust end-to-end registration process which would be a new alternative regulatory review pathway that has been developed to alleviate the backlog and reduce overall approval times. This process includes a risk classification applied before assessments, improved overall registration process, improved evaluation tools and amended peer review process. The pilot studies conducted using this new regulatory review pathway confirmed the reduced approval timelines.	recommendation 1 made by reviewer #2. The key points have been included as outlined in the author guide checklist.
3	**1 Background** In the effort to protect public health, access to free or affordable essential medicines is one of the main obligations by Governments to fulfill the	**1 Background** In the effort to protect public health, access to free or affordable essential medicines is one of the main obligations	Paragraph 1 and 2 in page 3 have now been

	right to health [1]. The World Health Organisation (WHO) has reported that one-third of the world's population does not have timely access to such medicines and has encouraged countries to amend their national legislation or constitutions to provide for this right [2]. Regulatory authorities are established by Governments with a mandate to safeguard the patients by ensuring that safe, efficacious and quality medicine is accessible at an accelerated rate [2]. The median approval times by several regulatory authorities are outlined in Table 1 for the period of 2015-2019 to illustrate the average approval times for access to medicines [3-6]. The table illustrates the median approval times reported with the lowest as 247 calendar days for 48 applications by the United States Federal Drug Administration (USFDA) [3], and the highest with a median approval time of 1622 calendar days for 121 NCE applications by the South African Health Products Regulatory Authority (SAHPRA) [6]. In 2020 a study was conducted by SAHPRA and a median approval time of 790 calendar days reported for 244 generic applications [7]. Table 1, therefore, demonstrates that SAHPRA has significantly longer approval times compared to other Authorities. The large influx of medicines from pharmaceutical companies due to the emerging pharmaceutical market as a result of the increasing disease burden, has made access to medicines a challenge to regulatory authorities in low to middle-income countries [4]. **Table 1**: The reported median approval times from various regulatory authorities between 2013-2019.	by Governments to fulfill the right to health [1]. The World Health Organisation (WHO) has reported that one-third of the world's population does not have timely access to such medicines and has encouraged countries to amend their national legislation or constitutions to provide for this right [2]. Regulatory authorities are established by Governments with a mandate to safeguard the patients by ensuring that safe, efficacious and quality medicine is accessible at an accelerated rate [2]. The median approval times by several regulatory authorities are outlined in Table 1 for the period of 2015-2019 [3-6]. The table illustrates the median approval times reported with the lowest as 247 calendar days for 48 applications by the United States Food and Drug Administration (USFDA) [3], and the highest with a median approval time of 1622 calendar days for 121 New Chemical Entity (NCE) applications by the South African Health Products Regulatory Authority (SAHPRA) [6]. In 2020 a study was conducted by SAHPRA and a median approval time of 790 calendar days was reported for 244 generic applications [7]. Table 1, therefore, demonstrates that SAHPRA has significantly longer approval times compared to other Authorities. The large influx of medicines from pharmaceutical companies due to the emerging pharmaceutical market as a result of the increasing disease burden and the growth of the pharmaceutical generic sector	combined into one paragraph since the first paragraph was very short. The sentence "to illustrate the average approval times for access to medicines [3-6]" has been deleted as per recommendation 1 made by the Editor under specific comments. Definition error for USFDA was corrected to the United States Food and Drug Administration in line with the recommendation from the Editor under general comments. The abbreviation for NCE was stated for the first time on page 3 and this has been

Authority	Median approval times (calendar days)	Number of applications
USFDA, 2017-2019	247	48
Health Canada, 2015-2019	347	30
Australian Therapeutic Goods Administration (TGA), 2015-2019	351	25
European Medicines Agency (EMA), 2015-2019	433	27
Swiss Medic, 2015-2019	527	28
Agência Nacional de Vigilância Sanitária (ANVISA), 2013-2016	795	138
SAHPRA, 2015-2018	1622	121

1.1 SAHPRA's organisational structure

SAHPRA, with internationally recognised standing, is aimed at facilitating the availability, evaluation and approval of the quality, safety and efficacy of medicinal products and related substances intended for

amongst others has made access to medicines a challenge to regulatory authorities in low to middle-income countries [4, 8].

Regulatory authorities in developing countries such as SAHPRA face a number of resource constraints with the main one being insufficiently skilled individuals for dossier assessments and manufacturing site inspections. The delays were also attributed to deficient operational processes and increased volume of applications for registration. The long regulatory decision timeframes have serious public consequences, as these delay access to life-saving medicines. In addition, the Medicines and Related Substances Act, 1965 (Act 101 of 1965), Section 22F [9], did not prevent or state how many generics the regulatory authority should register per active pharmaceutical ingredient (API). This Act encouraged "dossier farming" within the industry which created a significant backlog within the Regulator [10, 11]. SAHPRA received an average of 1200 applications annually between 2006-2015 and the authority could therefore not evaluate all the applications received within the period due to resource constraints and other factors as mentioned above. This

expanded as required, based on the recommendation by reviewer #2.
The last part of the paragraph has been expanded as per recommendation **e** by reviewer #4, to include the reason for the large influx of medicines. This statement is also supported by a reference which has now been included.

Since the previous paragraph on the reasons for the formation of a backlog, the paragraph which further expanded on the reasons for backlog which was initially on page 4 has now been moved to page 3. This is in line with recommendation **e** made by reviewer #4

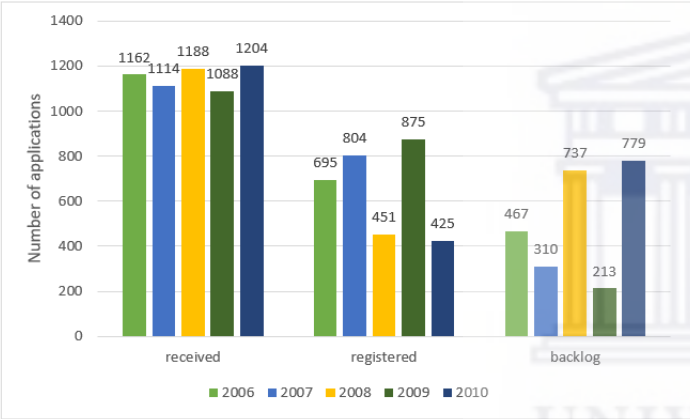
Table 1 has been moved to page 21 of the revised manuscript in line with the author guide which states that

	humans and animals. In the years in which SAHPRA (formerly Medicine Control Council, MCC) has been in effect, over 20 000 medicinal products have been registered [8]. SAHPRA assumed the roles of both the MCC as well as the Directorate of Radiation Control (DRC) which were housed at the South African National Department of Health (NDoH) [9]. Subsequently, SAHPRA was constituted as an independent entity that reports to the National Minister of Health through its Board [9]. The organisation is headed by the Chief Executive Officer (CEO) with support from the Chief Financial Officer (CFO), Chief Operating Officer (COO), Chief Regulatory Officer (CRO) and the Human Resource Executive who all form part of the Executive Committee of the organisation (Figure S1a, supplementary material). Within the office of the CRO lies the programmes; Pharmaceutical Evaluation Management (PEM), Clinical Evaluation Management, Inspectorate and Regulatory Compliance, and Medical device and Radiation control as illustrated in the supplementary material (Figure S1b).	resulted in the formation of a backlog of applications, delaying access to medicines for patients. **1.1 SAHPRA's organisational structure** SAHPRA, with internationally recognised standing, is aimed at facilitating the availability, evaluation and approval of the quality, safety and efficacy of medicinal products and related substances intended for humans and animals. In the years in which SAHPRA (formerly Medicine Control Council, MCC) has been in effect, over 20 000 medicinal products have been registered [12]. SAHPRA assumed the roles of both the MCC as well as the Directorate of Radiation Control (DRC) which were housed at the South African National Department of Health (NDoH) [13]. Subsequently, SAHPRA was constituted as an independent entity that reports to the National Minister of Health through its Board [13]. The organisation is headed by the Chief Executive Officer (CEO) with support from the Chief Financial Officer (CFO), Chief Operating Officer (COO), Chief Regulatory Officer (CRO) and the Human Resource Executive who all form part of the Executive Committee of the organisation (See Online resource 1). Within the office of the CRO lies the programmes; Pharmaceutical Evaluation Management (PEM), Clinical Evaluation Management, Inspectorate and Regulatory Compliance, and Medical device and Radiation control as	all tables should be placed at the end of the manuscript after the reference list. Due to the relocation of Table 1, the first paragraph of section 1.1 is now on page 3. The only amendments to the paragraph were on the renaming of the figures which detail the organisational structure of SAHPRA, included as supplementary information. The author guide checklist stipulates that this should be titled as Online resource 1 and 2.

		illustrated in the supplementary material (See Online resource 2).	
4	The programmes are in turn subdivided into Units responsible for coordination and execution of various activities. Within the PEM programme, lies the Pharmaceutical and Analytical (P&A) pre-registration Unit. The work of the Unit involves the evaluation of the quality and efficacy (bioequivalence) aspects of products submitted as a dossier in the Common Technical Document (CTD) format by pharmaceutical companies. The clinical aspects i.e., to confirm that the labelling of the generic products is in accordance with the registered innovator products and efficacy of the NCEs is evaluated by the clinical pre-registration Unit. Inspection of manufacturing sites is conducted by the Inspectorate Unit. Appropriate naming and scheduling status of the products is conducted by the Names and Scheduling Unit (Figure S1b) [10]. Regulatory authorities in developing countries such as SAHPRA face a number of resource constraints with the main one being insufficiently skilled individuals for dossier assessments and manufacturing site inspections. The delays were also attributed to deficient operational processes and increased volume of applications for registration. The long regulatory decision timeframes have serious public consequences, as these delay access to life-saving medicines. In addition, the Medicines and Related Substances Act, 1965 (Act 101 of 1965), Section 22F [11], did not prevent or state how many generics the regulatory authority	The programmes are in turn subdivided into Units responsible for coordination and execution of various activities. Within the PEM programme, lies the Pharmaceutical and Analytical (P&A) pre-registration Unit. The work of the Unit involves the evaluation of the quality and efficacy (bioequivalence) aspects of products submitted as a dossier in the Common Technical Document (CTD) format by pharmaceutical companies. The clinical aspects i.e., to confirm that the labelling of the generic products is in accordance with the registered innovator products and efficacy of the NCEs is evaluated by the clinical evaluations, pre-registration Unit. Inspection of manufacturing sites is conducted by the Inspectorate Unit. Appropriate naming and scheduling status of the products is conducted by the Names and Scheduling Unit (Online resource 2) [14]. The PEM, P&A pre-registration Unit has proven to be the rate-limiting part of the registration process since the bulk of the evaluations which include quality and bioequivalence assessments are conducted in the Unit. The growing application backlog in SAHPRA demonstrates the need for mechanistic interventions such as the RBA	The second paragraph of section 1.1 which details the organisational structure of SAHPRA is relocated to page 4. Due to the rearrangement of the next paragraph, it was essential to connect the two paragraphs by introducing section 1.2 on risk-based assessments.

	should register per active pharmaceutical ingredient (API). This Act encouraged "dossier farming" within the industry which created a significant backlog within the Regulator [12, 13]. SAHPRA received an average of 1200 applications annually between 2006-2015 and the authority could not evaluate all the applications received within the period due to resource constraints. Figure 1 and 2 quantitatively illustrates how the backlog resulted within SAHPRA in this period. For example, in 2010, SAHPRA received 1204 applications and could only register 425, resulting in 779 backlog applications.	approach to alleviate the backlog by reducing the scientific evaluation timelines. **1.2 Risk-based assessments** Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm [15, 16]. The evaluation of risk requires the identification of a hazard and the likelihood of its occurrence [17, 18]. In pharmaceuticals, managing risk is of prime importance to ensure that the patient gets medicines/products of acceptable safety, efficacy and quality, according to WHO standards, as set out in WHO guidelines [15-16, 18-19]. Risk assessment is applied on the diseases to be treated as well as in the technology involved in the development and manufacture of the pharmaceuticals. The technology level affects the feasibility of the manufacturing process, including packaging and quality control testing, the overall quality assurance system of the manufacturer, as well as the capacity of the local National Regulatory Authority (NRA) to effectively assess the resultant dossier [20]. Thus, one of the main factors that affect the quality of the product is the quality of the manufacturing process which produces both the API and the Final Pharmaceutical Product (FPP). Hence, sound and reliable processes produce quality products.	Section 1.2 now initiates on page 4. The paragraph on definition of risk under section 1.2 has been moved to be the first paragraph in this section as per recommendation 3 by reviewer #2. Note that section 1.2 was on page 6 and 7 of the original manuscript. The corrections on the paragraph on definition of risk were made as per recommendation 4 by reviewer #2. The sentence on risk assessment being applied on the diseases to be treated and on the technology involved in the development and manufacture of pharmaceuticals.

		Quality cannot be tested into the product, but it is to be built into the product during its manufacturing. In order to expeditiously provide the public with access to quality, safe and efficacious medicines, a risk-based approach to the assessment of a pharmaceutical product should be explored. This approach is discussed in the publication by the Centre of Innovation in Regulatory Science (CIRS) which describes measures that regulatory authorities should consider to apply in the risk-based approach [21]. The review highlights the importance of the level of experience of the evaluators used and the assessment tools employed during assessments to ensure that there is no compromise in the quality and that all critical components are appropriately detailed in the assessments. The component of the level of experience of the evaluators used in the assessments of the dossiers is supported by the results of the project previously undertaken by SAHPRA. In July 2009 - September 2010, the Regulator had a backlog of 2114 applications and initiated a project aimed at alleviating the backlog of applications. Only 16.6% of the products were registered while 1.6% were rejected and 6% were cancelled or withdrawn [22]. The reason for the unsatisfactory results were due to substandard reports that were submitted by inexperienced evaluators which required	A definition error was made for the abbreviation CIRS which stands for Centre of Innovation in Regulatory Science. This has been corrected as advised by the Editor under general comments.

		re-assessment by the PEM, P&A pre-registration Unit. This, therefore, illustrates the importance of experienced evaluators who are well knowledgeable with vast experience in the field of regulatory science and scientific assessments with a thorough scientific understanding of the benefit and risk involved[23].	
5	 **Figure 1**: A depiction of the registered products within SAHPRA between 2006-2010 resulting in the backlog.	The second component mentioned in the CIRS article is the scientific review tools which play a major role in the efficiency and effectiveness of the authority and could result in delayed registration, depending on the tools and strategies used to conduct scientific assessments [21]. In the effort to attain shorter registration turnaround times, authorities need to incorporate the benefit-risk factors at the assessment stage. This entails adopting and implementing a systematic process of assessment of the dossier that builds quality into the assessment. Understanding what critical information is needed to reach an acceptable level of certainty to resolve scientific questions and meet regulatory standards for registration is important [23]. Therefore, identification of critical aspects in the Common Technical Document (CTD) and International Conference for Harmonisation (ICH) E3 bioequivalence structures is paramount.	Figure 1 and 2 as well as the paragraph describing these in page 5 of the original manuscript, has been moved to the results section of the body of the manuscript. This is based on the proposed revision by the Editor. The information included in the figures serve as part of the results for the study aligning with the indicated objective of quantification of the backlog. Due to the relocation of contents that were on page 5, the paragraphs moved some pages up. Page 5 now consists of a continuation of section

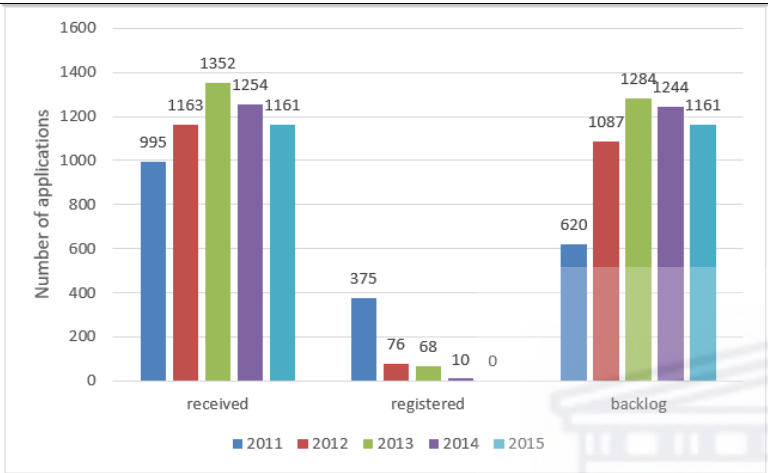


Figure 2: A depiction of the registered products within SAHPRA between 2011-2015 further exacerbating the backlog.

The collective backlog by May 2016 was 7902 applications and only 3779 were registered between 2006-2015 as depicted in Figure 3 [14]. There were 3505 applications in the process of evaluation and not yet approved, while evaluation had not been initiated for 4397 of the applications [15]. This resulted in two separate projects, the first one for the in-process applications which was initiated in 2015, and the second phase for the new applications initiated in 2016. The results from these two phases were investigated and the outcomes are detailed in the results section.

This information was on page 6 of the original manuscript.

Risk-based assessments, involving the thorough evaluation and reporting of only critical sections in the dossier which affect the quality of the specific product, are now commonly applied by a number of regulators [24, 25]. By applying a risk-based assessment, the following are questions to be considered:

- What is the risk to the user and how serious is it?
- What is the weight of evidence that supports that a risk exists?
- What is the expected and the actual benefit for a specific patient?
- Will the risk intensify over time?
- Does the risk outweigh the benefit? [26]

Both practical and theoretical knowledge of regulatory assessment is desirable to achieve a good understanding of the issues likely to be associated with the product under review and identify the risk and the critical aspects [16-17, 27].

1.3 Objectives

The objectives of the study are four-fold:

- quantification of the backlog that developed within SAHPRA,
- defining risk and developing robust criteria for risk classification of products,

1.2 which was previously located on pages 6 and 7.

Section 1.3 Objectives has been included, which is aligned with the author guide

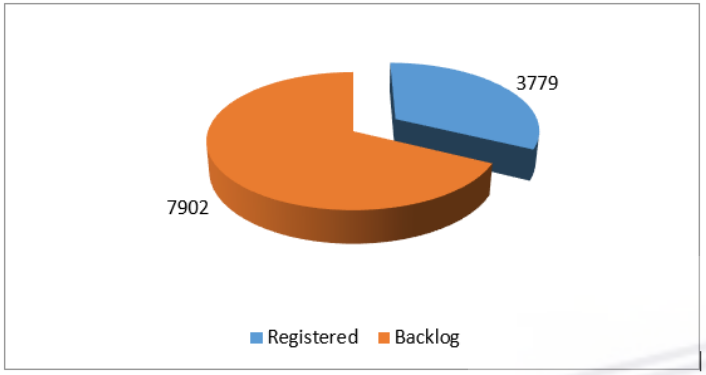


Figure 3: The cumulative outcome of the backlog and registered products between 2006-2015.

Regardless of the great strides in the two phases as detailed below, by 2018 the backlog of applications had expanded tremendously and this necessitated the authority to embark on the Backlog Clearance Programme aimed at clearing the excess applications over a specified timeframe. All 8 220 applications received by SAHPRA prior to 01 February 2018 were part of the backlog project and the ones received after were assessed in the Business-As-Usual (BAU) stream with newly developed assessment models [7]. These assessment models however did not employ the risk-based assessment approach and will therefore not be reported in detail.

- developing a new robust mechanistic review pathway called the risk-based approach and evaluate the review process based on the results of the pilot study conducted,
- detailed description of the implementation of the RBA process aimed at reducing the scientific evaluation timeframes and thereby reduce the overall registration turnaround time within SAHPRA.

2 Methods

2.1 The 2015 backlog project

checklist and recommendation by the Editor.

Figure 3 was deleted as recommended by the Editor and the prescribing paragraph moved to the discussion section.

	(Note that this section was on page 8 of the original manuscript, inclusion here is for comparison purposes) **2 Methods** **2.1 The 2015 backlog project** The backlog project undertaken in 2015 was divided into two phases. The initial phase entailed the identification of the status of 3505 in-process applications and the second phase was on 4397 applications not yet allocated for review. The extensive planning of the backlog project required the collaboration of all Units involved in the registration process which resulted in the formation of a backlog working group. The status of most of these applications by the different Units was unknown and required an extensive investigation in order to obtain the exact status of the products. The list was created, and the documents were titled in the backlog spreadsheet (Microsoft Excel® 2016, Windows 10) which consisted of all the in-process applications in the pre-registration phase.	The backlog project undertaken in 2015 was divided into two phases. The initial phase entailed the identification of the status of in-process applications and the second phase was on applications not yet allocated for review. The extensive planning of the backlog project required the collaboration of all Units involved in the registration process which resulted in the formation of a backlog working group. The status of most of these applications by the different Units was unknown and required an extensive investigation in order to obtain the exact status of the products. The list was created, and the documents were titled in the backlog spreadsheet (Microsoft Excel® 2016, Windows 10) which consisted of all the in-process applications in the pre-registration phase.	Page 5 also consists of the description of the Methods, section 2.1. The section was modified to detail how and when the data was obtained without detailing the results of the study.
	Due to the changes made thus far with the rearrangement of the figures and tables, the comparison will now be on sections rather than pages.		
2.1.1	**2.1.1 Obtaining the status of in-process applications**	**2.1.1 Obtaining the status of in-process applications**	There were no changes to section 2.1.1 under methods.

	SAHPRA initiated an overtime project during weekends to allow for the extraction of the information from the registry files, brown files, dossiers, Committee meeting minutes, applicants etc. For instance, if the product status is unknown, obtaining the information involved the following sequential order and if it is not obtained in one document area, it moves to the next: ● the brown files which should consist of the communications sent to the applicant; ● the Committee meeting minute documents which consist of the history and dates of each application discussed and the outcome thereof; ● registry files which contain the full history of documents received from applicants were checked to see the available history; ● if no information is obtained from the above, the applicant was contacted for a re-submission. It was discovered from this process that a number of Units were not aligned when it comes to evaluations, i.e. one Unit would have finalised an application while another Unit was only at the initial evaluation stage. Therefore, although there might be finalisation in one Unit, registration cannot be executed because another Unit has not finalised the application. When documentation was obtained from the above four areas, it was promptly shared or communicated with the applicant to facilitate review and accelerated the registration process.	SAHPRA initiated an overtime project during weekends to allow for the extraction of the information from the registry files, brown files, dossiers, Committee meeting minutes, applicants etc. For instance, if the product status is unknown, obtaining the information involved the following sequential order and if it is not obtained in one document area, it moves to the next: ● the brown files which should consist of the communications sent to the applicant; ● the Committee meeting minute documents which consist of the history and dates of each application discussed and the outcome thereof; ● registry files which contain the full history of documents received from applicants were checked to see the available history; ● if no information is obtained from the above, the applicant was contacted for a re-submission. It was discovered from this process that a number of Units were not aligned when it comes to evaluations, i.e. one Unit would have finalised an application while another Unit was only at the initial evaluation stage. Therefore, although there might be finalisation in one Unit, registration cannot be executed because another Unit has not finalised the application. When documentation was obtained from the above four areas, it was promptly shared or communicated	

		with the applicant to facilitate review and accelerated the registration process.	
	2.2 New applications – Risk-based review The project was initiated with the available new applications on a first come first serve basis. During this time, the Authority was allocating applications received in 2011 while those received prior, were either registered or in the pre-registration phase under review. There were 208 line-item applications which equate to 150 master applications that were received towards the end of 2011 to 2012 that were not yet reviewed. These were used in the pilot study as they were next in the queue to ensure fairness to all applicants. The intent of the pilot study was to observe the effects of the proposed process with the aim of implementing it to all applications upon assessing the results. The stakeholders such as the applicants and the Expert Committees were a wealth of knowledge regarding processes, historical information, industry insight and in the planning and execution of the project for new applications. It was therefore imperative that they were consulted in the decision-making of the project to allow for a seamless process to occur. The proposed process was outlined, and modifications were made where necessary until a consensus was reached to initiate the pilot project. The proposed process was communicated with all stakeholders involved, which included the CEOs of the pharmaceutical companies in the pilot	**2.2 New applications – Risk-based review** The 2016 pilot project was initiated with the available new applications on a first come first served basis. During this time, the Authority was allocating applications received in 2011 while those received prior, were either registered or in the pre-registration phase under review. There were 208 line-item applications which equate to 150 master applications that were received towards the end of 2011 to 2012 that were not yet reviewed. These were used in the pilot study as they were next in the queue to ensure fairness to all applicants. The intent of the pilot study was to observe the effects of the proposed process with the aim of implementing it to all applications upon assessing the results. There were two separate phases within the project, the first one for the in-process applications which was initiated in 2015, and the second phase for the new applications initiated in 2016. For the 2021 pilot study, the applications that were next in line for allocation were in re-submission window eight (8) and were therefore used for further optimisation and efficiency of the process.	Section 2.2 under methods was amended drastically as it was realised that some information included formed part of the results and discussion. Therefore, the information was moved to the relevant sections. This section now strictly includes information on how data was collected, how the pilot studies were initiated and when the studies were conducted.

	study, the P&A expert Committee members and the Unit, the Clinical evaluations expert Committee members and Unit, the members of the MCC registration Committee and the Industry Technical Group (ITG). It was agreed that all new applications not yet reviewed, should be resubmitted to facilitate review. This is because the submission for these products were between 2011-2012, thus, the information in the dossiers was outdated. It was observed that the frequent recommendations for the old applications, since five years had lapsed, were on updates of the stability data, updated Certificate of Suitability (CEP), changes in the methods of synthesis, changes in the API manufacturers, changes in the FPP manufacturers etc. This meant that several changes had occurred to a product over time and in some instances, the product was considered non-existent as the final product manufacturers were no longer in business or were no longer manufacturing it. Thus, after registration, the applicant would apply for post-registration amendments, and by registering the products that essentially no longer exist, MCC was shifting the work to the post-registration Unit without eliminating the burden the Authority faced. Hence, applicants were requested to uplift, update and re-submit the paper documents. Uplifting of the paper dossiers was conducted two months prior to the re-submission date, which gave applicants enough time to update their applications. Consultation with the applicants resulted in withdrawal of 31% of the application due to the lack of business need for the product and only 99 master applications were left for the pilot study. The dossiers were re-		The remaining paragraphs were moved to the results and discussion sections as they expand on the outcomes of the study.

	submitted between 12-16 September 2016, distributed to the respective Units and evaluated by the PEM pre-registration Unit during evaluation week held on 19-23 September 2016. The developed risk-based review process and approach were further piloted in 2021 using the knowledge gained from the 2016 study for optimisation of efficiency. The process was employed within the Backlog Clearance Programme using 63 master applications in re-submission window eight. The study was initiated on 21 September 2021. Even with the two phases as detailed above, by 2018 the backlog of applications had increased to 8 220. In 2018, the authority embarked on a project called the Backlog Clearance Programme aimed at clearing the existing backlog over a specified time. The planning and development of the project was initiated in February 2018 through the assistance of a project consulting firm which assisted in the quantification of the backlog. Inherited processes and practices from the former MCC were re-assessed and the backlog project was initiated in August 2019 to support new methodologies required to achieve the goal of clearing the backlog of applications [15]. However, it should be noted that risk-based assessment was not employed for this project. The applicants were initially requested to indicate if they would like to include their applications in the Backlog Clearance Project. Upon analysis of the business need and proposed timeframe to submit there were 4 610 applications that opted out of the project and 99 applications were		

	withdrawn. Not being part of the backlog project meant once the dossier was ready for resubmission with the new requirements, it would be submitted to the BAU section of SAHPRA. The in-process applications that were near finalisation, by either Units, were assessed in the BAU and concluded. Thus, SAHPRA initiated the Backlog Clearance Project in August 2019 with 3343 applications which translates to 1364 master applications. The Backlog Clearance programme utilised 56 external domestic and international evaluators to conduct the scientific assessments as well as the internal evaluators from the BAU section working overtime to assist with the project. By May 2021, 34% of the applications had been cleared. This was nearly two years after the initiation of the project where the intent was to eliminate the backlog in two years. The program was extended by one year and five months to December 2022 and the delay in the clearance was attributed to the assessments conducted within the P&A pre-registration component due to the bulk of the work done in this Unit [27]. Hence, the necessity for the refinement of the risk-based assessment in September 2021 in effort to conclude the Backlog Clearance Project in the set time.		
3.1	**3 Results and Discussion** **3.1 The 2015 backlog project**	**3 Results** **3.1 The 2015 backlog project**	The results and discussion was combined, however, this was not in line with the author guide, therefore this has been separated.

	The backlog pilot project on the in-process applications succeeded in the registration of 198 products as depicted in Figure 4, while 189 products were withdrawn by applicants after analysis of the business need. For the 2015/2016 cycle, in quarter one (April – June 2015) 34 products were registered, in quarter two (July – September 2015) 43 products were registered, in quarter three (October – December 2015) 88 products were registered and in quarter four (January – March 2016) 33 products were registered. The project achieved the clearance of 387 products in 2015 as well as obtaining the status of all the applications that were pending registration (see Figure 5). The 448 registered applications in Figure 6 include 250 registrations via the normal process that were not part of the pilot project.	For quantification of the backlog, Fig. 1 and 2 illustrates how the backlog resulted within SAHPRA in the period 2006-2015. For example, in 2010, SAHPRA received 1204 applications and could only register 425, resulting in 779 backlog applications. The collective backlog by May 2016 was 7902 applications and only 3779 were registered between 2006-2015 [28]. There were 3505 in-process applications in the initial phase for identification of the status of and 4397 applications not yet allocated for review in the second phase [28]. The results from these two phases were investigated and the outcomes are detailed below. The backlog pilot project on the in-process applications succeeded in the registration of 198 products, while 189 products were withdrawn by applicants after analysis of the business need. For the 2015/2016 cycle, in quarter one (April – June 2015) 34 products were registered, in quarter two (July – September 2015) 43 products were registered, in quarter three (October – December 2015) 88 products were registered and in quarter four (January – March 2016) 33 products were registered. The project achieved the clearance of 387 products in 2015 as well as obtaining the status of all the applications that were pending registration (see Fig. 3). The 448 registered applications include 250	The paragraph that was initially on page 5 detailing the contents displayed in figures 1 and 2 have now been placed in section 3.1 as part of the results section. Figures 1 and 2 as well as all the other figures have been removed from the main body of the manuscript and have now been placed as separate files in line with the author guide. This paragraph was retained in this section and no changes were made.

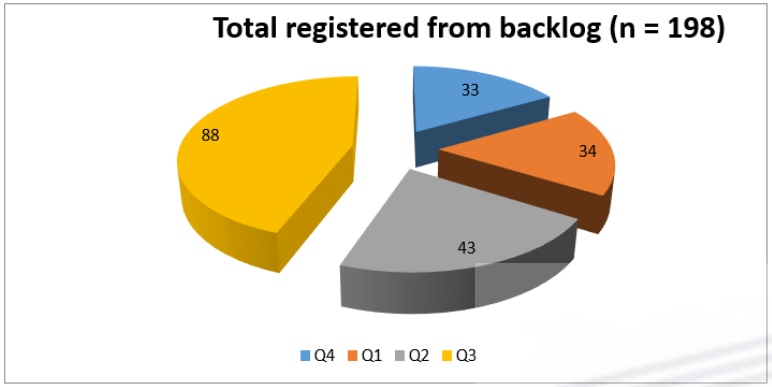


Figure 4: Registration outcome of the project on pending applications in 2015.

Figure 5 shows the grouping of the status of applications obtained during the 2015 project. The exercise managed to identify and classify the status of all pending applications, a task that was historically difficult for the authority. The authority did not have a central database or tracker for applications and relied on individual Units to monitor the applications which led to misalignment within the Units as they were not communicating with one another on evaluations of applications. As a result, there were 707 applications with P&A finalised status, and 519 applications with Clinical finalised status. There were also 244 applications with P&A and Clinical finalised status, however, these could not be approved since the Inspectorate and Names and Scheduling Units had not finalised the applications. These applications were classified as "the low hanging fruits" since they were near registration and only

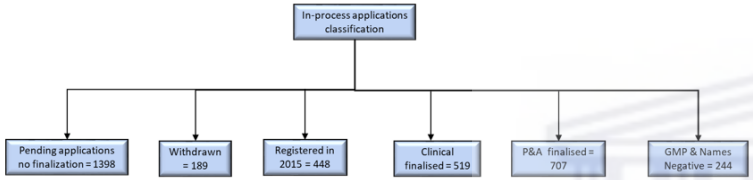
registrations via the normal process that were not part of the pilot project.

Fig. 3 shows the grouping of the status of applications obtained during the 2015 project. The exercise managed to identify and classify the status of all pending applications, a task that was historically difficult for the authority. The authority did not have a central database or tracker for applications and relied on individual Units to monitor the applications which led to misalignment within the Units as they were not communicating with one another on evaluations of applications. As a result, there were 707 applications with P&A finalised status, and 519 applications with Clinical finalised status. There were also 244

Figure 4 has been deleted in line with the recommendation from the Editor. This is because the paragraph above adequately describes the figure thus no need to have the figure as well.

Due to the deletion of 2 of the figures, the remaining figures were renumbered, Figure 5 is now figure 3.

This paragraph was retained in the results section and no changes were made.

	required finalisation by one or two Units. For the P&A finalised applications, it meant that other Units needed to focus on those products to attain registration and vice versa for the other finalised groups.  **Figure 5**: The grouping of the different statuses of the pending products. The identification of the status of each pending application proved to be a success as it allowed for better coordination and management of applications. In addition, obtaining the status of the finalised products from each Unit as outlined in Figure 5 provided a list of applications that each Unit can focus on. Although allocation was conducted at the same time by the Health Products Authorisation (HPA) section, the Units did not initiate the evaluations at the same time. With the improved process this was alleviated as communication to the applicant was synchronised for all the applications.	applications with P&A and Clinical finalised status, however, these could not be approved since the Inspectorate and Names and Scheduling Units had not finalised the applications. These applications were classified as "the low hanging fruits" since they were near registration and only required finalisation by one or two Units. For the P&A finalised applications, it meant that other Units needed to focus on those products to attain registration and vice versa for the other finalised groups.	Figure 5 is now removed and included as a separate file called Fig3. The title of the figure was amended to be more descriptive as recommended by the Editor. The new title is "Status classification and quantification of the in-process applications once phase 1 of 2015 project was concluded." This paragraph was moved to the discussion section in 4.1 as it explains the findings.
3.2 3.2.1	**3.2 Risk-based assessment process** **3.2.1 Registration process** Once the status of the pending applications was concluded, the authority moved on to reviewing the evaluation pathways for the new applications.	**3.2 Risk-based assessment process** **3.2.1 Registration process**	No changes were made in this paragraph

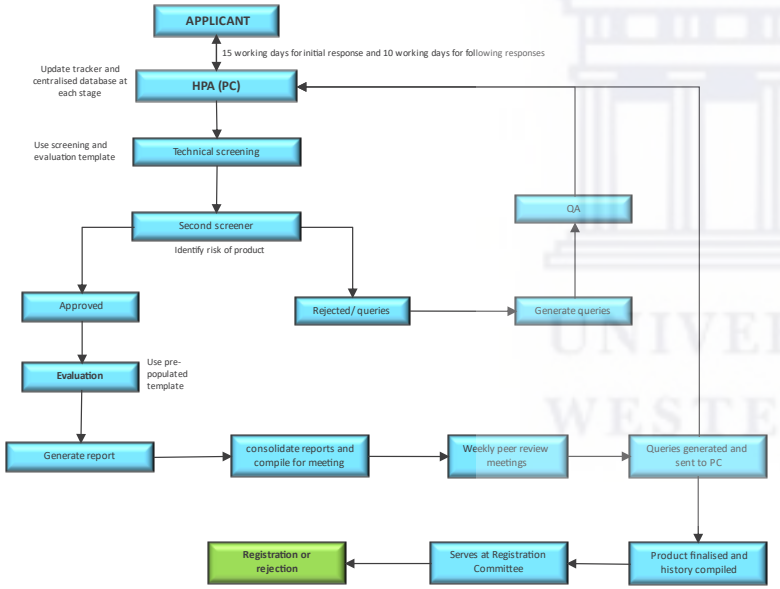
	Strategic planning over a two-year period between 2014-2016 was employed in order to alleviate the backlog by improving the existing registration process. It was important that the process be revisited to ensure that the proposed process is seamless and avoids the formation of a backlog in future. The overall developed and refined process involved changes to the previous practices thereby promoting efficiency and timely access of medicines to patients.  The process is repeated for the response cycle and only 10 working days are allocated for the second response cycle. PC = Portfolio Coordinator.	Once the status of the pending applications was concluded, the authority moved on to reviewing the evaluation pathways for the new applications. Strategic planning over a two-year period between 2014-2016 was employed in order to alleviate the backlog by improving the existing registration process. It was important that the process be revisited to ensure that the proposed process is seamless and avoids the formation of a backlog in future. The overall developed and refined process as detailed in Fig. 4 involved changes to the previous practices thereby promoting efficiency and timely access of medicines to patients.	except the inclusion of the word figure 4. Figure 6 which is now Fig 4 has been moved to a separate file titled Fig 4.

	Figure 6: Proposed risk-based assessment end-to-end registration process in the P&A pre-registration Unit for quality and bioequivalence assessments. The following were improved in the developed process illustrated in Figure 6: ● Previously, the Units were only allocated an application by HPA, thereafter communication with the applicants would be made by the separate Units. There was an introduction of the Portfolio Coordinator (PC) responsible for coordinating and collating outcomes from the Units as one communication to the applicants. ● The introduction of the Inspectorate Unit confirming the Good Manufacturing Practice (GMP) status before allocation to other Units was included since previously, this would only occur once the scientific assessments have been concluded by the P&A and clinical evaluations of pre-registration Units. The inspections being conducted towards the end of the process would further delay the registration of applications. ● The use of a risk-based approach to conduct scientific assessments to reduce the assessment times by the P&A pre-registration Unit with assessments focused on the critical quality attributes of the product. ● The use of a pre-populated evaluation template to aid in the reduction of evaluation times. This allowed for the technical		The discussion on the changes made in the refined process has been moved to the discussion section under 4.3.1, registration process.

	person to screen the applications to check if the updated information such as the updated stability data is as per the requested shelf-life, the updated Certificate of Suitability (CEP) is included etc. ● Frequent peer review meetings. For the 2016 pilot study, an evaluation week approach was used where a week was blocked for evaluation, wherein towards the end of each day evaluators discussed the reports and query letters sent to HPA. This promoted scientific knowledge sharing and ensured that queries going out to the applicants were critical aspects to be addressed in the dossier and that the queries were standardised. This was only conducted once, and the rest of the applications awaited the P&A Committee meetings held on a six-weekly basis. This resulted in some delays. In the refined process in 2021, there were weekly peer review meetings introduced which allowed for better throughput of query letters to the applicants. The selection of the date for each peer review session was based on the availability of evaluators using the When Available poll [28]. The reports were then compiled into meeting documents and uploaded on Google Docs [29] well in advance to allow evaluators to provide their comments. The living document would then show all comments in real-time, allowing all evaluators to see each other's comments. This assisted in drastically reducing the meeting sessions as only specific points of discussion, highlighted by the		

	peer review panel, were discussed. Most other aspects were collaboratively deliberated on during the real-time discussions via the Google Docs. ● The response time was reduced from 90 calendar days to 30 calendar days and only two response cycles were allowed which the pharmaceutical companies agreed on for the 2016 study. In the refined process this was further reduced to 10 working days, however, applicants could request an extension if required. The requests for extension were for 41% of the responses, therefore the response timeline was increased to 15 working days for initial responses and 10 working days for further responses. Once this robust process had been concluded, the products were classified according to risk.		
3.2.2	**3.2.2 Risk classification** Upon re-assessment and refining of the two pilot studies for scale-up and implementation in the BAU section of SAHPRA, the risk classification template was refined through consultation with a number of experts and extensive literature review [22, 30-48]. This resulted in the developed	**3.2.2 Risk classification** Upon re-assessment and refining of the two pilot studies for scale-up and implementation in the BAU section of SAHPRA, the risk classification template was refined through consultation with numerous experts and extensive literature review [21, 30-48]. This resulted in the developed	The first paragraph of section 3.2.2 was expanded to address the query from reviewer #2 on the use of the risk-based assessment for

	risk classification template (Table 2) used for determining the risk of a product. The critical aspects considered during quality and efficacy (bioequivalence) aspects of products submitted for approval are detailed below to assist in the overall classification of the product. When it comes to defining the risk pertaining to the API, the following key aspects of the API are assessed: ● Availability of a valid CEP/CPQ (Certificates of Prequalification (CPQs)), ● Pharmacopoeial status of the API, ● Biopharmaceutics Classification System (BCS) of the API (in particular aqueous solubility), ● Solid state properties (solubility, hygroscopicity, particle size distribution (PSD) and polymorphism), ● The concentration of the API in the FPP. The key aspects to be considered in the FPP are: ● Pharmacopoeial status of the FPP, ● Type of dosage form, ● Complexity of the manufacturing process, ● Excipients, ● Container closure system (CCS). The key aspects in the bioequivalence study:	risk classification template (Table 2) used for determining the risk of generic products including essential medicines that qualify to fall under this pathway.	essential medicines that are of urgent need. The approach will indeed be used for such applications if they qualify to fall under the pathway. This information was moved to the discussion section as it describes the contents on table 2 and 3 further as well as how they were designed. Table 2, 3 and 4 have been moved to the end of the manuscript after the reference list.

	• The bioequivalence (BE) with the reference products and comparative dissolution with the reference products. The model and structure detailed in the concept paper by the WHO was used whereby a scoring is assigned for each aspect to consider and the overall scores was used to determine the risk class of the product using Table 2 [22]. Table 3 indicates the risk classification matrix employed to deduce the overall outcome. **Table 2:** The designed risk classification template. **Table 3:** The risk classification matrix employed to deduce the overall outcome Tables not included due to size. Based on the identified aspects to consider as stated in Table 2, a product could be classified as low- or high-risk. For the products that were part of the pilot studies, the overall risk classification of products was deduced using Table 3 and overall classification detailed in Table 4 according to dosage forms. This shows that the classification largely depends on the dosage form of the product and the manufacturing process of the final product as stated by Tran *et. al*. [34]. **Table 4**: The risk classification outcomes for the products used in the pilot studies. Table not included due to size.	The model and structure detailed in the concept paper by the WHO was used whereby a scoring is assigned for each aspect to consider and the overall scores was used to determine the risk class of the product using Table 2 [21]. Table 3 indicates the risk classification matrix employed to deduce the overall outcome. Note that NCEs and biologicals or biosimilars will not be reviewed using this pathway, full review would be conducted for these applications. For the products that were part of the pilot studies, the overall risk classification of products was deduced using Table 3 and overall classification identified.	It was also included that the RBA pathway is not for NCEs and biological medicines. This paragraph was moved to section 3.2.3, summary of results, as it still forms part of the results of the study but is more relevant in that section.

	From the findings reported, evaluation templates were designed according to the level of risk for evaluators, clearly identifying critical sections for the different risk classifications. The templates are included in the supplementary information. The sections identified as critical are discussed below.	From the findings reported, evaluation templates were designed according to the level of risk for evaluators, clearly identifying critical sections for the different risk classifications. The templates are included as Online Resource 3 and 4. The sections that are critical are identified under the discussion section.	Supplementary material renamed as Online Resource 3 and 4.
3.2.3	**3.2.3 Critical areas to be reviewed for low-risk products** A combination of literature reported by Tran *et. al.* [34] and the concept paper by the WHO [22], as well as a wide array of expert advice garnered on the approach, categorically assisted in the determination of the critical attributes of manufacturing and overall risk ranking of the product. With this information, the CTD sections and extent of evaluation thereof could be established. The areas of concern have been included below and will be thoroughly evaluated for low-risk applications. The relevant templates are used for assessment with the critical sections included. The identified critical sections of the CTD for low-risk applications are as follows: ● Module 1.3 Labelling and packaging (Professional Information (PI), Patient Information Leaflet (PIL) and Label) Quantitative and qualitative composition Storage conditions		Section 3.2.3 of the original manuscript was moved to the discussion section as section 4.3.3.

	Container closure system Appearance ● Module 1.7.4.1 Batch Release API and Inactive Pharmaceutical Ingredient (IPI) batch release Release (Final Product Release Control (FPRC)/Final Product Release Responsibility (FPRR)) ● Module 1.10 Foreign regulatory status Marketing authorisation information for reliance ● Module 3.2.S. Active Pharmaceutical Ingredient 3.2.S.1.3 Physico-chemical properties (depending on dosage form) 3.2.S.2.2 Method of synthesis (N/A if CEP/CPQ is submitted) 3.2.S.3.2 Impurities (N/A if CEP/CPQ is submitted) 3.2.S.4.1/2 Specifications (N/A if CEP/CPQ is submitted, however, assess the API specifications by the FPP manufacturer) 3.2.S.7 Stability (N/A if retest period is stipulated on CEP/CPQ) ● Module 3.2.P Finished Pharmaceutical Product 3.2.P.1 Components and composition of the final product 3.2.P.3.3 Manufacturing process/Batch Manufacturing Record (BMR) 3.2.P.5.1 Specifications		

	3.2.P.7 Container closure system 3.2.P.8 Stability ● Bioequivalence The sections proposed for the bioequivalence section are included below and are in line with ICH and EMA requirements [50-51]. In the case where a BCS-based biowaiver is requested (BCS class I and III applications), only two sections would be assessed. These include the details of the test and reference product used in the study and comparative dissolution profiles, thus reducing the assessment review times. This template, used as an evaluation tool, would reduce the current reported evaluation timelines, as it is designed to point out and discuss critical aspects of the biostudy. The identified sections from the bioequivalence template are as follows: ● Details of the test and reference product used in the study (applicable for biowaiver request) ● Comparative dissolution profiles (applicable for biowaiver request) ● Study method and design ● Summaries of statistical and pharmacokinetic data ● Bioanalytical report parameters		

	Certain sections are excluded from evaluation for low-risk applications. The rationale for these exclusions, which addresses the risk mitigation for each, are as follows: ● Batch analyses (3.2.S.4.4 and 3.2.P.5.4) are not evaluated for low-risk applications because the stability results (3.2.S.7.3 and 3.2.P.8.3) at the initial time point essentially serve as batch analyses. In addition, the impurities section also includes profiling of the impurities and residual solvents formed, thus these sections mitigate the risk since they are assessed. ● Reference materials sections (3.2.S.5 and 3.2.P.6) are for documentation purposes and do not need to be assessed since the API would have been confirmed already in preceding sections, such as the method of synthesis, impurity section and specifications. In most cases, 3.2.P.6 refers to section 3.2.S.5 of the dossier. The working standard and primary standards are those manufactured by the applicant and synthesis would, therefore, be in line with the proposed methods. ● Pharmaceutical development (3.2.P.2) is not assessed for low-risk applications, because this is research and development conducted by the manufacturer for optimisation of the final manufacturing process for commercial product/s. The final proposed manufacturing process is then assessed in section 3.2.P.3.3 and the		

		information is verified by the batch manufacturing records. In addition, for the oral solid dosage forms which require the submission of a bioequivalence study, certain critical aspects of the pharmaceutical development section are evaluated. These include *in vitro* dissolution studies as these are covered in the bioequivalence template for evaluation. For solid oral dosage forms, selection of inactive pharmaceutical ingredients (IPIs) is covered by the bioequivalence assessment where similarity to the reference product is reviewed, and in the case where the excipients are not similar to the reference product, API-excipient compatibility should be confirmed under 3.2.P.2. In the case of liquid dosage forms, excipient similarity to the reference is confirmed under Module 3.2.R.1.4.1 and in the case where the excipients are not similar to the reference product, API-excipient compatibility would be confirmed under 3.2.P.2. The designed templates therefore provide guidance for these. • Module 3.2.P.3.1 details the full name and address of the final product manufacturer. The name of the final product manufacturer is confirmed in the administrative table at the beginning of the pre-populated template. In addition, the Inspectorate Unit confirms and validates this during inspections.		

	• Batch formula (3.2.P.3.2) is not assessed since it is confirmed during assessment of the batch manufacturing records, which consist of actual quantities of API/s and IPI/s used for the proposed batch(es). • Validation of analytical methods (3.2.S.4.3 and 3.2.P.5.3) is not assessed because the product would either be pharmacopoeial and only verification is then required. In addition, specification limits provided found to be within ICH requirements will be confirmed since the specification section is assessed for low-risk applications. At most, the evaluator may only confirm the submission of the reports for noting for low-risk applications.		
3.2.4	**3.2.4 Critical areas to be reviewed for high-risk products** If a product is classified as high-risk, additional sections would also require thorough evaluation and reporting on the respective templates. The additional sections to assess for high-risk products include the following: • Module 1.3 Labelling and packaging (PI, PIL and Label) – same as low-risk • Module 1.7 Good Manufacturing Practice – same as low-risk • Module 1.10 Foreign regulatory status – same as low-risk • Module 3.2.S Active Pharmaceutical Ingredient 3.2.S.4.3 Validation of analytical methods for the API – additional section for high-risk applications		Section 3.2.4 of the original manuscript was moved to the discussion section as section 4.3.4.

	• Module 3.2.P Finished Pharmaceutical Product 3.2.P.2 Pharmaceutical development of the FPP 3.2.P.3.5 Process evaluation of the FPP validation 3.2.P.5.3 Validation of analytical methods for the FPP 3.2.P.7 Container closure system (for sterile applications) • Bioequivalence • Details of the test and reference product used in the study (applicable for biowaiver request) • Comparative dissolution profiles (applicable for biowaiver request) • Study method and design • Summaries of statistical and pharmacokinetic data • Bioanalytical report parameters The justification stated above for the sections that are not to be assessed are also applicable for high-risk applications. Note that risk classification will not be applied to NCEs and biological applications, instead full review will be conducted due to the criticality of the medicines.		
3.2.5 now 3.2.3	**3.2.5 Summary of results on the risk-based approach** Table 5 provides a summary of the results from the backlog pilot project conducted in September 2016 and September 2021 by SAHPRA. There were 10 evaluators used in both pilot studies; for the 2016 pilot, seven were external evaluators and three were internal evaluators while for the	**3.2.3 Summary of results on the risk-based approach** Table 4 provides a summary of the results from the backlog pilot project conducted in September 2016 and September 2021 by SAHPRA. There were 10 evaluators used in both	Due to the relocation of section 3.2.3 and 3.2.4 to the discussion sections, the next section would be numbered as 3.2.3. Table 4 and 5 were swapped for better

	2021 pilot study eight were external and two were internal evaluators. The reported finalisations times and approval times for both studies are depicted in Figure 7 which illustrates the median values for the finalisation times in both pilot studies as well as the reported minimum and maximum times. A number of outliers are witnessed in the depictions for applications that took longer to finalise than the other applications due to applicants not addressing the queries as required. Delays in approval times after finalisations are attributed to other Units not yet finalising the products hence delaying registration. **Table 5**: The summary results of the backlog Phase 1 pilot projects conducted by SAHPRA in 2016 and 2021. **2016 risk-based approach in P&A pre-reg Unit** / **2021 risk-based approach in Backlog clearance program** Product total (master applications): 150 / 63 (RW 8) Withdrawn (opted out): 51 / 6 Product used in the pilot project: 99 / 57 Number of Evaluators used: 10 / 10 Evaluation week (products evaluated): 54 / Weekly meetings for 10 weeks Finalisation time: median: 90 calendar days (3 months) / median: 68 calendar days (2.3 months) Approval time: median: 109 days / median: 110 days	pilot studies; for the 2016 pilot, seven were external evaluators and three were internal evaluators while for the 2021 pilot study eight were external and two were internal evaluators. The reported finalisations times and approval times for both studies are depicted in Fig. 5 which illustrates the median values for the finalisation times in both pilot studies as well as the reported minimum and maximum times. A number of outliers are witnessed in the depictions for applications that took longer to finalise than the other applications due to applicants not addressing the queries as required. Delays in approval times after finalisations are attributed to other Units not yet finalising the products hence delaying registration. This also illustrates how the rate-limiting PEM, P&A pre-registration Unit managed to finalise applications before other Units which has always been a historic problem. Table 5 provides the outcomes of the risk classification of the products that were in the two risk-based assessment pilot studies. This shows that the classification largely depends on the dosage form of the product and the manufacturing process of the final product as stated by Tran *et. al*. [33].	flow of information on the section. Sentence included to elaborate on how the results show that the PEM pre-registration Unit managed to finalise applications before other Units which has always been a historic problem. This paragraph was initially on section 3.2.2 as indicated above and has been moved to section 3.2.3 as it reports on the contents in table 5.

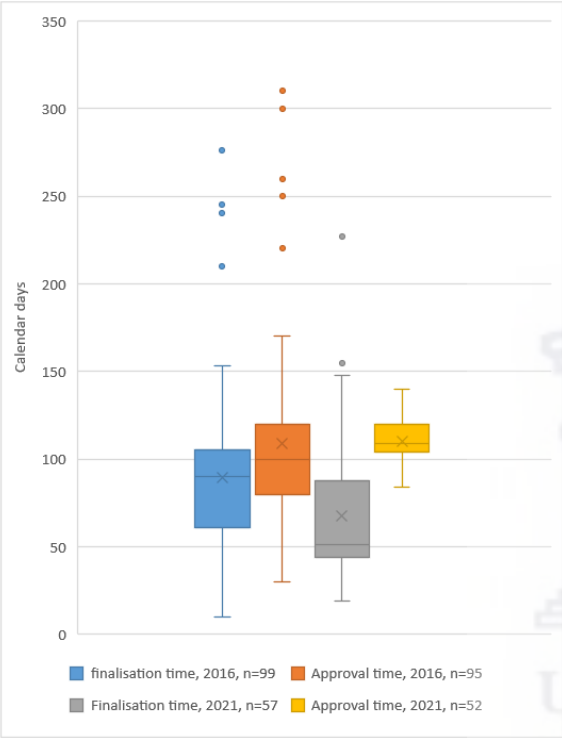


Figure 7: The distribution of finalisation times and approval times for applications in the backlog Phase 1 (2016) and 2021 pilot studies. Box: 25th and 75th percentiles. Whiskers: 5th and 95th percentiles.

In the initial pilot project for new applications, all 99 master applications were finalised within nine months, with the median time calculated as 90 calendar days. The outliers were noted as seven, eight and nine months

Table 5 includes the outcomes of the risk classifications of the products that were part of the two RBA pilot studies.

Figure 7 is now Fig 5 and is included in a separate file called Fig 5.

	as indicated in Figure 7. These were due to the FPP manufacturers receiving a negative status and therefore inspection had to be arranged by the Inspectorate Unit before evaluation could take place. There were other instances where the applicants requested an extension to submit responses and this led to the delay in finalisation. For the refinement of the process in 2021, a median finalisation time of 68 calendar days was obtained as observed in Figure 7. Of the 63 applications, 6 were withdrawn while in-process in the response phase. However, the initial evaluation was already conducted for these so they were included in the calculations of evaluation times. From the 63 applications, 21 applications were classified as high-risk and 42 classified as low-risk as depicted in Table 4. From Table 4, it is observed that all immediate-release tablets and capsules were low-risk which constitute 51% of the applications. From the 90% generic applications that SAHPRA receives, most of these are pharmacopoeial and well-known with readily available extensive research conducted on them therefore due to this, classification would be low-risk. In addition, the dosage forms were not novel therefore overall classification was low-risk. The same applies for the other dosage forms classified as low-risk.		This paragraph has been moved to the discussion section, 4.3.5 on summary of results of the RBA pilot studies.
3.2.6 now 3.2.4	**3.2.6 Assessment timelines** The assessment times were recorded for each application. Figure 8 illustrates the median times obtained for assessment of a simplified low-risk application, high-risk application, bioequivalence assessment, biowaiver assessment and a response assessment. For the 2021 pilot	**3.2.4 Assessment timelines** The assessment times were recorded for each application. Fig. 6 illustrates the median times obtained for assessment of a simplified low-risk application, high-risk application, bioequivalence assessment, biowaiver assessment and a	No changes made to the first paragraph.

	study, four of the applications were omitted from the calculations since two were clones of already registered products and two had pre-approvals by the P&A pre-registration Unit before February 2018, and only minor variations were submitted for review. Hence, the total n value was 59 which is 38 low-risk applications and 21 high-risk applications as depicted in figure 8.	response assessment. For the 2021 pilot study, four of the applications were omitted from the calculations since two were clones of already registered products and two had pre-approvals by the PEM, P&A pre-registration Unit before February 2018, and only minor variations were submitted for review. Hence, the total n value was 59 which is 38 low-risk applications and 21 high-risk applications (Fig. 6). It should be noted that a Phase 2 pilot study was conducted in 2022 in order to monitor upscaling of the number of applications to 156, a different template was used and included as Online Resource 5 which was pre-populated by the applicant and used as an evaluation template for quality assessments. The reported evaluation times for the second phase in 2022 was a median time of 14 hours for high-risk and 10 hours for low-risk applications. The BE, biowaiver and response assessments remained the same as the templates remained the same as the 2021 pilot study results.	Paragraph included to expand on the reported evaluation timelines for a recent study where the quality template was changed. Note that the phase 2 study is not yet concluded in terms of approval of all applications hence not fully reported in this study, however, the timelines mimic that of the 2021 study.

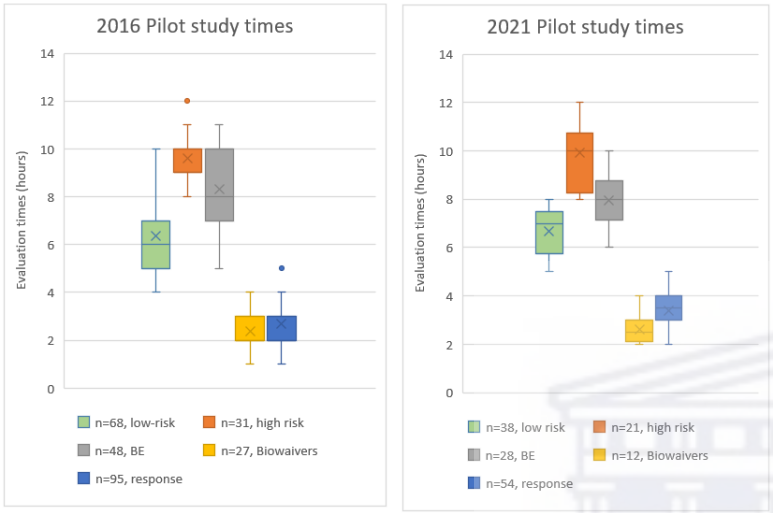


Figure 8: Median evaluation times reported in the two risk-based assessment pilot studies for low-risk, high-risk, BE, biowaiver and responses. (n) = number of product applications. Box: 25th and 75th percentiles. Whiskers: 5th and 95th percentiles.

Figure 8 is now Fig 6 and moved to a separate file called Fig6.

Figure 8 illustrates the reported evaluation times by the evaluators who were part of the two risk-based assessment pilot studies in 2016 and 2021. The graphical depiction shows the calculated median values as 6.3 and 7.0 hours in 2016 and 2021 for low-risk quality assessment timelines. As observed from Table 4, products classified as low-risk were immediate-release tablets and capsules, topical gels, mouth wash, throat spray, oral syrups and oral solutions. The median values for high-risk quality

This paragraph has been moved to the discussion section,

	assessments were reported as 9.5 and 10 hours from the two pilot studies respectively. Products classified as high-risk were sterile intravenous injections and infusions, ophthalmic solutions, delayed-release tablets and sterile lyophilised powders. The bioequivalence study assessment times were 8.4 and 8.0 hours using the proposed template and biowaivers reported as 2.3 and 2.6 hours with initial response assessment times as 2.6 and 3.4 hours. The calculations above were based on a simplified submission that contains one API from one API manufacturer who submitted an Active Pharmaceutical Ingredient Master File (APIMF) with only one FPP manufacturer applied for. In a case where a CEP was submitted the median evaluation times were 5-6 hours for low-risk and 7-8 hours for high-risk, when two APIMFs were submitted, the evaluation times were 11-12 hours for low-risk and 13-14 for high-risk products. This resulted in the deduction that one APIMF assessment takes 4-5 hours and one FPP takes 5-6 hours to assess for high-risk applications. The reported medians have resulted in a reduction in the assessment times without the compromise to quality as only critical sections which will impact the quality of the product are adequately assessed.		4.3.6 on assessment timelines.
4.1	There was no section 4 as discussion on the original manuscript.	**4 Discussion** **4.1 2015 backlog project** For the initial phase of the project, the identification of the status of each pending application proved to be a success as	This paragraph was moved from section 3.1 as indicated above.

		it allowed for better coordination and management of applications. In addition, obtaining the status of the finalised products from each Unit provided a list of applications that each Unit can focus on (Fig. 3). Although allocation was conducted at the same time by the Health Products Authorisation (HPA) section, the Units did not initiate the evaluations at the same time. With the improved process this would be alleviated as communication to the applicant was synchronised for all the applications.	
4.2		**4.2 New applications – Risk based assessments** The planning of second phase of the 2015 backlog involved engagements with other stakeholders in order for the success of the project. The stakeholders such as the applicants and the Expert Committees were a wealth of knowledge regarding processes, historical information, industry insight and in the planning and execution of the project for new applications. It was therefore imperative that they were consulted in the decision-making of the project to allow for a seamless process to occur. The proposed process was outlined, and modifications were made where necessary until a consensus was reached to initiate the pilot project.	This was moved from section 2.2 on new applications, risk-based assessments to this section as this served as a discussion on how the study was planned, reasons why and how it was conducted.

		The proposed process was communicated with all stakeholders involved, which included the CEOs of the pharmaceutical companies in the pilot study, the P&A expert Committee members and the Unit, the Clinical evaluations expert Committee members and Unit, the members of the MCC registration Committee and the Industry Technical Group (ITG). It was agreed that all new applications not yet reviewed, should be resubmitted to facilitate review. This is because the submission for these products were between 2011-2012, thus, the information in the dossiers was outdated. It was observed that the frequent recommendations for the old applications, since five years had lapsed, were on updates of the stability data, updated Certificate of Suitability (CEP), changes in the methods of synthesis, changes in the API manufacturers, changes in the FPP manufacturers etc. This meant that several changes had occurred to a product over time and in some instances, the product was considered non-existent as the final product manufacturers were no longer in business or were no longer manufacturing it. Thus, after registration, the applicant would apply for post-registration amendments, and by registering the products that essentially no longer exist, MCC was shifting the work to the post-registration Unit without eliminating the burden the Authority faced. Hence,	

		applicants were requested to uplift, update and re-submit the paper documents. Uplifting of the paper dossiers was conducted two months prior to the re-submission date, which gave applicants enough time to update their applications. Consultation with the applicants resulted in withdrawal of 31% of the application due to the lack of business need for the product and only 99 master applications were left for the pilot study. The dossiers were re-submitted between 12-16 September 2016, distributed to the respective Units and evaluated by the PEM, P&A pre-registration Unit during evaluation week held on 19-23 September 2016. Even with the two phases as detailed above, by 2018 the backlog of applications had increased to 8 220. In 2018, the authority embarked on a project called the Backlog Clearance Programme aimed at clearing the existing backlog over a specified time. The planning and development of the project was initiated in February 2018 through the assistance of a project consulting firm which assisted in the quantification of the backlog. Inherited processes and practices from the former MCC were re-assessed and the backlog project was initiated in August	

		2019 to support new methodologies required to achieve the goal of clearing the backlog of applications [7]. The applicants were initially requested to indicate if they would like to include their applications in the Backlog Clearance Project. Upon analysis of the business need and proposed timeframe to submit there were 4 610 applications that opted out of the project and 99 applications were withdrawn. Not being part of the backlog project meant once the dossier was ready for resubmission with the new requirements, it would be submitted to the BAU section of SAHPRA. The in-process applications that were near finalisation, by either Units, were assessed in the BAU and concluded. Thus, SAHPRA initiated the Backlog Clearance Project in August 2019 with 3343 applications which translates to 1364 master applications. The Backlog Clearance programme utilised 56 external domestic and international evaluators to conduct the scientific assessments as well as the internal evaluators from the BAU section working overtime to assist with the project. By May 2021, 34% of the applications had been cleared. This was nearly two years after the initiation of the project where the intent was to eliminate the backlog in two years. The program was extended by one year and five months to	

		December 2022 and the delay in the clearance was attributed to the assessments conducted within the PEM, P&A pre-registration component due to the bulk of the work done in this Unit [49]. Hence, the necessity for the refinement of the risk-based assessment in September 2021 in effort to conclude the Backlog Clearance Project in the set time. The 63 applications that were next in line for allocation were in re-submission window eight (8) and were therefore used in the 2021 pilot study. In 2019 when the backlog clearance programme was initiated, the business-as-usual (BAU) section were provided the opportunity to start on a clean slate while the backlog clearance programme dealt with all the ~8220 applications. In the period 2019 and 2022, SAHPRA amended its processes and put systems in place such as the inclusion of a tracker that allows all Units to monitor each other, however, even with that, a backlog has formed within the BAU section of SAHPRA. The tracker was aimed at providing transparency and synchonisation within the Units, however, this did not correct the misalignment as Units could still allocate the same applications at different times and communicate the queries at different times. The solution to this would have been having one set of queries from the different Units communicated at the same time by	This paragraph has been included in order to provide clarity on queries raised by reviewer #2 and #4. Reviewer #2 raised a query on whether alignment of the Units alone would solve the backlog while reviewer #4 wanted to know if there were steps that SAHPRA ha taken to correct this.

		the PC, as conducted in the 2016 study. This ensures alignment within Units at all times. This meant some Units would finalise applications before others which leads to the misalignment. It should be noted that the root cause of the backlog is not as a result of one factor such as the misalignment of Units only, there is a number of reasons which are detailed in the study which is why the risk-based assessment approach was developed as an end-to-end registration process providing corrective or preventative measures or solutions to prevent the root causes from occurring in future.	
4.3.1		**4.3 Risk-based assessment process** **4.3.1 Registration process** A reassessment of processes was a necessity for the authority for improved efficiencies. An improved registration process was employed as detailed in Fig. 4. The following were improved in the developed process illustrated in Fig. 4: ● Previously, the Units were only allocated an application by HPA, thereafter communication with the applicants would be made by the separate Units. There was an introduction of the Portfolio Coordinator (PC) responsible for coordinating and	This section was moved from the results section, 3.2.1, as indicated above.

		collating outcomes from the Units as one communication to the applicants. ● The introduction of the Inspectorate Unit confirming the Good Manufacturing Practice (GMP) status before allocation to other Units was included since previously, this would only occur once the scientific assessments have been concluded by the PEM, P&A and clinical evaluations of pre-registration Units. The inspections being conducted towards the end of the process would further delay the registration of applications. ● The use of a risk-based approach to conduct scientific assessments to reduce the assessment times by the PEM, P&A pre-registration Unit with assessments focused on the critical quality attributes of the product. ● The use of a pre-populated evaluation template to aid in the reduction of evaluation times. This allowed for the technical person to screen the applications to check if the updated information such as the updated stability data is as per the requested shelf-life, the updated Certificate of Suitability (CEP) is included etc.	

		• Frequent peer review meetings. For the 2016 pilot study, an evaluation week approach was used where a week was blocked for evaluation, wherein towards the end of each day evaluators discussed the reports and query letters sent to HPA. This promoted scientific knowledge sharing and ensured that queries going out to the applicants were critical aspects to be addressed in the dossier and that the queries were standardised. This was only conducted once, and the rest of the applications awaited the P&A Committee meetings held on a six-weekly basis. This resulted in some delays. In the refined process in 2021, there were weekly peer review meetings introduced which allowed for better throughput of query letters to the applicants. The selection of the date for each peer review session was based on the availability of evaluators using the When Available poll. The reports were then compiled into meeting documents and uploaded on Google Docs well in advance to allow evaluators to provide their comments. The living document would then show all comments in real-time, allowing all evaluators to see each other's comments. This assisted in	

		drastically reducing the meeting sessions as only specific points of discussion, highlighted by the peer review panel, were discussed. Most other aspects were collaboratively deliberated on during the real-time discussions via the Google Docs. • The response time was reduced from 90 calendar days to 30 calendar days and only two response cycles were allowed which the pharmaceutical companies agreed on for the 2016 study. In the refined process this was further reduced to 10 working days, however, applicants could request an extension if required. The requests for extension were for 41% of the responses, therefore the response timeline was increased to 15 working days for initial responses and 10 working days for further responses. Once this robust process had been concluded, the products were classified according to risk.	
4.3.2		**4.3.2 Risk classification** Ahead of assessing the aspects of the API and FPP, prior work conducted by other NRAs or Regulatory Institutions should be considered. Recognition of the work previously done is termed as reliance. And, according to the WHO, reliance is defined as the act whereby one regulatory	This paragraph was included to address the recommendation **d** from reviewer #4. The paragraph now introduces external

		authority in one jurisdiction may consider and give significant weight to totally or partially rely upon scientific assessments or inspection reports performed by another authority or trusted institution in reaching its own decision [21]. The relying authority uses this work according to its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities. The authorities which SAHPRA aligns itself with and uses the unredacted reports of are the European Medicines Agency (EMA), Health Canada, Medicines and Health Products Regulatory Agency (MHRA) in the United Kingdom, Ministry of Health, Labour and Welfare (MHLW) in Japan, Swiss Agency for Therapeutic Products (Swissmedic), Therapeutic Goods Administration (TGA), Australia and USFDA [50]. SAHPRA is also currently utilising partial reliance through the use of submissions such as CEPs by the European Directorate for the Quality of Medicines (EDQM) and Certificates of Prequalification (CPQs) of the API by the World Health Organisation Prequalification Team: Medicines (WHO PQTm). The developed template in Table 2 therefore accommodates the reliance aspect as well during risk classification. The non-reliance critical aspects are also considered during quality and efficacy (bioequivalence) aspects of products	reliance which is an aspect that is assessed first during risk classification as shown in the developed template as table 2. The paragraph further details the authorities which SAHPRA aligns with and will accept the unredacted reports of. Partial reliance is also described which is an aspect the authority also uses which assists in reduced approval times.

		submitted for approval and detailed below to assist in the overall classification of the product. When it comes to defining the risk pertaining to the API, the following key aspects of the API are assessed: ● Availability of a valid CEP/CPQ (Certificates of Prequalification (CPQs)), ● Pharmacopoeial status of the API, ● Biopharmaceutics Classification System (BCS) of the API (in particular aqueous solubility), ● Solid state properties (solubility, hygroscopicity, particle size distribution (PSD) and polymorphism), ● The concentration of the API in the FPP. The key aspects to be considered in the FPP are: ● Pharmacopoeial status of the FPP, ● Type of dosage form, ● Complexity of the manufacturing process, ● Excipients, ● Container closure system (CCS). The key aspects in the bioequivalence study: ● The bioequivalence (BE) with the reference products and comparative dissolution with the reference products.	This paragraph has been moved from section 3.2.2 as indicated above.

		Based on the identified aspects to consider as stated in Table 2, a product could be classified as low- or high-risk.	
		4.3.3 Critical areas to be reviewed for low-risk products A combination of literature reported by Tran *et. al.* [33] and the concept paper by the WHO [20], as well as a wide array of expert advice garnered on the approach, categorically assisted in the determination of the critical attributes of manufacturing and overall risk ranking of the product. With this information, the CTD sections and extent of evaluation thereof could be established. The areas of concern have been included below and will be thoroughly evaluated for low-risk applications. The relevant templates are used for assessment with the critical sections included. The identified critical sections of the CTD for low-risk applications are as follows: ● Module 1.3 Labelling and packaging (Professional Information (PI), Patient Information Leaflet (PIL) and Label) Quantitative and qualitative composition Storage conditions Container closure system Appearance ● Module 1.7.4.1 Batch Release	Moved from section 3.2.2 as indicated above.

		API and Inactive Pharmaceutical Ingredient (IPI) batch release Release (Final Product Release Control (FPRC)/Final Product Release Responsibility (FPRR)) • Module 1.10 Foreign regulatory status Marketing authorisation information for reliance • Module 3.2.S. Active Pharmaceutical Ingredient 3.2.S.1.3 Physico-chemical properties (depending on dosage form) 3.2.S.2.2 Method of synthesis (N/A if CEP/CPQ is submitted) 3.2.S.3.2 Impurities (N/A if CEP/CPQ is submitted) 3.2.S.4.1/2 Specifications (N/A if CEP/CPQ is submitted, however, assess the API specifications by the FPP manufacturer) 3.2.S.7 Stability (N/A if retest period is stipulated on CEP/CPQ) • Module 3.2.P Finished Pharmaceutical Product 3.2.P.1 Components and composition of the final product 3.2.P.3.3 Manufacturing process/Batch Manufacturing Record (BMR)	

		3.2.P.5.1 Specifications 3.2.P.7 Container closure system 3.2.P.8 Stability ● Bioequivalence The sections proposed for the bioequivalence section are included below and are in line with ICH and EMA requirements [51-52]. In the case where a BCS-based biowaiver is requested (BCS class I and III applications), only two sections would be assessed. These include the details of the test and reference product used in the study and comparative dissolution profiles, thus reducing the assessment review times. This template, used as an evaluation tool, would reduce the current reported evaluation timelines, as it is designed to point out and discuss critical aspects of the biostudy. The identified sections from the bioequivalence template are as follows: ● Details of the test and reference product used in the study (applicable for biowaiver request) ● Comparative dissolution profiles (applicable for biowaiver request) ● Study method and design	

		• Summaries of statistical and pharmacokinetic data • Bioanalytical report parameters Certain sections are excluded from evaluation for low-risk applications. The rationale for these exclusions, which addresses the risk mitigation for each, are as follows: • Batch analyses (3.2.S.4.4 and 3.2.P.5.4) are not evaluated for low-risk applications because the stability results (3.2.S.7.3 and 3.2.P.8.3) at the initial time point essentially serve as batch analyses. In addition, the impurities section also includes profiling of the impurities and residual solvents formed, thus these sections mitigate the risk since they are assessed. • Reference materials sections (3.2.S.5 and 3.2.P.6) are for documentation purposes and do not need to be assessed since the API would have been confirmed already in preceding sections, such as the method of synthesis, impurity section and specifications. In most cases, 3.2.P.6 refers to section 3.2.S.5 of the dossier. The working standard and primary standards are those	

		manufactured by the applicant and synthesis would, therefore, be in line with the proposed methods. ● Pharmaceutical development (3.2.P.2) is not assessed for low-risk applications, because this is research and development conducted by the manufacturer for optimisation of the final manufacturing process for commercial product/s. The final proposed manufacturing process is then assessed in section 3.2.P.3.3 and the information is verified by the batch manufacturing records. In addition, for the oral solid dosage forms which require the submission of a bioequivalence study, certain critical aspects of the pharmaceutical development section are evaluated. These include *in vitro* dissolution studies as these are covered in the bioequivalence template for evaluation. For solid oral dosage forms, selection of inactive pharmaceutical ingredients (IPIs) is covered by the bioequivalence assessment where similarity to the reference product is reviewed, and in the case where the excipients are not similar to the reference product, API-excipient	

		compatibility should be confirmed under 3.2.P.2. In the case of liquid dosage forms, excipient similarity to the reference is confirmed under Module 3.2.R.1.4.1 and in the case where the excipients are not similar to the reference product, API-excipient compatibility would be confirmed under 3.2.P.2. The designed templates therefore provide guidance for these. • Module 3.2.P.3.1 details the full name and address of the final product manufacturer. The name of the final product manufacturer is confirmed in the administrative table at the beginning of the pre-populated template. In addition, the Inspectorate Unit confirms and validates this during inspections. • Batch formula (3.2.P.3.2) is not assessed since it is confirmed during assessment of the batch manufacturing records, which consist of actual quantities of API/s and IPI/s used for the proposed batch(es). • Validation of analytical methods (3.2.S.4.3 and 3.2.P.5.3) is not assessed because the product would either be pharmacopoeial and only verification is then required. In addition,	

		specification limits provided found to be within ICH requirements will be confirmed since the specification section is assessed for low-risk applications. At most, the evaluator may only confirm the submission of the reports for noting for low-risk applications.	
		4.3.4 Critical areas to be reviewed for high-risk products If a product is classified as high-risk, additional sections over and above the ones identified for low-risk, would also require thorough evaluation and reporting on the respective templates. The additional sections to assess for high-risk products include the following: ● Module 1.3 Labelling and packaging (PI, PIL and Label) – same as low-risk ● Module 1.7 Good Manufacturing Practice – same as low-risk ● Module 1.10 Foreign regulatory status – same as low-risk ● Module 3.2.S Active Pharmaceutical Ingredient 3.2.S.4.3 Validation of analytical methods for the API – additional section for high-risk applications ● Module 3.2.P Finished Pharmaceutical Product	Moved from section 3.2.2 as indicated above.

		3.2.P.2 Pharmaceutical development of the FPP 3.2.P.3.5 Process evaluation of the FPP validation 3.2.P.5.3 Validation of analytical methods for the FPP 3.2.P.7 Container closure system (for sterile applications) ● Bioequivalence ● Details of the test and reference product used in the study (applicable for biowaiver request) ● Comparative dissolution profiles (applicable for biowaiver request) ● Study method and design ● Summaries of statistical and pharmacokinetic data ● Bioanalytical report parameters The justification stated above for the sections that are not to be assessed are also applicable for high-risk applications. Note that risk classification will not be applied to NCEs and biological applications, instead full review will be conducted due to the criticality of the medicines.	

		4.3.5 Summary of results on the risk-based approach In the second phase of the 2015 backlog pilot project for new applications, all 99 master applications were finalised within nine months, with the median time calculated as 90 calendar days. The outliers were noted as seven, eight and nine months as indicated in Fig. 5. These were due to the FPP manufacturers receiving a negative status and therefore inspection had to be arranged by the Inspectorate Unit before evaluation could take place. There were other instances where the applicants requested an extension to submit responses and this led to the delay in finalisation. For the refinement of the process in 2021, a median finalisation time of 68 calendar days was obtained (Fig. 5). Of the 63 applications, 6 were withdrawn while in-process in the response phase. However, the initial evaluation was already conducted for these so they were included in the calculations of evaluation times. From the 63 applications, 21 applications were classified as high-risk and 42 classified as low-risk as depicted in Table 5. From Table 5, it is observed that all immediate-release tablets and capsules were low-risk which constitute 51% of the applications. From the 90% generic applications that	Moved from section 3.2.3 as indicated above.

		SAHPRA receives, most of these are pharmacopoeial and well-known with readily available extensive research conducted on them therefore due to this, classification would be low-risk. In addition, the dosage forms were not novel therefore overall classification was low-risk. The same applies for the other dosage forms classified as low-risk.	
		4.3.6 Assessment timelines Fig. 6 illustrates the reported evaluation times by the evaluators who were part of the two risk-based assessment pilot studies in 2016 and 2021. The graphical depiction shows the calculated median values as 6.3 and 7.0 hours in 2016 and 2021 for low-risk quality assessment timelines. As observed from Table 4, products classified as low-risk were immediate-release tablets and capsules, topical gels, mouth wash, throat spray, oral syrups and oral solutions. The median values for high-risk quality assessments were reported as 9.5 and 10 hours from the two pilot studies respectively. Products classified as high-risk were sterile intravenous injections and infusions, ophthalmic solutions, delayed-release tablets and sterile lyophilised powders. The bioequivalence study assessment times were 8.4 and 8.0 hours using the proposed template and biowaivers reported as 2.3 and 2.6 hours with initial response assessment times as 2.6 and 3.4 hours. The calculations above were based on	Moved from section 3.2.6 as indicated above.

		a simplified submission that contains one API from one API manufacturer who submitted an Active Pharmaceutical Ingredient Master File (APIMF) with only one FPP manufacturer applied for. In a case where a CEP was submitted the median evaluation times were 5-6 hours for low-risk and 7-8 hours for high-risk, when two APIMFs were submitted, the evaluation times were 11-12 hours for low-risk and 13-14 for high-risk products. This resulted in the deduction that one APIMF assessment takes 4-5 hours and one FPP takes 5-6 hours to assess for high-risk applications. The reported medians have resulted in a reduction in the assessment times without the compromise to quality as only critical sections which will impact the quality of the product are adequately assessed. For the Phase 2 pilot study conducted in 2022, the quality assessment timelines for high-risk is reported as a median of 14 hours and 10 hours for low-risk. The increased assessment timeline is due to the different quality template used which has been pre-populated by the applicant. The evaluators therefore would spend time validating the information populated by the applicant with the scientific information in the dossier to ensure that accurate information was completed.	Expanded to discuss the reported results on the assessment timelines for the RBA Phase 2 pilot study.

		Once applications that undergo the risk-based assessment pathway are registered, the following post-marketing-surveillance or monitoring procedures were proposed and will be conducted: • The applicant will be requested to provide the post-registration reports on a yearly basis to Pharmacovigilance and annual product review report to the Inspectorate Unit. Depending on the information submitted on the reports, the Inspectorate could perform inspections of the non-compliant manufacturer/applicant. • Ongoing post-marketing surveillance will be conducted on the products by the Inspectorate Unit. • Re-evaluation of the information (dossiers) after five (5) years will be conducted on all applications.	This paragraph has been included to address the recommendation **c** by reviewer #4. Once the applications are registered, post-marketing surveillance will be conducted as described in the paragraph.
	4 Conclusions The large influx of applications as a result of "dossier farming" as well as resource constraints experienced by SAHPRA over the years resulted in the formation of a backlog as large as 8 220 applications. The organisation needed to implement drastic changes in order to reduce the timelines to promote timely access to medicines. A backlog pilot project was conducted in 2016 to alleviate the existing backlog of applications at	**5 Conclusions** The large influx of applications as a result of "dossier farming" as well as resource constraints experienced by SAHPRA over the years resulted in the formation of a backlog as large as 8 220 applications. The organisation needed to implement drastic changes in order to reduce the timelines to promote timely access to medicines. A backlog	

	the time. The pilot project consisted of 99 master applications and managed to reduce the finalisation timelines to a median value of 90 calendar days. The refined and efficient process was described in detail as well as the knowledge gained from the project. These learnings were used in the refined and optimised risk-based assessment pilot study in 2021. This pilot study was initiated with applications from re-submission window 8 of the Backlog clearance programme project initiated by SAHPRA in 2019. The study was resumed with 63 applications and a median finalisation time of 68 calendar days recorded which is significantly lower compared to the initial pilot study. The risk-based approach is discussed in detail as it involves the robust risk classification matrix to employ which allows for the categorisation of a product to the adequate risk class. The approach also details which sections of the CTD and bioequivalence study are considered critical for comprehensive assessment. The identified sections for the assessment of the two risk classes ensures that quality, safety and efficacy are not compromised while accelerated access to medicine for patients. The risk-based approach therefore essentially aims to reduce the finalisation timelines for quality and bioequivalence assessments for authorities which will greatly reduce the overall registration timelines. Implementation of this approach by other regulatory authorities will assist in the reduction of the backlog of applications created due to resource constraints and the large influx of applications that are of urgent need to the public.	pilot project was conducted in 2016 to alleviate the existing backlog of applications at the time. The pilot project consisted of 99 master applications and managed to reduce the finalisation timelines to a median value of 90 calendar days. The refined and efficient process was described in detail as well as the knowledge gained from the project. These learnings were used in the refined and optimised risk-based assessment pilot study in 2021. This pilot study was initiated with applications from re-submission window 8 of the Backlog clearance programme project initiated by SAHPRA in 2019. The study was resumed with 63 applications and a median finalisation time of 68 calendar days recorded which is significantly lower compared to the initial pilot study (90 calendar days) and the current process employed by SAHPRA for the backlog clearance programme initiated in 2019, which resulted in the finalisation time of 501 calendar days. The risk-based approach is discussed in detail as it involves the robust risk classification matrix to employ which allows for the categorisation of a product to the adequate risk class. The approach also details which sections of the CTD and bioequivalence study are considered critical for comprehensive assessment. The identified sections for the assessment of the two risk classes ensures that quality, safety and efficacy are not compromised while accelerating	Inclusion of comparison of finalisation times with the current process as recommended by reviewer #2 and in line with the conclusion of the abstract.

		access to medicine for patients. The risk-based approach therefore essentially aims to reduce the finalisation timelines for quality and bioequivalence assessments for authorities which will greatly reduce the overall registration timelines. Implementation of this approach by other regulatory authorities will assist in the reduction of the backlog of applications created due to resource constraints and the large influx of applications that are of urgent need to the public.	
	References	**References**	All references were reviewed and aligned with the requirements of the author guide as recommended by the Editor. URLs and required information were included where available.
		Tables	All tables were included at the end of the manuscript in line with the author guide checklist. Table 1 is revised to include the additional column with the names of the countries as recommended by reviewer #2. All tables include the full name of the

			abbreviation as a footnote where abbreviation is included.
		List of Figures	The list of all figures has been included in line with the author guide checklist.

RESPONSE TO JOURNAL REVIEWERS

Chapter 7

Regulatory registration timelines of generic medicines in South Africa: Assessment of the performance of SAHPRA between 2011-2022

Lerato Moeti[1,2], Madira Litedu[1], Jacques Joubert[2]

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[2] School of Pharmacy, University of the Western Cape, Cape Town, South Africa.

Response to the Journal of Pharmaceutical Policy and Practice

Response to reviewer #1

Reviewer #1: Your study is in an important area of access to medicines. You will need to address the following aspects to improve on the quality of the paper:

1) The compared three registration processes are not clearly described in the paper. It would be helpful to include a short description of each of the processes with their respective steps, and timeframes if known.

This is well noted. A brief description for the three processes has now been included under the results section on page 6 of the manuscript. A subheading has been created to allow for an adequate flow of information and a figure (Fig. 1) depicting the registration processes.

2) Please clarify which registration process is the "reliance process", P&A pre-registration or another country's registration?

The reliance process is relying on another country's registration. This has been described on page 11 of the manuscript. The sampled applications reported in the manuscript for the three processes MCC, BCP and RBA do not utilise the reliance process. The discussion section initiates with a description of this reliance process on page 11 and addresses the drawbacks of the process to provide context. It was reported that approximately 20% of applications received qualify to undertake the reliance route which is why this may not be the solution to alleviating the backlog.

3) It is unclear what is meant by "finalisation" of product registration process. What are the steps in the registration process and how many Units at the SAHPRA are involved in each of the three studied registration processes?

Finalisation is the conclusion of an assessment by each respective Unit before registration. This is described on page 6 under methods and on page 19 under the subheading finalisation timeframe. The brief description included in the results section now expands the steps within each registration process and the Units involved in finalising the medicine before registration. The application should be finalised by the P&A pre-registration Unit, the Clinical evaluations Unit, Inspectorate Unit and the Names and Scheduling Unit.

4) It is questionable what is/are the root causes of the backlog: shortage of human resources? Inefficient registration processes? Lack of monitoring? Or all these factors. This issue weakens the findings and conclusion/s thereof.

The backlog was not created by one isolated factor, the calculation of the timelines in the findings shows that the root cause is by all these factors as described below.

The root cause of the backlog was identified as inefficient registration processes, comparison of the timelines at each stage of the processes shows the drastic differences further confirming that the MCC and BCP had inefficiencies. These were described in the discussion section for each stage of the process.

Lack of monitoring also contributed to the formation of a backlog since it was shown from the MCC process that a large number of applications had no monitoring mechanism implemented which led to higher timelines at each stage that far exceeded the targeted timeframes.

Shortage of human resources partly played a role in the contribution of a backlog and this is observed from the large queue time reported before allocation for each process. For example, the MCC process reported the time that application waited for initial allocation as 682 calendar days. With more human resources this reduced to 278 calendar days in the BCP process. However, this reduction cannot be attributed to the increase in human resources alone.

5) Please have the manuscript proofread for better structure and flow.

Noted, the manuscript has now been proofread for better structure and flow.

SUPPLEMENTARY MATERIAL

Chapter 3

Common deficiencies found in the Active Pharmaceutical Ingredient (API) section of non-sterile generic products submitted for registration by SAHPRA

Lerato Moeti[1,2], Madira Litedu[1], Jacques Joubert[2]

[1] South African Health Products Regulatory Authority (SAHPRA), Pretoria, South Africa

[2] School of Pharmacy, University of the Western Cape, Cape Town, South Africa.

1. Appendix for equations used to calculate the sample size

Appendix for equations

The equations consist of the following parameters:

z = The confidence level corresponds to a Z-score, for a 95% confidence level z is 1.96

p = The degree of variability,

q = Relates to degree of variability above, indicated as 1-p depending on the variability of the population,

e = Level of precision which is ± 5% for the selected confidence level of 95%,

n_0 = Sample size, note that equation 2 is used for a population size that is less than 3000 to reduce the sample slightly,

N = Population size.

$$n_{0.} = \frac{Z^2 pq}{e^2} \text{.....Equation (1)}$$

$$n = \frac{n.}{1+\frac{n.-1}{N}} \text{.....Equation (2)}$$

$$n_{0.} = \frac{Z^2 pq}{e^2} \text{.....Equation (1)}$$

$$= \frac{1{,}96^2 0{,}5^2}{0{,}05^2}$$

$$= 384.16$$

$$n = \frac{n.}{1+\frac{n.-1}{N}} \quad \text{...Equation (2)}$$

$$= \frac{384.16}{1+\frac{384.16-1}{2089}}$$

$$\underline{n = 325}$$

$$n* = \frac{N*}{kth} \text{...Equation (3)}$$

$$kth = \frac{N*}{n*} \quad \text{...Equation (4)}$$

$$= \frac{2089}{325} = 6.42 \text{ (rounded down to 6)}$$

SUPPLEMENTARY MATERIAL

Chapter 6

The implementation of a risk-based assessment approach by the South African Health Products Authority (SAHPRA)

Lerato Moeti[1,2], Madira Litedu[1], Jacques Joubert[2]

[1] *South African Health Products Regulatory Authority (SAHPRA), Pretoria, South Africa*

[2] *School of Pharmacy, University of the Western Cape, Cape Town, South Africa.*

1. **The organisational structure of SAHPRA**
2. **The quality evaluation template**
3. **The bioequivalence evaluation template**
4. **Risk-based assessment Score document**

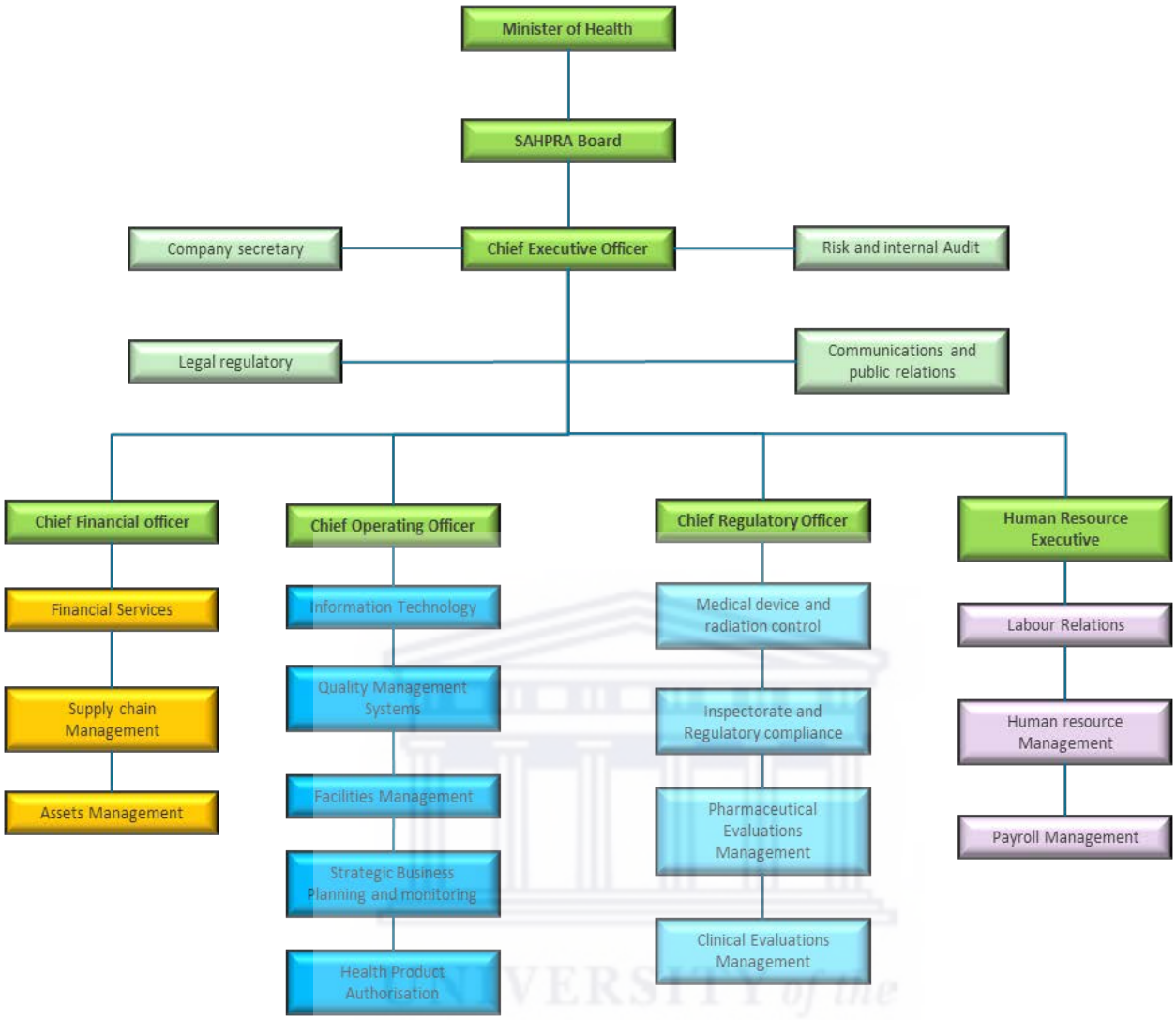


Figure S1a: High-level organisational structure of SAHPRA.

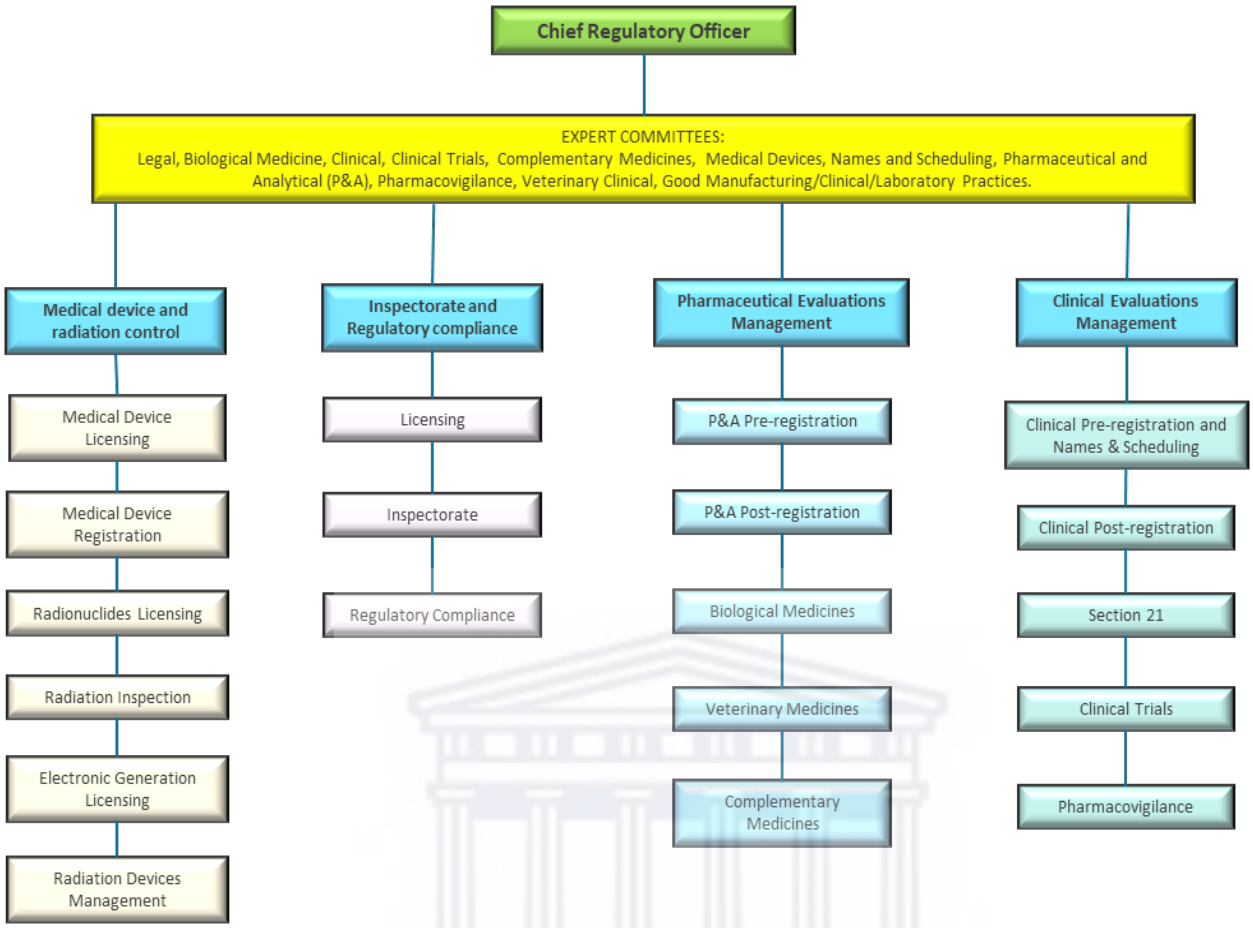


Figure S1b: The SAHPRA structure within the office of the Chief Regulatory Officer (CRO).

PHARMACEUTICAL EVALUATION MANAGEMENT

PRE-REG UNIT EVALUATION REPORT FORMAT

HUMAN	VETERINARY	BIOLOGICAL	NCE	GENERIC	LINE EXT

Date of submission		
Application number	**Number**	
Product (proprietary) name	**Bold and indicate whether compendial**	
Approved name(s) (INN)	Names of APIs and indicate whether compendial	
Applicant		
FPP Manufacturer (plot number and address)		
API manufacturer (plot number and address)	Indicate whether used in the biobatch or/and development batch. If the biobatch and development batch are produced by different manufacturers add an additional row.	
BCS Class and polymorph (if applicable to the final product)		
APIMF number and version/CEP/WHO PQ API		
APIMF/CEP/WHO PQ API date (declaration that is current)		
Scheduling		
Dosage form	State whether immediate or modified release	
Description of dosage form		
Route of Administration		
Risk classification		
Stability of the API		
Date of commencement of study:	**Data available**	**Requested shelf life**

Stability of the Final Product		
Date of commencement of study:	**Data available**	**Requested shelf life**
Strength per unit dose	Include all APIs	
Sterility of the final product	Indicate whether sterile or not, **if sterile use the sterile evaluation template**	
Packaging		
Country of origin	Formulation development	
Foreign registration	Countries where registered	

TECHNICAL SCREENING: The same template to be used for technical screening. The screener to state critical deficiencies found. The information to be populated by the screener are in black text highlighted in yellow. Once the information has been completed, the screener should remove the yellow highlight. The screener's report should be shared with the initial evaluator so that the populated information can be reproduced.

Key:
Red: Initial screener conclusions
Blue: Second screener conclusions.
Red: First reviewer's conclusions.
Comments pane: peer reviewer's comments and discussions
Green: peer review meeting conclusions.
Queries to the applicant by the screener and initial evaluator: Red text highlighted in yellow
MODULE 1

1 General comments on the dossier

Administrative/legal (Module 1)

Labelling (PI, PIL and Label) (Module 1.3)

2.1.1 Name of the product: Ensure this is the same as in the application form.

2.1.2 Qualitative and Quantitative Composition: Ensure this is the same as in the application form and **3.2.P.1**

2.1.3 Pharmaceutical Form: Ensure this is the same as in the application form and **3.2.P.7**

2.1.4 Pharmaceutical Particulars: Ensure the list of excipients is the same as in section **3.2.P.1**

2.1.5 Shelf life: Ensure this is the same as in section **3.2.P.8**

2.1.6 Special precautions for storage: Ensure this is the same as in the application form and **3.2.P.8**

2.1.7 Nature and contents of container: Ensure this is the same as in section **3.2.P.7**

2.1.8 Posology: State the recommended dose, this is important in order to determine the identification and qualification thresholds for related impurities [refer to ICH Q3A (API) and Q3C (Final product). The thresholds are based on maximum daily dose (MDD) and the duration of treatment (acute vs chronic).

Good manufacturing practice (Module 1.7)

2.2.1 Release API, IPIs
2.2.2 Release FPRC/FPRR

Foreign regulatory status

2.3.1 Relevant for reliance pathway. Presence of the reports will be checked at screening.

MODULE 2 – CTD SUMMARIES

Quality Overall Summary - Introduction

3.1.1 (No comments on QOS). Presence will be checked at screening.

MODULE 3 - QUALITY

ACTIVE PHARMACEUTICAL INGREDIENT (Module 3.2.S)

Active Pharmaceutical Ingredient no 1 [Manufacturer 1]

4.1.1 General Information should be confirmed by the screener in order to populate the table above.

Include Structure, molecular formula and few details of the API for completeness of the report.

4.1.2 Sources(s) or Manufacturer of the API should be confirmed by the screener.

4.1.3 Method of Synthesis:
3.2.S.2.2 Assess the appropriateness of the method of synthesis and acceptability of Starting material

3.2.S.2.2 Assessment of nitrosamines should be conducted to confirm potential formation (all products):
The above-mentioned product/s was/were assessed for the presence of N-nitrosamine impurities. The evaluator finds risk assessment acceptable. The evaluator's risk assessment demonstrated that there is no risk of nitrosamines. This is considered acceptable and therefore qualifies the product as safe. OR

The applicant has not provided a risk assessment to SAHPRA as this is not currently available. The applicant has therefore provided a commitment to submit such information as soon as it becomes available. OR

N-nitrosamine impurities are of concern as they are probable human carcinogens. Based on the reaction conditions observed which show potential of formation of nitrosamine impurities it is requested that the possibility of nitrosamine being present in the API be evaluated. OR

A CEP/CPQ has been submitted, therefore the nitrosamine investigation is currently underway and will be concluded by EDQM/WHOPQ.

4.1.4 Degradation Products, Impurities and Related Substances: Check if the proposed specifications are not according to ICH Q3A and residual solvents, elemental impurities, nitrosamines, mutagenic impurities are not included.

4.1.5 Specifications: Ensure that the reference number, version, date are included and also signed. These must be included in the report as indicated in the example below. Confirm compliance with the claimed pharmacopoieal monograph. Ensure the proposed specifications are according to ICH Q3A if not evaluate the impurity section.
The approved FPP manufacturer's API specification:

API manufacturer's API specifications:

4.1.6 Validation of methods: Evaluate for the sterile and non-pharmacopoeial APIs and write a summary of the findings.

4.1.7 Stability protocol, data and retest period: Evaluate data and approve the retest period as the paragraph below. The screener should check this information so they could populate the table above.

A retest period of …. months is approved for API manufactured by ….API manufacturer…. when packed in an inner HMHDPE and outer black polyethene bags enclosed in a fibre drum and stored at or below 30 °C.

Active Pharmaceutical Ingredient no 1 [Manufacturer 1]

4.2.1 xxx
4.2.2 Check 3.2.R.4

Active Pharmaceutical Ingredient no 2 [Manufacturer 1]

4.3.1 xxx

PHARMACEUTICAL PRODUCT (Module 3.2.P)

5.1 Description and Composition of the FPP (Module 3.2.P.1)

5.1.1 INN or approved names, and/or chemical names of all APIs, and polymorph (if relevant to the final formulation).
5.1.2 Names and quantities to correspond with PI/PIL/Label
5.1.3 Purpose of each component
5.1.4 Potency of active
5.1.5 Overages and reasons
5.1.6 Total quantity of unit dose

5.2 Pharmaceutical development (Module 3.2.P.2)

5.2.1 Formulation Development: Assess for the high risk dosage forms
5.2.2 Production History: Assess for the high risk dosage forms
5.2.3 Final product specifications: Assess for the high risk dosage forms
5.2.4 Stability, etc. See stability guideline

5.3 Manufacture (Module 3.2.P.3)

A. [Manufacturer 1]**:**

5.3.1 Batch formula
5.3.2 Manufacturing Process: Assess this in conjunction with the 3.2.R.7 Executed and blank BMRs
5.3.3 Packaging Process: Important for high risks dosage forms
5.3.4 In-Process Controls: Important for high risks dosage forms
5.3.5 Process Validation: Important for high risks dosage forms

B. [Manufacturer 2]:

5.3.6 Check data in 3.2.P.2 and 1.5.2.3 and 3.2.R.1.4

5.4 Control of Inactive Pharmaceutical Ingredients (Module 3.2.P.4): Important for high risks dosage forms

5.4.1 Specifications and limits
5.4.2 Test procedures
5.4.3 Check module 1.7.4
5.4.4 Source (human/animal?)/ TSE/BSE certifications

5.5 Control of the Pharmaceutical Product (Module 3.2.P.5)

5.5.1 Specifications: Ensure that the reference number, version, date are included and also signed. These must be included in the report as indicated in the example below. Confirm compliance with the claimed pharmacopoieal monograph. Ensure the proposed specifications are according to ICH Q3C. If not according to ICH guidance check the impurity profile of the product

5 mg Specification number and version
Release:
Shelf-life:
10 mg Specification number and version
Release:
Shelf-life:

5.5.2 Test Procedures: Important for high risks dosage forms
5.5.3 Validation of Analytical Methods: Important for high risks dosage forms
5.5.4 Batch analysis: Important for high risks dosage forms

5.6 Container closure system (Module 3.2.P.7). Important for high risk dosage form

5.6.1 Specifications and limits
5.6.2 Test procedures

5.7 Stability (Module 3.2.P.8)

5.7.1 Stability Program
5.7.2 Stability Data
5.7.3 Shelf-life. This is important for the screener to populate the table above
5.7.4 Preserving Ability (if applicable)

A shelf life of …. months is approved for …….(product)…. manufactured by ….(FPP manufacturer)….with API manufactured by ….. (API manufacturer)…., when packed in … and stored at or below 30 °C.

Regional information (Module 3.2.R)

6.1 Certificates of Suitability CEPs/ WHO CPQ

6.1.1 Include the number and validity thereof in the report

EVALUATORS

Full name	Signature	Date
1 Screener:		
2 Second screener		
3 Evaluator		
4 Peer reviewer (Group Meeting)		

PHARMACEUTICAL EVALUATION MANAGEMENT

PRE-REG UNIT EVALUATION REPORT - INJECTIONS

HUMAN	VETERINARY	NCE/GENERIC	LINE EXT

Date of submission					
Application number					
Product (proprietary) name					
Approved name(s) (INNM)					
Applicant					
Manufacturer (plot number and address)					
API manufacturer (plot number and address)					
APIMF number and version/CEP/WHO PQ API					
APIMF/CEP/WHO PQ API date (declaration that is current)					
Scheduling					
Dosage form	Solution/Concentrate for dilution	Lyophilized Powder for solution	Powder for solution or suspension	Suspension for injection	Emulsion
Volume of Injection	(≥ 100 ml)			(<100 ml)	
Single dose/Multi dose	Single dose			Multi dose	
Sterilisation method	Autoclaving/Heat	Sterile filtration	Aseptic processing	Other	
Dosage					
Risk classification					
Stability of the API					

Date of commencement of study:	**Data available**		**Requested shelf life**	
Stability of the Final Product				
Date of commencement of study:	**Data available**		**Requested shelf life**	
Strength per unit dose				
Description of dosage form				
Route of administration	IV	IM	IV/IM/SC	Other (Intrathecal)
Packaging				
Country of origin				
Foreign registration				

TECHNICAL SCREENING: The same template to be used for technical screening. The screener to state critical deficiencies found. The information to be populated by the screener are in black text highlighted in yellow. Once the information has been completed, the screener should remove the yellow highlight. The screener's report should be shared with the initial evaluator so that the populated information can be reproduced.

Key:
Red: Initial screener conclusions
Blue: Second screener conclusions.
Red: First reviewer's conclusions.
Comments pane: peer reviewer's comments and discussions
Green: peer review meeting conclusions.
Queries to the applicant by the screener and initial evaluator: Red text highlighted in yellow

1. General

2. Module 1.3 Labeling (PI, PIL and label)

2.1. Are reconstitution or dilution required (*Concentrate for dilution/Lyophilized powder/powder*)?

If so check the instructions in "*Dosage and Directions for use*" for complete instructions including diluents and diluent - volume.

Comments:

2.2. In "*Dosage and Directions for use*" check compatibility information with recommended IV solutions and check whether this has been investigated either in 3.2.P.2 or 3.2.P.8.

Comments:

2.3. Confirm the stability information of the reconstituted/diluted product ("*Dosage and Directions for use" and "Storage instructions").*

2.4. Check that a statement is included for the reconstituted/diluted product to be used immediately and/or include the following statement (unless it is a multi-dose injection and preservative efficacy has been established)

"From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions"

Comments:

2.5. For single dose injections, indicate on the labels that it is for single use and that any unused portion should be discarded.
For multi-dose injections and eye drops indicate that it should not be used for the validated period (normally 30 days) after first opening the container

Comments:

2.6 Name of the product: Ensure this is the same as in the application form.

2.7 Qualitative and Quantitative Composition: Ensure this is the same as in the application form and **3.2.P.1**

2.8 Pharmaceutical Form: Ensure this is the same as in the application form and **3.2.P.7**

2.9 Pharmaceutical Particulars: Ensure the list of excipients is the same as in section **3.2.P.1**

2.10 Shelf life: Ensure this is the same as in section **3.2.P.8**

2.11 Special precautions for storage: Ensure this is the same as in the application form and **3.2.P.8**

2.12 Nature and contents of container: Ensure this is the same as in section **3.2.P.7**

2.13 Posology: State the recommended dose, this is important in order to determine the identification and qualification thresholds for related impurities [refer to ICH Q3A (API) and Q3C (Final product). The thresholds are based on maximum daily dose (MDD) and the duration of treatment (acute vs chronic).

3. Module 1.7 Good manufacturing practice

3.1. Release API, IPIs

Comment:

3.2. Release FPRC/FPRR

Comment:

4 Module 1.10 Foreign regulatory status

4.1 Relevant for reliance pathway. Presence of the reports will be checked at screening.

5 Module 2 CTD Summaries

5.1 This should reflect a summary of the essential information as indicated in 3.2.P.2.

Comment:

6 Module 3.2.S

6.1 The required information is the same as for all products except when the API is sterile and/or blended with another API or IPIs. See Quality and bioequivalence guideline 3.2.S.2.2 "Other relevant aspects, e.g. preparation of sterile material (full description of aseptic or sterilisation process including conditions), if there is no further sterilisation of the FPP". See also attached Policy regarding the Manufacture of Blended Powders for Injection.

6.2 Microbial purity and Bacterial endotoxins should be included as a specification when the API is used for the manufacture of sterile products. This is normally not part of the specifications for the API by the API manufacturers or pharmacopoeial specifications and should be added.

6.3 Method of Synthesis: 3.2.S.2.2 Assess the appropriateness of the method of synthesis and acceptability of Starting material

3.2.S.2.2 Assessment of nitrosamines should be conducted to confirm potential formation (all products):

The above-mentioned product/s was/were assessed for the presence of N-nitrosamine impurities. The evaluator finds risk assessment acceptable. The evaluator's risk assessment demonstrated that there is no risk of nitrosamines. This is considered acceptable and therefore qualifies the product as safe. OR

The applicant has not provided a risk assessment to SAHPRA as this is not currently available. The applicant has therefore provided a commitment to submit such information as soon as it becomes available. OR

N-nitrosamine impurities are of concern as they are probable human carcinogens. Based on the reaction conditions observed which show potential of formation of nitrosamine impurities it is requested that the possibility of nitrosamine being present in the API be evaluated. OR
A CEP/CPQ has been submitted, therefore the nitrosamine investigation is currently underway and will be concluded by EDQM/WHOPQ.

6.4 Degradation Products, Impurities and Related Substances: Check if the proposed specifications are not according to ICH Q3A and residual solvents, elemental impurities, nitrosamines, mutagenic impurities are not included.

6.5 Specifications: Ensure that the reference number, version, date are included and also signed. These must be included in the report as indicated in the example below. Confirm compliance with the claimed pharmacopoieal monograph. Ensure the proposed specifications are according to ICH Q3A if not evaluate the impurity section.
The approved FPP manufacturer's API specification:
The approved API manufacturer's API specification:

6.6 Validation of methods: Evaluate for the sterile APIs and write a summary of the findings.
6.7 Stability protocol, data and retest period: Evaluate data and approve the retest period as the paragraph below. The screener should check this information so they could populate the table above.

6.8 A retest period of …. months is approved for API manufactured by ….API manufacturer…. when packed in …and stored at or below 30 °C.

7 Module 3.2.P.1 Description and Composition of the FPP

7.1 If Nitrogen is used as a pressure source for filtration, it must be included in the unitary and batch formula and indicated in a footnote that it is not present in the final product. It must be controlled in 3.2.P.4.

7.2 INN or approved names, and/or chemical names of all APIs, and polymorph (if relevant to the final formulation).
7.3 Names and quantities to correspond with PI/PIL/Label
7.4 Purpose of each component
7.5 Potency of active
7.6 Overages and reasons
7.7 Total quantity of unit dose

8 Module 3.2.P.2 Pharmaceutical development

8.1 The information in this module is very important and the following should be adhered to.

Formulation Development: Assess for the high-risk dosage forms such as steriles and metered dose inhalations.
Production History: Assess for the high-risk dosage forms
Final product specifications: Assess for the high-risk dosage forms

Stability, etc. See stability guideline

8.2 Of specific importance to injections are the physical form of the injection, the route of administration (IV,IM,SC or other) and the volume of the injection. The primary concern is:

- Sterility and maintanance of sterility of the product
  - Sterilisation method
  - Container-closure integrity
  - Preservative efficacy (multi-dose injections)
- Bacterial endotoxins
  - Control of the APIs and IPIs (specifications)
  - Depyrogenation of glass containers
- Physiological acceptability
  - pH
  - isotonicity
  - partuculate matter
  - viscosity
  - density

Comments:

All these aspects should be addressed during Formulation development and Manufacturing process development where appropriate to the dosage form, volume of injection and route of administration, e.g.:

- The choice of sterilization method must be investigated according to the decision tree for the choice of sterilization methods. Autoclaving is the method of choice. Any other method should be motivated.
- Container-closure integrity should always be validated
- The solubility of the API and the influence of pH on the solubility in water or the chosen solvent should be investigated for APIs of poor solubility.
- Compatibility of the product with production equipment, filter-media, and diluents for IV administration and container components should be addressed.
- Possible precipitation of poorly soluble APIs during storage and after administration should be addressed
- Viscosity is essential for IM injections
- Density and viscosity is important in injections in the spinal column e.g. epidural injections.
- Droplet size distribution is of major concern for IV oil-in-water emulsions(propofol).
- Preservative efficacy in multi-dose containers must be addressed; however, often this is being addressed in 3.2.P.8.
- In-use stability of reconstituted or diluted injections must be addressed.

- For Lyophilized injections the development and validation of the lyophilisation cycle is important.
- When a product is sterilized by filtration, the APIs and IPIs need not be sterile but should have a very low bioburden and should be endotoxin-free. All steps after filtration should take place in a Class A area with a Class B background.
- For products such as powders, all APIs and IPIs should be sterile and the whole manufacturing process should take place in a Class A/B area.

9 Module 3.2.P.3 Manufacture

9.1 The Quality and Bioequivalence guideline **3.2.P.3.3** specifies that the following should be submitted:

- A comprehensive flow diagram, detailing the various stages of manufacturing - and
- A comprehensive description of the manufacturing procedures detailing the various stages of manufacturing – derived from the master manufacturing records.

9.2 A. [Manufacturer 1]:

Manufacturing Process: Assess in conjunction with the BMRs and 3.2.P.3.5 process validation.

Packaging Process: Important for high risks dosage forms

In-Process Controls: Important for high risks dosage forms

Process Validation: Assess in conjunction with 3.2.P.3.3

B. [Manufacturer 2]:

Check data in 3.2.P.2 and 1.5.2.3 and 3.2.R.1.4

Comments:

Depending on the nature of the injection and method of sterilization, the description should be **both comprehensive but concise** and the description or the flow diagram and preferably both should indicate the grades of clean areas of the various areas of production; methods and conditions of sterilisation/depyrogenation (time/temperature) of manufacturing components and filter media; the pressure source used for filtration and it's method of sterilisation; the final method of sterilisation; in-process controls such as bioburden testing and acceptance criteria,; filter integrity testing; the maximum validated processing times (holding times) for the various stages of manufacturing.

9.3 Over and above the requirement of 3.2.P.3.5 and depending on the product, container-closure system and method of sterilization, the following should be submitted:

- Process validation report or protocol,
- validation report of aseptic processing by media fill
- summary report of the validation of the final sterilization process (including load patterns)
- summary report on the depyrogenation process of glass containers
- summary report on autoclaving of production equipment and filter media

- report on the validation of the maximum processing times of the various stages of manufacturing (chemical/physical and microbiological)

Comments:

10 Module 3.2.P.4 Control of Excipients - Important for high risks

10.1 Provide specifications and control procedures for the Nitrogen used as pressure source for filtration if applicable.

11 Module 3.2.P.5 Control of Pharmaceutical Product

The guidance in the assessors guide 3.2.P.5 should be followed.

11.1 3.2.P.5.1 Specifications for in-process controls must be included. If the in-process controls are submitted in 3.2.P.3.3 a cross will suffice.

11.2 3.2.P.5.1 Visible particulate matter must be specified as a final release criteria or in-process control specification in addition to sub-visible particulate matter.

11.3 Evaluation of FPP intermediates for parenterals (powder blends) should also include homogeneity, and FPP intermediate sterile powders should also include evaluation of sterility and bacterial endotoxin testing (BET).

11.4 The preservative efficacy of relevant dosage forms and/or presentations, e.g. multi-dose vials, eye drops should be specified in 3.2.P.5.1 and presented in 3.2.P.8. However, once established for **the lowest limit of preservative content** specification, it is not a routine batch test requirement.

11.5 For Bacterial endotoxin determination the validation data required by the USP / BP/ Ph Eur, should be submitted.

11.6 Specifications: Ensure that the reference number, version, date are included and also signed. These must be included in the report as indicated in the example below. Confirm compliance with the claimed pharmacopoieal monograph. Ensure the proposed specifications are according to ICH Q3C. If not according to ICH guidance check the impurity profile of the product

11.7 Test Procedures: Important for high risks dosage forms

11.8 Validation of Analytical Methods: Important for high risks dosage forms

Comments:

12 **Module 3.2.P.7** Container closure system

12.2 For Injections packed in **glass containers** the Type of glass must be specified and compliance with pharmacopoeial specifications must be confirmed.

12.3 Specifications for **rubber caps** must comply with pharmacopoeial requirements and compatibility with the formulations must be proven either here or in 3.2.P.2.

12.4 For injections packed in **plastic containers** the type and formulation of the plastic material must be specified, it must comply with pharmacopoeial specifications and CPMP-QWP-4359-03 including sorption studies, migration studies and toxicological information.

12.5 The container-closure integrity must be validated unlesss it has already been done in 3.2.P.2.

12.6 Specifications and limits

12.7 Test procedures

Comments:

13 **Module 3.2.P.8** Stability

13.2 Follow the general guidance of the P&A Guideline (2.25_PA_CTD,3.2.P.8) and the stability guideline (2.05 Stability Feb11 v6).

13.2 Injections packed in glass vials with rubber caps must be stored upright and inverted to test for any interaction of the product with the rubber caps (sorption or extraction).

13.3 Injections packed in semi-permeable containers (Plastic containers) must be tested for water loss at low humidity.

13.4 The protocol and results of preservative efficacy testing where relevant must be provided.

13.5 Where relevant specifications and results for preservative concentration and antioxidant concentration must also be included.

13.6 Where relevant in-use stability must be tested.

13.7 Photo stability study must be presented unless it has been done in 3.2.P.2.

13.8 The compatibility with the listed IV solutions under *"Dosage and Directions for use*" in the PI must be reported on.

13.9 Stability Program

13.10 Stability Data

13.11 Shelf-life. This is important for the screener to populate the table above

13.11 Preserving Ability (if applicable)

A shelf life of …. months is approved for …….(product)…. manufactured by ….(FPP manufacturer)….with API manufactured by ….. (API manufacturer)…., when packed in …and stored at or below 30 °C.

Comments:

14 **Module 3.2.R** Regional information

14.1 Pharmaceutical and Biological availability (3.2.R.1.4.2)

Exemption must be requested from submitting a proof of equivalence study in Module 3.2.R.1 based on the fact that the formulation is essentially the same as innovator product and contains the same active ingredient in the same molar concentration as the reference product. Essential similarity to the innovator product must be proven (Sometimes proven in 3.2.P.2). Injections in solution intended for IV or IM administration are normally exempt.

Comments:

15 Certificates of Suitability CEPs/ WHO CPQ

15.1 Include the number and validity thereof in the report.

EVALUATORS

Full name	**Signature**	**Date**
1 Screener:		
2 Second screener		
3 Evaluator		
4 Peer reviewer (Group Meeting)		

PHARMACEUTICAL EVALUATION MANAGEMENT

PRE-REG UNIT EVALUATION REPORT FORMAT

BIOEQUIVALENCE EVALUATION REPORT

Application number	
Product (proprietary) name	
Approved name (INN) (INNM)	pKa: BCS Classification:
Applicant	
Date of application	
Manufacturer	
Manufacturer applied for	
API Manufacturer	
API manufacturer applied for	
Dosage form	
Dosage & relation to food intake	
Foreign registration	
Review pathway	

**biostudy in-vivo, invitro as applicable*

TECHNICAL SCREENING: The same template to be used for technical screening. The screener to state critical deficiencies found. The information to be populated by the screener are in black text highlighted in yellow. Once the information has been completed, the screener should remove the yellow highlight. The screener's report should be shared with the initial evaluator so that the populated information can be reproduced.

Key:
Red: Initial screener conclusions
Blue: Second screener conclusions.
Red: First reviewer's conclusions.
Comments pane: peer reviewer's comments and discussions
Green: peer review meeting conclusions.
Queries to the applicant by the screener and initial evaluator: Red text highlighted in yellow

Protocol (in-vivo, in-vitro, waiver)	
API pk	
Linearity	

Food effect		
Absorption		
T max		
Elim half-life		
Sample size calculation		
Ethics		
Study title (BE, dissolution, biowaiver)		
CRO (BE)		
Principal investigator Sponsor (BE)		
Study Protocol Number(s) (BE)		
Report number(s)		
Study design – washout 5 x t½ dose within SA approved range?		
Test batch name and strength Test Batch size, batch number		
Date of manufacture		
Reference product / HCR Batch Number & Exp date		
RSA Innovator Product/Applicant Batch Number & Exp date		
Study period (dates)	Clinical: Period I	
	Period II	
	Completion	
	Analytical method validation	
	Analysis	
	Bioanalytical	

	Final report	
Dates of report and submission i.e. Biostudy age at the time of submission; if more than 5 years, then include standard sentence *(stated in next column – delete if not relevant)*	Confirm that the Sponsor and investigational sites, facilities and laboratories, and all data (including source data) and documentation and reports concerning the data including participant files are available for verification by the Inspectorate and indicate the facility(ies) where they may be inspected	
Subjects		
Sample collection and storage		
Peak concentration normally		
Samples in absorption phase		
Samples in elimination phase		
Protocol BE parameters		
Primary parameters *Note: Change values if not same as minimum*	AUC_{0-t}, C_{max} …… for: *state analyte* Minimum 90 % CI of the relative mean of test & reference between 80,00 % and 125,00 % for log transformed data.	
Secondary parameters (indicate with x)	AUC_{0-inf} | T_{max} | $T_{1/2}$ | K_{el}	
Statistical procedure		
Study reporting – GCP, GLP, cGMP		
Analytical method validation		
Date *if old check for appendices*		
Experimental Parameters		
Analyte		
Biological matrix & anticoagulant		
Selectivity incl haemolysis		
Carryover (internal & active analytes)		
Analytical range		

Calibration curve/linearity						
Accuracy	LQC		MQC		HQC	
Dilution integrity						
Precision (inter and intra)						
Freeze-thaw cycles						
Working soln stability for controls and sample						
Drug interference (more recently applicable)						
Analytical report (BE)						
Analytical method						
LOQ and CC range						
Number of samples collected						
Number of samples received						
Number of samples analysed						
Repeat analysis						
Reanalysis/incurred analysis						
Representative chromatograms						
Comprehensive index to identify subject number						
Calibration curves and QC samples included in correct sequence						
Calibration curves correspond						
Injection sequence chronological with no gaps, interspersed with control samples						
Dates are logical						
Annotations logical, correspond with the chromatograms						
Are samples identifiable?						
Pk and statistical report						

Pre-dose concentrations	
AUC_{0-t} / AUC_{0-inf} (80 %) / AUC extrapolated < 20 %	
***Results (*or copied below if there is a similar table)**	
Proposed professional insert	Time to peak ; elimination half-life
Safety evaluation	Adverse events
Test and Ref Comparable?	
In line with API safety profile?	
Test and ref product similarity BE, in-vitro, biowaiver	
Formulations test and reference	Qualitatively the same? Tabulated comparison with formulation of test product could also be under 3.2.R1.1.10; 3.2.R.1.2 and 3.2.P.2.3
Assay	Test and reference CoAs + spec in 32P51 *see table below*
Dissolution if applicable	Pharmaceutical availability 32R14 – *incl dissoln summary below* Test and reference CoAs + spec in 32P51 *see separate table below* *For abridged or reliance application pathways: Include the approved dissolution specifications if these are stated in the approval letter, especially US FDA.*
Dissolution discriminating ability	
Impurity profile	Test and reference CoAs + spec in 32P51 *see separate table below*

Conclusion re specifications	
More than one strength	
Formulations different strengths	Proportionally similar? Tabulated comparison of strengths?
Assay	Test and reference CoAs + spec in 32P51 *see table below*
Dissolution if applicable	Pharmaceutical availability 32R14 – *incl dissoln summary below* Test and reference CoAs + spec in 32P51 *see separate table below*
Impurity profile	Test and reference CoAs + spec in 32P51 *see separate table below*
Conclusion re specifications	
BCS biowaiver additional aspects	
Dose/volume solubility	
Relevant solubility values	
Other	
Overall study conclusions	
BE of the test & reference prod (in-vivo and in-vitro)	
Similarity of Bioref & RSA ref	
Proportional similarity	
Final product specifications	
Recommendations: I recommended II recommended provided that III not approved until IV not recommended	

Essential similarity of test & reference products & comparison with specifications 32P51

	Specifications 3.2.P.5.1			Ref batch	Test Batch
	Aa mg	Bb mg	Cc mg	Results 3.2.r.1.3	Results 3.2.r.1.3
Assay % Release Stability					
Dissolution %					
Medium & conditions					
Total impurities R S					

3.2.R.1.4 Dissolution

NB Include the actual dissolution results (mean values)

Repeat tables as necessary

BE Reference(s) name strength country			BN		SA innovator(s) name strength RSA		BN	
Mins	**0,1 N HCl**	**pH 4,5**	**pH 6,8**	**QC**	**0,1 N HCl**	**pH 4,5**	**pH 6,8**	**QC**
10								
15								
20								
30								
45								

SA Innovators name strength country			BN		Test name strength		BN	
Mins	**0,1 N HCl**	**pH 4,5**	**pH 6,8**	**QC**	**0,1 N HCl**	**pH 4,5**	**pH 6,8**	**QC**
10								
15								
20								
30								
45								

EVALUATORS

Full name	Signature	Date
1 Screener:		
2 Second screener		
3 Evaluator		
4 Peer reviewer (Group Meeting)		

SAHPRA
SOUTH AFRICAN
HEALTH PRODUCTS
REGULATORY AUTHORITY

SUMMARY OF CRITICAL REGULATORY ELEMENTS (SCoRE) DOCUMENT

General guide to applicants:

- The Summary of Critical Regulatory Elements (SCoRE), is required for all new registration and variation applications, to facilitate evaluation by SAHPRA, and should be submitted with applications at the time of submission
- When updating a SCoRE for a variation, any changes should be marked in track changes, however, the document submitted to SAHPRA must be highlighted in yellow. Information should be included for all strengths. The following is applicable:
    - For variations to applications registered with a SCoRE, the complete SCoRE should be submitted
    - For variations to applications registered without a SCoRE, a partial SCoRE: (completing only the relevant sections affected by the change), should be submitted
- Please note that the SCoRE does not replace the Quality Overall Summary (QOS), nor does it replace the requirements outlined in the relevant guidelines
- The PDF version of the document should be included in Module 3.2.R.8 (Other) of the CTD submission
- An additional MS Word text version (i.e. editable) of SCoRE should be included in the working documents folder
- Font used in the main text must be Arial, size 11. Tables may be Arial size 10.
- As per revised SAHPRA APIMF[1] Procedure, if information is in the closed part of the APIMF, reference to the closed part should be made (where applicable) with the understanding that the API manufacturer submits the closed part directly to SAHPRA
- Please delete all light grey text in square brackets ([ ]) (guides and examples) when submitting the SCoRE
- Do not change or delete the titles and the numbering (add “Not applicable” if necessary)
- Add additional rows to tables where required
- Please duplicate Module 3.2.S and Module 3.2.P for multiple API and FPP in the product

Please note that hyperlinking or referencing sections of the dossier is **not acceptable**; information should be summarised in the SCoRE

[1]. Also referred to as the DMF (Drug Master File), DSMF (Drug Substance Master File) and ASMF (Active Substance Master File)

Note to evaluators:

The risk assignments and scoring of the products have been confirmed using a risk classification template. This is included in the Summary of Critical Regulatory Elements table below**.** The relevant sections to be evaluated for specific risk categories are highlighted in blue next to the heading.

Key:

Red: Initial screener conclusions

Blue: Second screener conclusions.

Red: First reviewer's conclusions

Queries to the applicant: Highlighted in yellow

Black with blue highlight: Prompts on the evaluation for the first reviewer

Blue: second reviewer

Green: Peer review meeting conclusions

Table of Contents

Update history

The SCoRE document version should start with V001 for the first submission. Each resubmission of the SCoRE document should incrementally increase the version by 1 (i.e. V002 for the second version, or first resubmission of an amended SCoRE document). This version number should be included in the header of the document, as well as the document name.

The 'reason for update' should reference key amended sections by their number in order to aid the evaluator.

An example has been included in blue text and italicised below – please delete this text before submitting the SCoRE document to SAHPRA.

Date	Pre-registration/ post-registration	Reason for update	Version
[2019/01/01]	*[Pre-registration]*	*[Initial submission]*	*[V001]*
[2019/01/31]	*[Pre-registration]*	*[Module 3.2.P.5 (Section 2.5.9 of SCoRE) updated in response to recommendation from P&A committee on 2019/01/15]*	*[V002]*
[2019/03/25]	*[Post-registration]*	*[Variation Type II (Description)]*	*[V003]*

[Please add additional rows as required]

List of abbreviations

API	Active Pharmaceutical Ingredient
APIMF	Active Pharmaceutical Ingredient Master File
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical
BCS	Biopharmaceuticals Classification System
BP	British Pharmacopoeia
CAS	Chemical Abstracts Service
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
cGMP	Current Good Manufacturing Practices
CMC	Chemistry, Manufacture and Control
CoA	Certificate of Analysis
CPQ	Confirmation of WHO API Prequalification
CRO	Contract Research Organisation
CTD	Common Technical Document
DMF	Drug Master File
DSMF	Drug Substance Master File
eCTD	Electronic Common Technical Document
EMA	European Medicines Agency
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practices
GMP	Good Manufacturing Practice
HCR	Holder of Certificate of Registration
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Non-proprietary Name
INNM	International Non-proprietary Name Modified
IPRP	International Pharmaceutical Regulators Programme
LOD	Limit of Detection

LOQ	Limit of Quantification
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Product Dossier
Ph. Eur	European Pharmacopoeia
Ph.Int	International Pharmacopoeia
PPL	Periplakin (protein coding gene)
PQ	Pre-qualification
PSD	Particle size distribution
PSUR	Periodic Safety Update Report
QIS	Quality Information Summary
QOS	Quality Overall Summary
RM	Regulatory Manager
RP	Responsible Pharmacist
RRA	Recognised Regulatory Authority
RSA	Republic of South Africa
SADC	Southern African Development Community
SAHPRA	South African Health Products Regulatory Authority
SCoRE	Summary of Critical Regulatory Elements
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRA	Stringent Regulatory Authority
TGA	Therapeutic Goods Administration (Australia)
US FDA	United States of America Food and Drug Administration
USP	United States Pharmacopeia

Summary of Critical Regulatory Elements (SCoRE)

Applicant (company)		
Application number	Master	Duplicate
Product (proprietary) name	Master	Duplicate
(Compendial status) *Check 3.2.P.1/ 3.2.P.2*		
Approved name (INN or INNM)		
(compendial/WHO-CPQ status) *Check 3.2.S*		
Dosage form		
Description of dosage form		
Strength		
Scheduling		
BCS class and polymorph (if applicable to the final product)		
Sterility of the final product		
Overall risk scoring and classification		
Date of initial application		
Date of current submission (SCoRE amendment)		
FPP manufacturer(s) used for developmental batches (name, address)		
FPP manufacturer(s) applied for (name, address)		
API manufacturer(s) used for developmental batches (name, address)		
API manufacturer(s) applied for (name, address)		
Stability of API		
Date of commencement of study	**Data available**	**Requested shelf life**
Stability of the FPP		

	Data available	Requested shelf life

TECHNICAL SCREENING: The screener to include found. The critical deficiencies for the screener are highlighted in yellow. The screener's report should be shared with the initial evaluator so that the populated information can be reproduced.

Foreign registration

Name of reference country	Date of registration	Full/unredacted assessment reports?	Letter of access?[2]
{Name of reference country 1}	{YYYY.MM.DD}	<Y/N>	<Y/N>
{Name of reference country 2}	{YYYY.MM.DD}	<Y/N>	<Y/N>
{Name of reference country 3}	{YYYY.MM.DD}	<Y/N>	<Y/N>

[Add additional rows as required]

Module 1

Module 1.3 South African labelling and packaging (Assess for all applications)

[For NCEs and generics with clinical data only:

Provide dossier hyperlinks to the location of the following clinical summary documents in a clearly structured, tabulated format (include a separate column for the title of each document):

i. Clinical overview(s)

ii. Clinical summaries

iii. Synopses of clinical studies

iv. Non-clinical overview(s)

v. Non-clinical summaries

[2]. Please note that a letter of access should only be provided if the applicant does not have access to full / unredacted assessment reports, and cannot obtain these reports.

Indicate if the NCE has been approved by any of the regulatory authorities with which SAHPRA aligns itself (Recognised Regulatory Authorities – RRAs): US FDA, EMA, MHLW (Japan), Health Canada, Swiss Medic, TGA (Australia) and MHRA (UK)

Indicate whether either of the following additional procedures are applicable to the NCE: World Health Organisation Prequalification (WHO PQ) and Zazibona collaborative procedure

For all NCEs and generics:

a. Comment if the most recent PSUR/PBRER and, if relevant, a Benefit/Risk analysis and applicable Risk Management Plan is included in your application, and whether the medicine applied for is already registered by one or more RRAs.

Reflect here that [product name, dosage form and strength] is manufactured by [name of the FPP manufacturer] [laboratory name] is/are generic product(s) to the innovator product [product name, dosage form and strength] from [name of the innovator manufacturer], where relevant.

Provide a motivation when a generic product has been used as a primary reference product.

Provide a brief commentary on indications, target population, posology (with regard to the ability of the FPP to deliver this posology, e.g. scored tablets), method of administration (if unusual, e.g. using a device) here.

Include pharmacological classification as well a mechanism of action.

Comment on the application content aligned with the most recent Regulations, policies, directives, monographs, position statements and guidelines of SAHPRA relevant to your application. Name and list the relevant documents that were used in the alignment process of your application.

The professional information (PI) and patient information leaflet (PIL) must be drafted in line with the current regulations and respective guidelines.

The applicant should refer to the following guidelines with regard to the requirements of the submission:

2.01 General Information Guideline

2.09 Clinical Guideline

2.14 Guideline for Patient Information Leaflet for Human Medicines (Categories A and D)

2.16 Guideline on Professional Information for Human Medicines (Categories A and D)

SAHPRA Variations Addendum for Orthodox Medicines

Example:

{TABLE OF HYPERLINKS TO CLINICAL SUMMARY DOCUMENTATION}

{Proposed Proprietary Name} {Product Strength(s)} {Product Dosage Form} manufactured by {Name of FPP manufacturer} are/is a generic product(s) to the innovator product {Innovator Product Name} {Product Strength(s)} {Product Dosage Form} from {Name of Innovator product manufacturer} are/is indicated for the treatment of {XXX} as add-on therapy in patients with mild to moderate persistent {XXX}, who are inadequately controlled on {XYX} as an alternative treatment option to {XYX} in patients with mild persistent {XXX} who do not have a recent history of serious {XXX} that required {XYY} and who have demonstrated that they are not capable of using {XYX}; and for the prophylaxis of {XXX} for patients in which the predominant component is {XYZ}.

The product has been registered by {list of RRAs}. Un-redacted reports have been provided from {insert list of RRAs, **OR** a Letter of Access for un-redacted reports has been included in Module 1.

Product {XYZ} tablet/injection/capsule is a cysteinyl leukotriene (CysLT) D4 receptor antagonist that binds with high affinity and selectivity to the CysLT1 receptor. This results in inhibition of bronchoconstriction, and decreased peripheral blood eosinophils.]

Quality evaluator to assess the following:

1.1.1 Name of the product: Ensure this is the same as in the application form.

1.1.2 Qualitative and Quantitative Composition: Ensure this is the same as in the application form and 3.2.P.1

1.1.3 Pharmaceutical Form: Ensure this is the same as in the application form and 3.2.P.1

1.1.4 Pharmaceutical Particulars: Ensure the list of excipients is the same as in section 3.2.P.1

1.1.5 Shelf life: Ensure this is the same as in section 3.2.P.8

1.1.6 Special precautions for storage: Ensure this is the same as in the application form and 3.2.P.8

1.1.7 Nature and contents of container: Ensure this is the same as in section 3.2.P.7

1.1.8 Posology: State the recommended dose, this is important in order to determine the identification and qualification thresholds for related impurities [refer to ICH Q3A (API) and Q3C (Final product). The thresholds are based on maximum daily dose (MDD) and the duration of treatment (acute vs chronic).

For sterile applications:

1.2 Are reconstitution or dilution required (*Concentrate for dilution/Lyophilized powder/powder*)?

If so check the instructions in "*Dosage and Directions for use*" for complete instructions including diluents and diluent - volume.

Comments:

1.3 In "*Dosage and Directions for use*" check compatibility information with recommended IV solutions and check whether this has been investigated either in 3.2.P.2 or 3.2.P.8.

Comments:

1.4 Confirm the stability information of the reconstituted/diluted product (*"Dosage and Directions for use" and "Storage instructions").*

1.5 Check that a statement is included for the reconstituted/diluted product to be used immediately and/or include the following statement (unless it is a multi-dose injection and preservative efficacy has been established).

"From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions"

Comments:

1.6 For single dose injections, indicate on the labels that it is for single use and that any unused portion should be discarded.

For multi-dose injections and eye drops indicate that it should not be used for the validated period (normally 30 days) after first opening the container

Comments:

Module 1.7 Good manufacturing practice (Assess for all applications)

1.7.4.1 & 2 Release API, IPIs
1.7.4.3 & 4 Release FPRC/FPRR

Indicate if the information provided under release for API, IPIs and FPRC/FPRR is adequate and acceptable.

Table 1.7-1: API manufacturer

Name of API	ASMF/DMF/ CEP/CPQ no. and open part version	ASMF/DMF/ CEP/CPQ holder name and address	Manufacturer name and address (include specific unit / block)	GMP		
				Date of last inspection	Authority	cGMP status
{API1}		{Supplier1}		{YYYY.MM.DD}		
{API1}		{Supplier2}		{YYYY.MM.DD}		

{API2}		{Supplier1}		{YYYY.MM.DD}		

[Repeat rows if necessary for multiple APIs or API manufacturers/manufacturing sites.]

Table 1.7-2: FPP manufacturer / packer / FPRC

Site (name and full address including units/blocks/plots)	Functions performed at site	GMP		
		Date of last inspection	Authority	cGMP status

Module 1.11 Bioequivalence (for generics)

Table 1.11-1: Bioequivalence information

CRO	
GCP status	
Study Protocol Number(s)	
Report number(s)	
Study design	
Test Batch size, batch number	
Date of manufacture of the test batch	
Reference product/HCR	
Batch Number & Exp date	
RSA Reference Product / Applicant	
Batch Number & Exp date	
Study period	
Principal investigator	
Sponsor	

No. of subjects enrolled in the study	
No. of subjects that completed the study	

Module 3: Quality aspects

[Please repeat Section 2.1 (3.2.S Drug substance) for each additional API **and** API source]

3.2.S Drug substance (Or Active pharmaceutical ingredient (API)) (Name, Manufacturer)

[Indicate which option applies for the submission of API information; please check one only]

Table 3.2.S-1: API information

Name of API:	
Name of API manufacturer:	
☐	1. Confirmation of API WHO prequalification document (CPQ)
☐	2. Certificate of suitability to the European Pharmacopoeia (CEP)
☐	3. Active pharmaceutical ingredient master file (APIMF[3]) procedure: APIMF number assigned by SAHPRA (if known): _____; version number(s) including amendments (and/or date(s)) of the open part: _____; version number(s) including amendments (and/or date(s)) of the restricted part: _____.
☐	4. Full details in the PD (open part of the APIMF) Document version number/identifier of current Module 3.2.S: _____

Table 3.2.S-2: Compliance with monograph/pharmacopoeia

Reference monograph/pharmacopoeia						
Comply with monograph/pharmacopoeia	**Yes**	☐	**Yes with deviations[4]**	☐	**No**	☐
List deviations if relevant						

3.2.S.1 General Information (name, manufacturer)

[3]. Also referred to as the DMF (Drug Master File), DSMF (Drug Substance Master File) and ASMF (Active Substance Master File)

[4]. List deviations from monograph. Deviations include additions and deletions.

[Guide:

Provide the description and general properties of the API. Include the chemical structure, empirical formula and the relative molecular mass of the API. Comment on any property that may impact on the quality and performance of the finished pharmaceutical product that may require additional user requirements (e.g. aqueous solubility over the physiological pH range and particle size distribution and polymorphism).

Example:

The active substance is chemically designated as sodium salt of {Chemical name}. It is described in the current USP- and/or the European Pharmacopeia (Ph. Eur). {Name of the API} is a white to pale yellow coloured, amorphous hygroscopic powder. {Name of the API} is poorly soluble in buffered media in the physiological pH range 1.2 to 7.5.

The API is known to exhibit <confirm absence/presence of polymorphism> and {API manufacturer(s) name} produces the {State the polymorphic form}. {API name} is <confirm absence/presence of chiral centers> e.g. chiral molecule containing single asymmetric carbon atom; {API manufacturer(s) name} <confirm absence/occurrence of isomers, and provide a brief discussion> e.g. produces the R-isomer. The other isomer {Isomer Name} is further monitored by the specification of not more than {specification limit} of the isomer by {Analytical method} e.g. chiral HPLC. {API name} consists of carbon-carbon double bond that gives rise to the scope for geometrical isomerism. Cis-isomer {Isomer Name} of drug substance is controlled in the final specification for the API. The isomer produced by {API manufacturer(s) name} is a trans-isomer.]

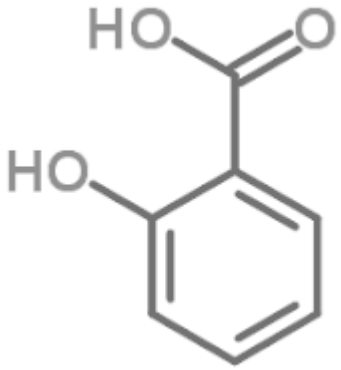
3.2.S.1.1 Nomenclature

Table 3.2.S.1.1-1: General information

International non-proprietary name (INN or INNM):	
Chemical names:	
Other name:	
Chemical Abstracts Service (CAS) registry number:	
Laboratory code:	
Molecular formula:	
Relative molecular mass:	

3.2.S.1.2 Structural formula

[Example



Molecular formula: $C_xH_xO_x$]

3.2.S.1.3 General properties (Assess for all applications – depending on dosage form and manufacturing process)

[Guide:

Specify the properties relevant to the performance of the product and give values, e.g., pKa, solubility in aqueous medium, polymorphism, isomers, particle size distribution etc. where relevant.]

Table 3.2.S.1.3-1: Summary of properties

Property	
Physical characteristics:	
pKa-value(s):	
Partition coefficient:	
Hygroscopicity:	
Stereochemistry:	
Polymorphism	
Particle size distribution (PSD)	
Refractive index (liquids):	

Table 3.2.S.1.3-2: Solubility in aqueous medium at 37 °C (required for all APIs)

pH (buffered)	**Solubility (mg/ml)**	**Dose/solubility volume**
1,2		
4,5		

6,8		
Other (provide pH)		

3.2.S.2 Manufacture (name, manufacturer)

Manufacturer(s) (name, manufacturer)

Name, address and responsibility (e.g. fabrication, packaging, labelling, testing, storage) of each manufacturer, including contractors and each proposed production site or facility involved in these activities:

Table 3.2.S.2-1: Manufacturer information

Name and address (including block(s)/unit(s))	**Responsibility**	**API-PQ number /APIMF/CEP number (if applicable)**	**Letter of access provided?[5] (Applicable to CEP & CPQ)**
			✓
			☐
			☐

[Guide:

The name, address (including unit/plot/block), and responsibility of each manufacturer, including contractors and manufacturer(s) of the intermediates (if sourced from a third party), and each proposed production site or facility involved in manufacturing and testing should be provided.

This includes the facilities involved in the manufacture and testing of the API or key intermediates. If certain companies are responsible only for specific steps of the process (e.g. milling, micronisation sterilisation, packaging, labelling, testing and

[5]. CEP letter of access from API manufacturer; CPQ letter of access from WHO

storage facilities of the drug substance or key intermediates), then this should be indicated.

The list of manufacturers should specify the actual addresses for the location, including the unit, plot or block (if any), where the relevant manufacturing or testing operation will be performed, rather than the administrative offices.

The API manufacturer is {Name of the API Manufacturer}, {address (including unit/plot/block)} and was deemed to be cGMP compliant based on inspection by {Name of the Authority}.]

3.2.S.2.2 Description of manufacturing process and process controls *(*Assess for all applications), except when CEP/CPQ is submitted.

[Guide:

Provide a brief description / sequential procedural narrative of the manufacturing process. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time). Provide a brief discussion on the starting material, for complex starting materials provide justification. If information is in the closed part of the DMF, reference to the closed part should be made.

The flow diagram of the synthesis process should include the chemical structures of starting materials, intermediates, reagents and the API reflecting stereochemistry. The flow diagram should identify reagents, catalysts and solvents used in each step.

Where intermediates are used that resemble the API closely, CoAs of these should be included.

If more than one manufacturing site is responsible for the last few stages of production, purification and/or micronisation (if applicable) of the drug substance, alternative processes undertaken at the different site(s) should be described and any significant differences should be assessed.

If the drug substance is prepared as sterile and used as sterile by the FPP manufacturer, a complete description should be provided for the method used in the sterilisation. The controls used to maintain the sterility of the drug substance during storage and transportation should be provided.

The information on the manufacturing process should start from well-characterized starting materials (or CoA).

Where CEP, CPQ and DMF procedure is followed, this section may not be applicable – simply stipulate N/A in this instance

Example:

The manufacturing process involves condensation of starting material to produce the tertiary butyl amine salt, purification and lastly formation of the sodium salt of xxxx. The starting material, although complex and only one step to the final API, was justified in line with ICH Q7, Q11 guidelines. The starting material is sourced from two manufacturers, and the controls for the starting material i.e. Specifications and test methods were provided and found to be sufficient. Potential impurities (including the Impurity A, Impurity B) have been well discussed in relation to their origin and potential carry-over into the final API. Manufacturing consistency was demonstrated with three API batches.]

Assess the appropriateness of the method of synthesis and acceptability of starting material/s, except when CEP/CPQ is submitted.

3.2.S.2.3 Control of materials (name, manufacturer) – for API option 4 only (full details of the API, please see *Table 3.2.S-1*)

(a) Name of starting material:

Name and manufacturing site address of starting material manufacturer(s):

3.2.S.3 Characterisation (name, manufacturer)

3.2.S.3.2 Impurities (Assess for all applications) except when CEP/CPQ is submitted.

[Guide:

A description of impurities, indicating the possible source of impurities and a clear distinction between actual and possible impurities should be provided. Are all the actual impurities included in the pharmacopeial monograph?

State the maximum observed levels (actual numerical results) from batch analysis (S4.4), at least three batches.

If residual solvents have been identified, then the solvent(s) used, their classification as per ICH Q3C, the synthesis step(s) in which they are used, the observed levels from batch analysis data and, if applicable, the LOQ and proposed limits must be indicated.

Discussion of the potential genotoxic impurities should be provided.

Please indicate N/A if a CEP or CPQ is submitted]

Table 3.2.S.3.2-1: Impurities (potential and actual)

Name and structure of impurity (API-synthesis related and/or degradation products)	**Acceptance Criteria**	**LOQ and LOD**	**Results from batch analysis (include batch number and use[6])**		

Degradation Products, Impurities and Related Substances: Check if the proposed specifications are not according to ICH Q3A and residual solvents, elemental impurities, nitrosamines, mutagenic impurities are not included.

[6] Use includes biolot, production, pilot, validation or stability batch

Table 3.2.S.3.2-2: Residual solvents

Residual solvents	Classification (ICH Q3C)	Step used	Limits	LOQ	Results (batch analysis – include batch numbers)		

3.2.S.4 Control of the API (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer (Assess for all applications) except when CEP/CPQ is submitted. (however assess the API specifications by the FPP manufacturer)

(a) API specifications of the FPP manufacturer:

Table 3.2.S.4.1-1: Summary of specifications

Standard (e.g. Ph. Int., Ph. Eur., BP, USP, in-house)		
Specification reference number and version		
Test	**Acceptance criteria**	**Analytical procedure (Type/Source/Version)**
Description		
Identification		
Impurities		
Assay		
etc.		

Specifications: Ensure that the reference number, version, date are included and also signed. These must be included in the report as indicated in the example below. Confirm compliance with the claimed pharmacopoieal monograph/CEP/CPQ. Ensure the proposed specifications are according to ICH Q3A if not evaluate the impurity section and if not supported by CEP or CPQ.

Microbial purity and Bacterial endotoxins should be included as a specification when the sterile API is used for the manufacture of sterile products. This is normally not part of the specifications for the API by the API manufacturers (should be if sterile API is sold) or pharmacopoeial specifications, however, these should be added.

[Guide:

Tabulated summary of the proposed specification (including test parameters and acceptance criteria)

The standard claimed by the APIMF/DMF Holder or applicant (e.g., Ph. Eur./BP/USP/In-house).

Indicate if there is reduced testing proposed for certain parameters.

A discussion/justification on the acceptability of the proposed specification and claimed standard.

Specifications should cover all of the relevant quality parameters such as identity, organoleptic, physical, chemical and stereochemical properties, potency and microbiological quality. Organoleptic properties may include appearance, colour and clarity of solution, but never taste or smell. Physical properties may include crystalline/polymorphic form, particle size distribution, specific optical rotation, solubility, melting point, molecular weight. For APIs with low BCS solubility (dos-soluble volume > 250 ml), PSD and polymorphic form are generally regarded critical and should be derived from the FPP biobatch.

Note: API specification controlled by the FPP manufacturer should be reflected here and it should be clearly separated from the specification controlled by the API manufacturer.

Example:

The API specification from the FPP manufacturer was noted to comply with the Ph. Eur pharmacopeia monograph for {XXX} sodium includes tests for appearance, solubility, identification (IR, enantiomeric purity, test for sodium), heavy metals, water content, Impurity A (enantiomer), related substances (HPLC- Impurity B, C, D, E, F, G), assay (HPLC), and residual solvents (GC). Particle size distribution (psd) limits at three levels based on characterization of the API lot used in the biobatch were included in the specs with limits d10 (less than 10 µm), d50 as a range (20 - 75 µm) and d90 (less than 250 µm). Sufficient data were provided from the five batches justifying the consistency in producing the desired polymorph for {XXX}, therefore, exclusion of the polymorphic identity test in the specifications was considered justified.

The analytical methods were described and comply with the Ph. Eur. monograph for {XXX} sodium. Nonetheless, the manufacturer performed full validation for the analytical methods. The specifications includes GC test for residual solvents, thus the GC method for residual solvents is considered acceptable and validated. Data on three consecutive batches of {XXX} sodium manufactured according to the proposed manufacturing process in the proposed manufacturing site was provided. All batches represented full-scale production and complied with the requirements in the API specification.]

3.2.S.4.3 Validation of analytical methods

Table 3.2.S.4.3: Validation of Analytical procedure detail (Assess for high risk applications except when CEP/CPQ is submitted)

Validation Parameter	Analytical Procedure			
	Assay	**Impurities**	**Residual Solvents**	**Other**
Method Type:	[HPLC]	[HPLC]	[GC]	
Method Number:	[*No. X*]	[*No. Y*]	[*No. Z*]	
Accuracy				
Precision:				
Repeatability				
Intermediate precision				
Specificity				
Detection limit (specify)				
Quantitation limit (specify)				
Linearity				
Range (specify)				
Robustness				
Solution stability				
+ indicates that the parameter is acceptably tested and validated - indicates that the parameter is not tested ? indicates that questions remain before the parameter is judged to be acceptable				

3.2.S.4.4 Batch analyses (name, manufacturer)

Table 3.2.S.4.4-1: Batch analyses information

Test	Specification	Results	
		Batch no:	**Batch No:**

3.2.S.5 Reference standard (name, manufacturer)

If a pharmacopoeial monograph is claimed, the pharmacopoeial standard should be used.

State if a certificate of analysis has been submitted.

State if a secondary reference standard (e.g. working standard) is standardized against the compendial reference standard or primary reference standard.

The source(s) of the reference standards or materials (e.g., in-house, Ph. Eur., USP) used in the testing of the drug substance (e.g., for the identification, purity, potency tests). If a Ph. Eur. reference standard is used for quantitative analysis, the reference standard should be for content (not for identity only).

3.2.S.6 Container closure system (name, manufacturer)

Table 3.2.S.6-1: Description of the container closure system(s) for the storage and shipment of the API:

Packaging component	**Specifications (e.g. identification (IR))**

3.2.S.7 Stability (Assess for all applications) except when CEP/CPQ is submitted with retest period included on the CEP/CPQ.

3.2.S.7.1 Stability summary and conclusions (name, manufacturer)

(a) Proposed storage conditions and re-test period (or shelf-life, as appropriate):

Table 3.2.S.7.1-1: Storage information

Container closure system	**Storage statement**	**Re-test period[7]**

[7]. Indicate if a shelf-life is proposed in lieu of a re-test period (e.g. in the case of labile APIs)

[Guide:

Summarise the studies undertaken to support the proposed re-test period/shelf-life. Information to state include: batch numbers and size, manufacturing site, manufacturing date, container closure system(s), storage conditions (long-term, intermediate (if applicable), accelerated) and completed testing intervals. A table is recommended.

Summarise the conditions and results of stress testing studies of the drug substance.

The storage requirements for the API as derived from the stability data generated by the API manufacturer and specified by the manufacturer of the API

A description of the API container closure system(s) must be included.

State the proposed re-test period/shelf-life and storage condition derived from the stability data

Please stipulate N/A if a CEP or CPQ is submitted

Example:

Stability studies were carried out according to ICH guidelines for real time (25°C/60% RH) and accelerated conditions (40°C/75% RH). Data for three batches were given with 60 months real time and 6 months accelerated data packed in triple low-density polyethylene (LDPE) bags placed in HDPE containers. In addition, forced degradation studies have been performed and demonstrated the stability indicating nature of the analytical method for assay. {XXX} sodium is sensitive to light as per Ph. Eur.

The stability studies confirmed the proposed re-test period of 48 months. The applicant provided commitment to perform stability studies at 30°C /75% RH to suit climatic conditions in the SADC region. In addition, the stability protocols were revised to include monitoring of the enantiomeric purity in stability studies as per revised specifications.

{XXX} Sodium is packed in a triple laminated LDPE bag along with silica gel bag and kept inside HDPE container. The product should be stored at controlled room temperature in a tightly closed container under nitrogen atmosphere, protect from light and moisture.]

Evaluate data and approve the retest period as the paragraph below. The screener should check this information so they could populate the table above.

A retest period of …. months is approved for API manufactured by ….API manufacturer…. when packed in an inner HMHDPE and outer black polyethene bags enclosed in a fibre drum and stored at or below 30 °C.

3.2.P Drug product (or Finished Pharmaceutical Product (FPP))

Table 3.2.P-1: Compliance with monograph/pharmacopoeia (if applicable)

Reference monograph/pharmacopoeia						
Comply with monograph/pharmacopoeia	**Yes**	☐	**Yes with deviations[8]**	☐	**No**	☐

3.2.P.1 Description and composition of the FPP (Assess for all applications)

A brief description of the final product

[Example:

{Product name, dosage form and strength} is white to off white, orange flavoured, round shaped biconvex chewable tablets Excipients used in the preparation of {Product name, dosage form and strength} are well known excipients used in chewable tablets preparations such as e.g. Magnesium stearate, microcrystalline cellulose, e.t.c. The tablets are packed in 10's Aluminium/Aluminium blister packs. Such three blisters are packed in a carton.

Guide:

The formulation should show the INN or approved names, and/or chemical names of all APIs, and polymorph (if relevant) and approved names of inactive pharmaceutical ingredients (IPIs), including those that do not remain in the final product after manufacturing e.g. granulating agents and gases used for flushing. IPIs not present in the final product should be indicated.

The name and the quantity of the API and the name and quantity stated under "Composition" in the professional information and PIL should correspond. The name and quantity of the API per dosage unit should also correspond to the final product specifications.]

Ensure that the INN or approved names, and/or chemical names of all APIs, and polymorph (if relevant to the final formulation), names and quantities to correspond with PI/PIL/Label, Purpose of each component is adequately stated, potency of active, overages (if applicable) and reasons should be clearly stated and total quantity of unit dose is stated.

If Nitrogen is used as a pressure source for filtration, it must be included in the unitary and batch formula and indicated in a footnote that it is not present in the final product. It must be controlled in 3.2.P.4

[8]. List deviations from monograph. Deviations include additions and deletions.

(a) Description of the FPP (in signed specifications):

(b) Composition of the FPP:

(i) Composition, i.e. list of all components of the FPP and their amounts on a per unit basis and percentage basis (including individual components of mixtures prepared in-house (e.g. coatings) and overages, if any):

Table 3.2.P.1-1: Composition of the FPP

Ingredient and grade	Reference	Function	Quantity per dosage unit

(ii) Composition of all components purchased as mixtures (e.g. colourants, coatings, capsule shells, imprinting inks):

(c) Description of accompanying reconstitution diluent(s), if applicable:

3.2.P.2 Pharmaceutical Development (name, dosage form) (Assess for high risk applications)

In addition, evaluate the API-excipient compatibility in the case where the excipient selection is different from the comparator, check qualitative comparison under 3.2.R.1.4.1.

3.2.P.2.2 Drug Product (name, dosage form)

3.2.P.2.2.1 Formulation Development

(a) Information on primary (submission, registration, exhibit) batches including comparative bioavailability or biowaiver, stability, commercial:

(i) Summary of batch numbers

Table 3.2.P.2.2.1-1: Summary of batch numbers

Batch number(s) of the FPPs used in	
Bioequivalence or biowaiver	<e.g. bioequivalence batch A12345> <e.g. biowaiver batch X12345>
For proportional strength biowaiver: the bioequivalence batch of the reference strength	
Dissolution profile studies	
Stability studies (primary batches)	

‹packaging configuration I›			
‹ packaging configuration II›			
‹Add/delete as many rows as necessary›			
Stability studies (production batches)			
‹ packaging configuration I›			
‹ packaging configuration II›			
(Add/delete as many rows as necessary)			
Validation studies (primary batches)			
‹ packaging configuration I›			
‹ packaging configuration II›			
(Add/delete as many rows as necessary)			
Validation studies (at least the first three consecutive production batches) or code(s)/version(s) for process validation protocol(s)			

(ii) Summary of formulations and discussion of any differences

Table 3.2.P.2.2.1-2: Summary of formulations

	Relevant batches							
	Comparative bioavailability or biowaiver		**Stability**		**Process validation**		**Commercial (3.2.P.3.2)**	
Batch No. & Size								
Component and quality standard (e.g., NF, BP, Ph. Eur, in-house)	**Theor. quantity per batch**	**%**	**Theor. quantity per batch**	**%**	**Theor. quantity per batch**	**%**	**Theor. quantity per batch**	**%**
<complete with appropriate titles e.g. Core tablet (Layer 1, Layer 2, etc. as applicable), Contents of capsule, Powder for injection>								
Subtotal 1								
<complete with appropriate title e.g. Film-coating >								
Subtotal 2								

Total								

[Guide:

Is the formulation development supported by clinical development?

Discussion of bioequivalence between commercial formulation and clinical trial formulations, if different, should be provided

Discuss if applicable differences in finished product quality attributes (e.g. impurity and dissolution profile) in case of different strengths or a line extension.

Discussion of the development of the dissolution test method, description of changes, demonstration of discriminatory properties.

Early development formulations for pre-clinical and clinical studies should be highlighted where relevant, and comments made relating to the findings of these studies.

Additional details should be given if the development encompasses a paediatric formulation including information for which age group this is intended, if appropriate

Example:

{XXX} Sodium Tablets {XXX} mg are marketed across USA and elsewhere under the trade name of {XXX} ® tablets {XXX} mg {Company XXX} containing {XXX} sodium. The aim of the pharmaceutical development was to develop stable, essentially similar formulation, bioequivalent to the innovator product, CC tablets {XXX} mg (Company ABCD USA). The tablets have been developed as immediate release solid dosage forms for oral administration. The qualitative formulation was developed and each of the excipient was selected for its intended use based on optimization studies.

The manufacturing process employs direct compression technique in the manufacturing of finished pharmaceutical product. Adequate justification was provided for selection of the direct compression procedure for manufacture of the FPP. Based on the process optimization at various stages it was demonstrated that the proposed formula and process is adequate to consistently get the required quality.

A bioequivalence study was conducted for the {XXX} mg strength, under fasting conditions, in order to prove in-vivo bioequivalence between {XXX} test and an acceptable reference product. Comparative in-vitro dissolution for the additional strength {XXX mg strength – batch number XXX} was performed against the higher strength {XXX mg strength – batch number XXX} in pH 0.5% SLS (official dissolution media), pH 6.8 Phosphate buffer, pH 4.5 Acetate buffer and 0.1N HCl. The formulation of {XXX} Sodium Tablets {XXX} mg is dose proportional to {XXX} Sodium Tablets {XXX} mg manufactured by {XXX}.

The release medium is 0.5% sodium lauryl sulfate (similar to the method for {XXX} tablets stated by Office of Generic Drugs, US FDA). The acceptance criterion has been derived from the dissolution profile in this medium …]

3.2.P.2.3 Manufacturing Process Development (name, dosage form)

[Guide:

Explain the selection and optimisation of the manufacturing process described in 3.2.P.3.3, in particular critical aspects. Where relevant, the method of sterilisation should be explained and justified, and compatibility with production equipment e.g. filter media established.

If the manufacturing process of the product influences important physicochemical properties of the API (e.g. polymorphic form in case of a BCS low soluble API), demonstrate that the property of the API is not changed during manufacture.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

Example:

The proposed manufacturing process is a standard process utilised in tablet manufacture and consists of several steps including sifting, blending, and direct compression. The process has been sufficiently characterized. In-process testing was done for the common blend (description, water content, assay and blend uniformity), during compression (appearance, diameter, average weight, hardness, thickness, friability and, as applicable, content uniformity or uniformity of weight) and at packaging (leak test). Critical steps and intermediates are adequate and these include preparation of the powder blend, compression of tablets. A flow diagram and detailed description of the manufacturing process have been provided.

The manufacturing process was verified to be consistent with that established under Pharmaceutical Development Data and this was verified with the BMR for the biobatch (batch No.) for the {XXX} mg strength and for the biowaiver batch for the {XXX} mg strength (batch No.). Process validation data (tool) were provided for three commercial scale batches (batch size 150,000 tablets for {XXX} mg strength and 100,000 tablets for the {XXX} mg strength). The results show consistence in the manufacturing for the three batches.]

For sterile products:

Of specific importance to injections are the physical form of the injection, the route of administration (IV,IM,SC or other) and the volume of the injection. The primary concern is:

- Sterility and maintanance of sterility of the product
  - Sterilisation method

- Container-closure integrity
- Preservative efficacy (multi-dose injections)

- Bacterial endotoxins
  - Control of the APIs and IPIs (specifications)
  - Depyrogenation of glass containers
- Physiological acceptability
  - pH
  - isotonicity
  - partuculate matter
  - viscosity
  - density

Comments:

All these aspects should be addressed during Formulation development and Manufacturing process development where appropriate to the dosage form, volume of injection and route of administration, e.g.:

- The choice of sterilization method must be investigated according to the decision tree for the choice of sterilization methods. Autoclaving is the method of choice. Any other method should be motivated.
- Container-closure integrity should always be validated
- The solubility of the API and the influence of pH on the solubility in water or the chosen solvent should be investigated for APIs of poor solubility.
- Compatibility of the product with production equipment, filter-media, and diluents for IV administration and container components should be addressed.
- Possible precipitation of poorly soluble APIs during storage and after administration should be addressed
- Viscosity is essential for IM injections
- Density and viscosity is important in injections in the spinal column e.g. epidural injections.
- Droplet size distribution is of major concern for IV oil-in-water emulsions(propofol).
- Preservative efficacy in multi-dose containers must be addressed; however, often this is being addressed in 3.2.P.8.
- In-use stability of reconstituted or diluted injections must be addressed.
- For Lyophilized injections the development and validation of the lyophilation cycle is important.
- When a product is sterilized by filtration, the APIs and IPIs need not be sterile but should have a very low bioburden and should be endotoxin free. All steps after filtration should take place in a Class A area with a Class B background.
- For products such as powders, all APIs and IPIs should be sterile and the whole manufacturing process should take place in a Class A/B area.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s) (name, dosage form)

(a) Name, address and responsibility (e.g. fabrication, packaging, labelling, testing) of each manufacturer, including contractors and each proposed production site or facility involved in manufacturing and testing:

Table 3.2.P.3.1-1: Manufacturer information

Name and address (include block(s)/unit(s))	**Responsibility**

3.2.P.3.2 Batch formula

Largest intended commercial batch size:

Other intended commercial batch sizes:

[Information on all intended commercial batch sizes should be in the SCoRE]

(b) List of all components of the FPP to be used in the manufacturing process and their amounts on a per batch basis (including components of mixtures prepared in-house (e.g. coatings) and overages, if any):

Table 3.2.P.3.2-1: FPP components

Strength (label claim)			
Master/blank production document reference number and/or version[9]			
Proposed commercial batch size(s) (e.g. number of dosage units)			
Component and quality standard (and grade, if applicable)	**Quantity per batch (e.g. kg/batch)**	**Quantity per batch (e.g. kg/batch)**	**Quantity per batch (e.g. kg/batch)**
[Complete with appropriate titles e.g. Core tablet (Layer 1, Layer 2, etc. as applicable), Contents of capsule, Powder for injection]			
Subtotal 1			
[Complete with appropriate title e.g. Film-coating]			

[9] SAHPRA requires an updated master / blank production document reference number and/or version if major changes to the process are made (i.e. not editorial or administrative), as the SCoRE must reflect the current information in the dossier. Please refer to the 2.02 Quality and Bioequivalence Guideline for more information about requirements for master / blank production documents.

Subtotal 2			
Total			

3.2.P.3.3 Description of manufacturing process and process controls (Assess for all applications)

For low API load, if manufacturing process involves wet granulation or API introduced in solution, uniformity is assured

if manufacturing process involves direct compression, in-process controls should be checked for content uniformity. If content uniformity is not conducted, it should be requested and proven.

(c) Flow diagram of the manufacturing process:

Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:

Manufacturing Process: Assess this in conjunction with the 3.2.R.7 Executed and blank BMRs

For sterile products:

Depending on the nature of the injection and method of sterilization, the description should be **both comprehensive but concise** and the description or the flow diagram and preferably both should indicate the grades of clean areas of the various areas of production; methods and conditions of sterilisation/dehydrogenation (time/temperature) of manufacturing components and filter media; the pressure source used for filtration and it's method of sterilisation; the final method of sterilisation; in-process controls such as bioburden testing and acceptance criteria,; filter integrity testing; the maximum validated processing times (holding times) for the various stages of manufacturing.

3.2.P.3.4 Controls of critical steps and intermediates

(a) Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:

Table 3.2.P.3.4-1: Summary of manufacturing process controls

Step (e.g. granulation, compression, coating)	**Controls (parameters/limits/frequency of testing)**

Proposed/validated holding periods for intermediates (including bulk product):

3.2.P.3.5 Process validation and/or evaluation (Assess for high risk)

(a) A process validation protocol (VP) or report (VR) Number:

The validation of the maximum holding time of the final product before packaging and the holding time of FPP intermediates before further processing:

Conditions during storage and/or shipping:

For sterile products:
Over and above the requirement of 3.2.P.3.5 and depending on the product, container-closure system and method of sterilization, the following should be submitted:

- Process validation report or protocol,
- validation report of aseptic processing by Media fill
- summary report of the validation of the final sterilization process (including load patterns)
- summary report on the depyrogenation process of glass containers
- summary report on autoclaving of production equipment and filter media
- report on the validation of the maximum processing times of the various stages of manufacturing (chemical/physical and microbiological)

3.2.P.5 Control of drug product (Assess for all applications)

3.2.P.5.1 Final product specifications

a) Specification(s) for the FPP:Table 3.2.P.5.1-1: FPP specifications

Standard (e.g. Ph. Int., BP, USP, in-house)			
Specification reference number and version			
Test	**Acceptance criteria (release)**	**Acceptance criteria (shelf-life)**	**Analytical procedure (type/source/ version)**
Description			
Identification			
Impurities			
Assay			
Bacterial endotoxin			
Dissolution			
etc.			

[Guide:

Specifications (titles and limits) should be listed in tabulated form for in-process controls, FPP intermediate controls, final product controls (batch release), stability controls, and in-use (if applicable). If the in-process controls are submitted in 3.2.P.3.3 a cross reference will suffice.

In-process controls should be clearly identified as such including those performed on bulk e.g. liquids and semi-solids prior to packaging.

If a product is included in a recognised pharmacopoeia any deviation from the relevant monograph should be justified.

The description of the final product and the description given under "Identification" in the professional information and patient information leaflet should correspond. The description should be such that visual identification of counterfeit medicines is facilitated where possible.

See the ICH Guidelines: Q3B, Q6A and Q6B and Appendix 2 of the Stability guideline for the specifications required for each dosage form. If any specification is not appropriate for a particular product, a motivation should be included. Other parameters not appropriate for stability testing should also be included as release specifications, e.g. a specification for residual organic solvents used during the coating procedure, or sterility.

Example:

The product specification is a standard one for tablets. The specifications contain tests with suitable limits for appearance, identification (HPLC and UV), uniformity of dosage units by content uniformity, friability of cores, water content (by Karl-Fisher), thickness of cores, hardness, disintegration, average weight, assay (HPLC), related substances

(HPLC), dissolution, microbial limits. Full details of all analytical methods have been provided. All non-pharmacopoeial methods have been satisfactory validated.

Batch analysis data was provided on three commercial scale batches of the finished product. Results demonstrate compliance with the proposed specification and confirm consistency and uniformity of the product. It has been shown that tablets can be manufactured reproducibly according to the finished product specifications.]

Specifications: Ensure that the reference number, version, date are included and also signed. These must be included in the report as indicated in the example below. Confirm compliance with the claimed pharmacopoieal monograph. Ensure the proposed specifications are according to ICH Q3C. If not according to ICH guidance check the impurity profile of the product.

3.2.P.5.1 Specifications for in-process controls must be included. If the in-process controls are submitted in 3.2.P.3.3 a cross will suffice.

3.2.P.5.1 Visible particulate matter must be specified as a final release criteria or in-process control specification in addition to sub-visible particulate matter.

Evaluation of FPP intermediates for parenterals (powder blends) should also include homogeneity, and FPP intermediate sterile powders should also include evaluation of sterility and bacterial endotoxin testing (BET).
The preservative efficacy of relevant dosage forms and/or presentations, e.g. multi-dose vials, eye drops should be specified in 3.2.P.5.1 and presented in 3.2.P.8. However, once established for **the lowest limit of preservative content** specification, it is not a routine batch test requirement.

For Bacterial endotoxin determination the validation data required by the USP / BP/ Ph Eur, should be submitted.

3.2.P.5.3 Validation of analytical procedures (Assess for high risk applications)

Table 3.2.P.5.3-1: Validation parameters

Validation Parameter	Analytical Procedure			
	Assay	**Related substances**	**Dissolution**	**Other**
Method Type:	[IR]	[HPLC]	[HPLC]	
Method Number:	[*No. X*]	[*No. Y*]	[*No. Z*]	
Accuracy				
Precision:				
- Repeatability				
- Intermediate precision				

Validation Parameter	Analytical Procedure			
	Assay	Related substances	Dissolution	Other
Specificity				
Detection limit (specify)				
Quantitation limit (specify)				
Linearity				
Range (specify)				
Robustness				
Solution stability				
+ indicates that the parameter is acceptably tested and validated - indicates that the parameter is not tested ? indicates that questions remain before the parameter is judged to be acceptable				

3.2.P.5.4 Batch analysis

Table 3.2.P.5.4-1: Batch analysis

Test	Specification	Results	
		Batch no:	Batch No:

3.2.P.6 Reference standards

(a) Purification method if applicable:

(b) Establishment of purity (potency):

(c) CoA, with a potency statement:

3.2.P.7 Container closure system (Assess for sterile products)

(a) Description of the container closure systems, including unit count or fill size, container size or volume:

Table 3.2.P.7-1: Description of container closure systems

Description (including materials of construction)	Strength	Unit count or fill size (e.g., 60s, 100s etc.)	Container size (e.g. 5 ml, 100 ml etc.)

For sterile products:

For Injections packed in **glass containers** the Type of glass must be specified and compliance with pharmacopoeial specifications must be confirmed.

Specifications for **rubber caps** must comply with pharmacopoeial requirements and compatibility with the formulations must be proven either here or in 3.2.P.2.

For injections packed in **plastic containers** the type and formulation of the plastic material must be specified, it must comply with pharmacopoeial specifications and CPMP-QWP-4359-03 including sorption studies, migration studies and toxicological information.

The container-closure integrity must be validated unless it has already been done in 3.2.P.2.

3.2.P.8 Stability (Asses for all applications)

3.2.P.8.1 Stability summary and conclusion

(a) Proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable):

Table 3.2.P.8.1-1: Storage information

Container closure system	Storage statement	Shelf-life

For sterile products:

Injections packed in glass vials with rubber caps must be stored upright and inverted to test for any interaction of the product with the rubber caps (sorption or extraction).

Injections packed in semi-permeable containers (Plastic containers) must be tested for water loss at low humidity.

The protocol and results of preservative efficacy testing where relevant must be provided.

Where relevant specifications and results for preservative concentration and antioxidant concentration must also be included.

Where relevant in-use stability must be tested.

Photo stability study must be presented unless it has been done in 3.2.P.2.

The compatibility with the listed IV solutions under *"Dosage and Directions for use*" in the PI must be reported on.

[Guide:

A tabulated summary of the data, clearly indicating the batch number and pack types/sizes (production, pilot or experimental) of batches, packaging material, storage conditions and storage period, and manufacturer of the API with API batch numbers, should be included for each final product manufacturer.

Discuss the relevance of the protocol, particularly with regard to the parameters tested in the studies. Bracketing & Matrix designs – acceptable?

Are the methods used the same as or different to those described in P.5? Are they well validated and shown to be stability indicating?

Confirm that the containers used in the stability studies are the same as those proposed for marketing of the product as described in the professional information and patient information leaflet.

Are the number of batches, and their sizes, used in the stability studies in accordance with the requirements of the stability guideline? Clarify.

Note that the qualification of impurities carried out on the API may not necessarily address degradants induced by the product matrix, product manufacturing process or product ageing. In addition, other product characteristics may change on storage and these need to be justified with reference to the preclinical and clinical results.

Confirm if the proposed shelf life and storage conditions are adequate.

In–Use stability:

Comment also on stability after opening and during use, e.g. for infusions to be diluted, stability after dilution and during administration, compatibility with commercially available administration equipment, etc.

Are In-use shelf life and storage conditions necessary? Are the applicant's proposals in line with the current guidelines? If not, are they still justified?

Example:

Stability studies under the following conditions of 30°C/75%RH (long term, 36 months) and 40°C/75%RH (accelerated, 6 months) were carried out on three commercial scale batches. Containers used in the stability studies were the same as those proposed for commercialization.

Tests conducted during stability studies were description, identification by HPLC, average weight, hardness, water content by KF, dissolution, related substances, assay, and microbial limit tests. No significant differences in xxxx assay and degradation products content were observed. In conclusion, stability results showed no increase of the impurities (known and unknown). The results are well within the specification limits.

In summary the stability data provided support the proposed shelf-life of 24 months (product demonstrated to be stable up to 36 months) and storage conditions of "store at or below 30°C, protect from light and moisture" when packed in Alu-Alu blister packs. Pack sizes 10 tablets in a blister, such three blisters packed in a carton, and cartons packed in a shipper.

3.2.P.8.2 Post-approval stability protocol and stability commitment

(a) Stability protocol for Primary stability batches (e.g. storage conditions (including tolerances), batch numbers and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Table 3.2.P.8.2-1: Stability protocol summary

Parameter	**Details**	
Storage condition(s) (◦C, % RH)		
Batch number(s)/batch size(s)	*<primary batches>*	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

Stability protocol for Commitment batches (e.g. storage conditions (including tolerances), batch numbers (if known) and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Table 3.2.P.8.2-2: Stability protocol summary – commitment batches

Parameter	Details	
Storage condition(s) (◦C, % RH)		
Batch number(s)/batch size(s)	*<not less than three production batches in each container closure system>*	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

Stability protocol for Ongoing Batches (e.g. storage conditions (including tolerances), number of batches per strength and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Table 3.2.P.8.2-3: Stability protocol summary – ongoing batches

Parameter	Details	
Storage condition(s) (◦C, % RH)		
Batch size(s), annual allocation	*<at least one production batch per year (unless none is produced that year) in each container closure system >*	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

Bracketing and matrix design for commitment and/or continuing (i.e. ongoing) batches, if applicable:

[*If applicable, include information here*]

3.2.P.8.3 Stability data

Table 3.2.P.8.3-1: Stability data

Storage conditions (◦C, % RH)	Strength and batch number	Batch size	Container closure system	Completed (and proposed) test intervals

Evaluate data and approve the shelf-life period as the paragraph below. The screener should check this information so they could populate the table above.

A shelf life of …. months is approved for …….(product)…. manufactured by ….(FPP manufacturer)….with API manufactured by ….. (API manufacturer)…., when packed in transparent PVC/PCTFE/ Aluminum blisters or Aluminum/ Aluminum blisters, which are subsequently packed into cardboard boxes and stored below 30°C.

Module 3.2.R Regional information

Pharmaceutical and Biological availability (3.2.R.1.4.2)

Exemption must be requested from submitting a proof of equivalence study in Module 3.2.R.1 based on the fact that the formulation is essentially the same as innovator product and contains the same active ingredient in the same molar concentration as the reference product. Essential similarity to the innovator product must be proven (Sometimes proven in 3.2.P.2). Injections in solution intended for IV or IM administration are normally exempt.

Comments:

In the case of liquid dosage forms, excipients similarity to the comparator is confirmed under section 3.2.R.1.4.1 and similarly, in the case where the excipients are not similar to the comparator product, API-excipient compatibility should be confirmed under 3.2.P.2.

Comments:

Certificates of Suitability CEPs/ WHO CPQ

Include the number and validity thereof in the report

Biostudies for generics (Refer to BE template, if applicable)

Bioequivalence for the X mg tablets

[Guide:

The study should be designed in such a way that the formulation effect can be distinguished from other effects However, under certain circumstances and provided the study design and the statistical analyses are scientifically sound, alternatively well-established designs such as

parallel designs for very long half-life substances, and replicate designs e.g. for substances with highly variable pharmacokinetic characteristics could be considered. In general, single dose studies will suffice, but there are situations in which steady-state studies may be required in which case the steady-state study design should be motivated.

Conduct of a multiple dose study in patients is acceptable if a single dose study cannot be conducted in healthy volunteers due to tolerability reasons, and a single dose study is not feasible in patients. Use of a multiple dose study instead of a single dose study, due to limited sensitivity of the analytical method, will only be accepted in exceptional cases as due to the recent development in the bio-analytical methodology, it is unusual that parent moiety cannot be measured accurately and precisely. e.g.,; A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study (……) of ……. (B. No.) manufactured by XY Laboratories Limited, India comparing BJ Tablets? mg (Lot No.: xxx), manufactured by Co., USA, in healthy, adult, male, human subjects was performed under fasting condition.

Additional information:

Multi-source (generic) drug products need to conform to the same standards of quality, efficacy and safety required of the originator's (innovator/brand) products. A reasonable assurance must be provided that they are, as intended, clinically interchangeable with innovator product or acceptable comparator products. Pharmaceutically equivalent multi-source pharmaceutical products must be shown to be therapeutically equivalent to one another in order to be considered interchangeable:

Example:

The study was conducted at BXX Clinical Research, Steve Biko Hospital, Pretoria – 0001, SA in 2018. MCC, SA and MHRA from UK recently inspected the CRO in 2017. Proof of acceptable GCP inspection in 2017 from South Africa Medicines Control Council for a study conducted in 2010 was provided. Therefore, this was found sufficient to demonstrate that the CRO conducts studies to acceptable levels of compliance with international GCP requirements. The study was conducted in 72 health subjects aged between 19 and 40 years.

xxxx sodium in plasma was analysed using a sufficiently validated UPLC-MS/MS method. Bioequivalence was demonstrated with the 90% confidence interval of the ratio of the geometric means for the test and reference product within acceptance limits of 80 – 125% for Cmax and AUC.

Provide a snapshot of tabulated "mean Pharmacokinetic and Statistical results of the Test and reference products" see template of table below:]

Parameter (n)	Test mean/ SD/CV	Reference mean/ SD/CV	Point estimate	90% Confidence limits		Intra-sub CV %
AUC_{0-t} [ng*h/ml]						
C_{max} [ng/ml]						
$AUC_{0-\infty}$ [ng*h/ml]						
t_{max} [h]						
$t_{1/2}$ [h]						

K_{el} [h^{-1}]						

Biowaiver for the X mg tablets

[Example

xxxx Sodium Tablets X mg (lower strength) proposed for commercial supplies is dose proportional to Xxxx Sodium Tablets Y mg (higher strength) used for performing bioequivalence study. Xxxx shows linear pharmacokinetics from 1 to 10 mg. The manufacturing process for the Xmg strength and Ymg strength were confirmed to the similar. The comparative dissolution in release media and buffered media at pH 1.2, pH 4.5 and pH 6.8 of the batch used in the bioequivalence study and the proposed commercial batch of Xxxx Sodium Tablets X mg demonstrated similarity in the dissolution profiles.]

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SUPPLEMENTARY MATERIAL

Regulatory registration timelines of generic medicines in South Africa: Assessment of the performance of SAHPRA between 2011-2022

Lerato Moeti[1,2], Madira Litedu[1], Jacques Joubert[2]

[1] *South African Health Products Regulatory Authority (SAHPRA), Pretoria, South Africa*

[2] *School of Pharmacy, University of the Western Cape, Cape Town, South Africa.*

The overview and approval times of the samples used in the Backlog clearance project and Risk-based assessment processes.

Table 1: The overview and approval times of the samples used in the Backlog clearance project and Risk-based assessment processes.

Resubmission window	Resubmission window	Registration process	Sample size	Median finalisation time (calendar days)	Median approval time (calendar days)
RW1	Human Immono deficiency Virus Tuberculosis Hepatitis	Backlog Clearance Project	129	501	591
RW5	Maternal and newborn health Diabetes Malaria Priority APIs				
RW6	Respiratory system diseases				
RW8	Haematological / immunological diseases Analgesics & NSAIDs1	Risk-Based Assessment Phase 1	63	68	110
RW10	Endocrine, nutritional and metabolic diseases Digestive system diseases	Risk-Based Assessment Phase 2	159	73	95
RW11	Musculoskeletal system and connective tissue diseases Skin and subcutaneous tissue diseases				
RW12	Eye and adnexa diseases Ear and mastoid diseases Other				

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RESEARCH ARTICLE 1: Common Deficiencies Found in the Active Pharmaceutical Ingredient (API) Section of Non-sterile Generic Products Submitted for Registration by SAHPRA.

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1. **Moeti L, Litedu M, Joubert J. Common Deficiencies Found in the Active Pharmaceutical Ingredient (API) Section of Non-sterile Generic Products Submitted for Registration by SAHPRA. Ther Innov Regul Sci, 2022:56;276–290. https://doi.org/10.1007/s43441-021-00359-9.**

2. **Moeti L, Litedu M, Joubert J. Common deficiencies found in Generic Finished Pharmaceutical Products (FPPs) submitted for registration by the South African Health Products Regulatory Authority (SAHPRA). J Pharm Pol Pract. 2022;15:1- 21.**

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4. **Moeti L, Litedu M, Joubert J. The implementation of a risk-based assessment approach by the South African Health Products Authority (SAHPRA), Pharm Med. 2023;37:71-91. https://doi.org/10.1007/s40290-022-00452-w**

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DIA

ORIGINAL RESEARCH

Common Deficiencies Found in the Active Pharmaceutical Ingredient (API) Section of Non-sterile Generic Products Submitted for Registration by SAHPRA

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Abstract

Purpose This research study aims to determine the qualitative and quantitative common deficiencies included in the API section of dossiers submitted to SAHPRA. The study was conducted retrospectively over a 7-year period (2011–2017) for non-sterile generic products that were finalised by the Pharmaceutical and Analytical pre-registration Unit. In this period, the restricted part of the CTD was evaluated when needed therefore this was not conducted on all applications. The requirement to evaluate the restricted part for all applications was initiated in January 2020, thus, a separate study has been conducted to identify the common deficiencies in the restricted part.

Methods There were 2089 applications finalised between 2011 and 2017 and in order to attain a representative sample for the study, the multi-stage statistical sampling called the 'stratified systematic sampling' was selected as the method of choice. Sample size was obtained using the statistical tables found in the literature and confirmed by a sample size calculation with a 95% confidence level, resulting in the selection of 325 applications. Subsequently, all the deficiencies were collected and categorised according to CTD subsections. For the restricted part study, all new applications evaluated between January to May 2020 were used.

Results A total of 1130 deficiencies were collected from 325 applications sampled. The majority of the identified deficiencies were from Module 3.2.S.3.1 (19.38%) on characterisation, Module 3.2.S.1.3 (19.11%) on general properties, Module 3.2.S.4.1 (10.44%) on specifications and Module 3.2.S.4.3 (8.32%) on validation of analytical methods. The study on the restricted parts included the five most common deficiencies that SAHPRA has identified, which are similar to those observed from the 2011–2017 applications. This confirms that the quality of the evaluations has been maintained over the years. Comparison of the deficiencies with those reported by other agencies such as the USFDA, EMA, WHOPQTm and TFDA are discussed with similarities clearly outlined.

Conclusions The most common deficiencies observed by SAHPRA were extensively discussed. These findings could serve as a guidance for API manufacturers to submit better quality APIMFs which will improve turnaround times for registration and accelerate access to medicines for patients.

Keywords South African Health Products Regulatory Authority (SAHPRA) · Common deficiencies · Active pharmaceutical ingredient master file (APIMF) · Drug master file (DMF) · Common technical document (CTD) · Active pharmaceutical ingredient (API)

Introduction

The South African government established a medicines regulatory authority in 1965 shortly after the implementation of the Medicines and Related Substances Act (Act 101 of 1965). [1] The quality and efficacy aspects of finished pharmaceutical products (FPP) are evaluated by the Department, Pharmaceutical Evaluations and Management (PEM) pre-registration Unit within SAHPRA. The pre-registration

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Unit utilised 15–20 external experts as evaluators. The experts formed part of the Pharmaceutical and Analytical (P&A) Committee, which provided the necessary support to the Unit and the Committee meetings served as a quality assurance measure for all applications. Committee members provided technical and scientific advice for evaluations in the pre-registration Unit. This meant that each report on the assessment of the information provided in the dossier was discussed in the meeting before communication with the applicant. The applications are submitted in the form of a dossier in the common technical document (CTD) format to the Health Products Authorisation (HPA) and distributed to different Units within SAHPRA for evaluation. A CTD is an internationally agreed format for the preparation of new product applications for submission to regional regulatory authorities. The CTD format is divided into five modules as illustrated in Fig. 1 [2].

The quality part of the dossier is divided into two main sections namely, information on the active pharmaceutical ingredient (API) and information on the finished pharmaceutical product (FPP). A list of deficiencies referred to as recommendations are then produced from the evaluation process and communicated to the applicant. The applicants are given three months to respond and update the dossiers with the requested information necessary to verify the quality of the product. There were no specified rounds of communication given between the applicant and the agency. Once all the requirements have been met by all the Units and the quality of the drug product is considered safe and efficacious as required by the agency, the FPP is finalised and is recommended for registration.

SAHPRA receives the API part in the form of a DMF/APIMF (applicant part), or requirements supported by a Certificate of Suitability (CEP) or a Certificate of prequalification (CPQ). The CEP and CPQ are certificates allocated for APIs where DMFs have been approved by EDQM [3] and WHO-PQTm [4], respectively. Authorities such as EMA, [3] USFDA, [5] TDFA [6] and Health Canada [7, 8] have implemented the APIMF/DMF procedure. In this procedure, the complete data are assessed including confidential information from manufacturers. This procedure has not been adopted by many authorities due to insufficient resources and capacity, therefore, only the applicant part of the DMF is submitted and assessed. International medicines regulators worldwide such as TFDA [6], USFDA [9, 10] and EMA [11–15] as well as WHO-PQTm [16, 17] have published several articles on various regulatory aspects in order to promote transparency between the authority and the manufacturers. Those publications are intended to assist applicants to improve the quality of their submitted dossiers, in order to facilitate and accelerate the approval process. This study therefore aims to highlight the common deficiencies observed from the API section submitted by APIMF holders to the health authority, SAHPRA. It is aimed at guiding the manufacturers in submitting better quality APIMFs which will decrease turnaround times for registration and accelerate access to medicines for patients.

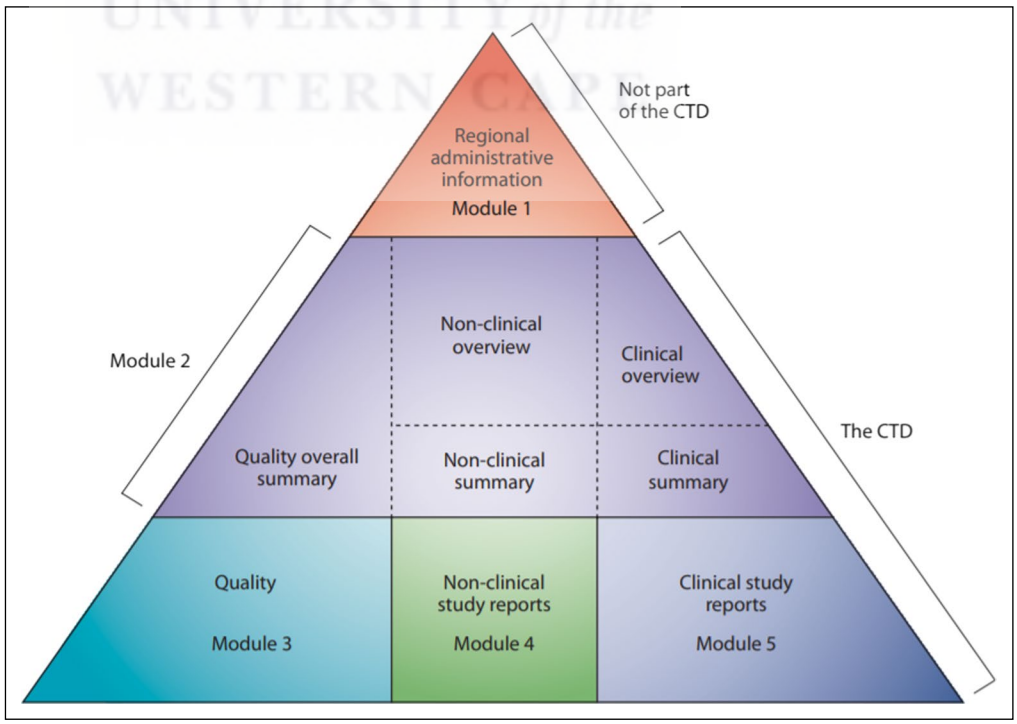

Fig. 1 The organisation of the CTD into five modules. Module 1 is intended to be region specific while the rest of the modules are common for all regions. [2]

Methods

Over the 7-year period (2011–2017), 2089 applications were finalised by SAHPRA. These applications were used to study the trends observed by the authority in order to refine the current processes and inform industry of the current requirements from a scientific viewpoint. Thus, due to the large number of applications received, a statistical sampling method became a requirement for this research. Sample selection in this study should provide a true representation of the population enabling the results to be generalised to the population as a whole. In statistics, stratified sampling is a method of sampling from a heterogeneous population which can be partitioned into subpopulations. [18] It involves dividing the entire population into homogeneous groups called strata. [18] The sampling method ensures that each subgroup is adequately represented within the whole sample of a research study. Sampling of medicinal products from a large population would require stratified sampling due to the different critical variables involved such as the applicant, the dosage form, the API used, the therapeutic category and finalisation time of the drug product. Thus, stratified sampling would be suitable for the population in this research study. In addition, systematic sampling is preferred as opposed to random sampling in order to ensure that proportional number of units are selected accordingly at the respective strata. [19–22] The multi-stage sampling technique used is therefore called stratified systematic sampling.

Sample size determination can be obtained using various methods such as a census for small populations, a sample of a similar study, published tables or statistical formulae. [23–25] For sample size calculation, the formula reported by Israel G. D, (1992) [24] contains three variables which are a requirement when determining a sample size (see Supplementary Information for equations and calculations). The variables are; level of precision, level of confidence and the degree of variability. [24, 25] The level of precision used is often expressed in percentage points and described as the percentage error which is selected as ± 5%. [24] In this regard, the level of confidence is therefore 95%. Cohran [22] developed an equation to yield a representative sample for proportions of large samples where the confidence level corresponds to a Z-score which is calculated as 1.96 for the selected confidence level as per the developed equation. The degree of variability (p) refers to the distribution of attributes in the population and a 50% variability is ideal for a heterogeneous population as it gives higher variability. [21, 22] thus a proportion of 50% (0.5) was selected. This equation was used in calculating the sample size for this research study. The calculated sample size obtained was 325 from a population of 2023. Comparison of the calculated sample size with the table reported by F.B. Mahammad [26] for a given population size showed a similar reported value for a population of 2000 of 322 with the same confidence interval and level of precision. There are many other tables reported [24–26] with sample size ranging between 322 and 333. The kth term serves as a constant value used for systematic sampling and is aimed at ensuring that adequate representative units are selected in each strata. This was calculated as six, which means selection was conducted at each 6th value in order to attain the representative sample size.

The full history of all products finalised between the 7-year period (2011–2017) were collected. The history comprises of all communication between the authority and applicants until finalisation. The documents include the recommendations sent to the applicant and the responses received, as well as the evaluation reports of responses. These paper documents were obtained from the P&A Committee meeting minutes and the registry files where all documents relating to the product are kept. The investigation process involved obtaining the type and extent of the deficiencies raised in the first deficiency letter following the initial evaluation process, thereafter, extracting all the responses and feedback during multiple follow-up rounds of communication.

For the investigation of common deficiencies in restricted parts of the dossier, initial query letters sent between January and May 2020 were obtained and the recommendations recorded. The investigation is initiated in order to alert pharmaceutical companies of the common deficiencies identified by SAHPRA in the restricted parts, allowing them to submit dossiers with the required information from the onset. These were obtained from SAHPRA's electronic dossier folder and recorded.

Information for 2018 and 2019 is not included in this study due to the disruptions caused by the protesting action in 2018 and the move to the new premises in 2019 which halted production. During the transition of the authority from MCC to SAHPRA, SAHPRA staff continued to be housed in Civitas building in Pretoria with the NDoH employees. From April 2018, the department employees working in the Civitas building embarked on a protest action because of concerns about working conditions in the building. SAHPRA as a Sect. 3A public entity, moved into new premises at the end of 2018. Flow of submissions regained momentum by the middle of 2019.

Results

Stratified systematic sampling ensures that sampling is representative and not biased and that all critical variables are considered. Aspects such as the applicant, the dosage form,

the API used, the therapeutic category and finalisation time of the drug product were considered as important variables. Out of the above five mentioned variables, the most critical and of importance is the therapeutic category since we are dealing with pharmaceutical products.

Regulation 25 of Act 101 classifies and categorise medicines in South Africa as follows:

- Category A for Medicines which are intended for use in humans and are without manipulation, ready for administration;
- Category B for Medicines which cannot be administered without further manipulation; and
- Category C for Medicines intended for veterinary use, which are without further manipulation, ready for administration [27].

All medicines in the population are category A. This category is subdivided into 34 pharmacological classifications, some of which are subdivided further. Each therapeutic category is considered a stratum. These are grouped into 33 categories. The sample size in each stratum as illustrated in Table 1 varies according to the relative importance of the stratum in the population, i.e. percentage contribution. For example, if 16% of the population are antiviral agents, then 16% of the sample should contain products in that group.

The sample sizes of all strata were combined to attain a representative sample size of 349 products. The rounding down of the kth term resulted in slightly more samples being selected in comparison to the findings on statistical tables and calculated values with the acceptable range of 322–333 as indicated above. Therefore, 330 samples were selected, five of these were omitted from the study as they undertook a different registration process called the ZaZiBoNa collaborative assessment process which SAHPRA joined in June 2016 [28] Therefore, the samples used in the study were 325 as per calculations (see Supplementary Information for equations and calculations).

The deficiencies were collected and information populated in the respective Microsoft Excel® Worksheets and quantified using the complete history of finalised products. This research focuses on the API, 3.2.S part of the CTD. The 3.2.S part of the quality section of the CTD consists of sections stipulated in Table 2 regarding the API used in the product. It contains seven sections in which five have subsections.

A total of 1130 API deficiencies were collected from 325 letters from products that were finalised in 2011–2017. The deficiencies observed were all collected as indicated in Table 3. The table outlines all the deficiencies recorded from 325 letters in the API section. These were categorised per subsection and quantified. The quantities per subsection were recorded as the number of times they were observed in the recommendation letters, then as the percentage of a subsection in a CTD section and lastly as a percentage in the whole 3.2.S CTD section. Figure 2 summarises the results of the common deficiencies per subsection in percentages thereby showing the frequent deficiencies.

In 2020, SAHPRA updated the requirements and introduced the request of the restricted part of generic products. A study was conducted which seeks to provide common deficiencies observed from the restricted part. This was conducted on applications evaluated between January and May 2020 by the PEM pre-registration Unit (business-as-usual, BAU section). The deficiencies collected from the 20 initial letters are stipulated in Table 4. Overall, 275 deficiencies were observed from the letters communicated to applicants.

Discussion

Common Deficiencies Observed by SAHPRA in the Submitted DMF/APIMFs

Highest Common Deficiencies

Subsection 3.2.S.3.1 had the highest deficiencies of 19.38% in section 3.2.S. It is a requirement that proof of correctness of the structure be submitted if no official standard is available in which case sufficient evidence, such as Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR), Infrared (IR), Mass Spectroscopy (MS), elemental analysis, etc., (with interpretation) should be provided in support of the structure and stereochemistry. These were either not submitted (1.5%), submitted with no interpretation (34.1%) or legible copies (35.1%) were not submitted and were therefore requested. The other 6.0% of the deficiencies were due to the characterisation of the polymorphic form. In instances where the API exists in more than one polymorphic form, the applicant is required to submit data on consecutive batches confirming that during the manufacturing process only one form is consistently produced. Studies should be performed comparing other polymorphic forms found in literature to the required polymorphic form. This is normally done by comparing their powder X-ray diffraction- (pXRD), differential scanning calorimetry- (DSC) or Fourier transform infrared (FTIR) spectra. Polymorphism is when the same molecule crystallizes into more than one type of crystal. The polymorphs are made of the same atoms but in different crystalline arrangements. The solubility and hence the bioavailability may be very different in the two different arrangements. [29] One API could have different polymorphic forms which differ in internal solid-state structure and may, therefore, possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. [30, 31] The unexpected appearance

Table 1 The different strata (pharmacological classifications) generated with respective population and sample sizes

Pharmacological/therapeutic classifications	Population (*N**)	%	Sample (n_*)
1.1 Central analeptics 1.2 Psychoanaleptics (antidepressants) 1.4 Respiratory stimulants	103	4.9	17
2.1 Anaesthetics 2.2 Sedatives, hypnotics 2.5 Anticonvulsants, including anti-epileptics	149	7.1	25
2.6 Tranquillisers 2.6.5 Miscellaneous structures	191	9.1	32
2.7 Antipyretics or antipyretic and anti-inflammatory analgesics 2.8 Analgesic combinations 2.9 Other analgesics 2.10 Centrally acting muscle relaxants and	51	2.4	9
3.1 Antirheumatics (anti-inflammatory agents) 3.2 Non-hormonal preparations 3.3 Anti-gout preparations	51	2.4	9
4.0 Local anaesthetics	5	0.2	1
5.2 Adrenolytics (sympatholytics) 5.3 Cholinomimetics (cholinergics)	69	3.3	11
5.4.1 Anti-Parkinsonism preparations	68	3.3	11
5.6 Histamine	10	0.5	2
5.7.1 Antihistaminics	29	1.4	5
7.1 Vasodilators, hypotensive medicines	51	2.4	9
7.1.3 Other hypotensives	328	15.7	55
7.1.5 Vasodilators—peripheral	48	2.3	8
7.3 Migraine preparations	25	1.2	4
7.4 Lipotropic agents 7.5 Serum-cholesterol reducers	92	4.4	15
8. Medicines acting on blood and haemopoietic system 8.2 Anticoagulants 8.4 Plasma expanders	13	0.6	2
10 Medicines acting on respiratory system 10.2 Bronchodilators 10.2.1 Inhalants	88	4.2	14
11. Medicines acting on gastro-intestinal tract 11.1 Digestants 11.4.3 Other 11.5 Laxatives 11.9.2 Special combinations and 11.10 Others	72	3.4	12
13.4.1 Corticosteroids with or without anti-infective agents 13.4.2 Emollients and protectives 13.9 Radiation protectants 13.11 Acne preparations 13.12 Others 14. Preparations for treatment of wounds 14.2 Wound dressings	15	0.7	3
5.8 Preparations for the common cold including nasal decongestants 16.1 Nasal decongestants 16.3 Surface anaesthetics 16.4 Naso-pharyngeal and bucco-pharyngeal antiseptics	24	1.1	4
18.1 Diuretics 18.2 Antidiuretics 18.3 Ion-exchange preparations 18.8 Ovulation controlling agents	24	1.1	4
20.1.1 Broad and medium spectrum antibiotics 20.1.2 Penicillins 20.1.6 Topical antibiotics	125	5.9	21
20.2 Antimicrobials, Other than antibiotics	13	0.6	2

Table 1 (continued)

Pharmacological/therapeutic classifications	Population (*N**)	%	Sample (n_*)
20.2.2 Fungicides 20.2.3 Tuberculostatics 20.2.6 Medicines against protozoa	34	1.6	5
20.2.8 Antiviral agents	213	10.2	36
21.1 Insulin preparations 21.2 Oral hypoglycaemics	37	1.8	6
21.3 Thyroid preparations	12	0.6	2
21.5.1 Corticosteroids and analogues	8	0.4	1
21.8.2 Progesterones with or without oestrogens	10	0.5	2
21.12 Hormone inhibitors	43	2.1	7
26 Cytostatic agents	31	1.5	5
32 Other substances or agents	10	0.5	2
34 Others	47	2.2	8
TOTAL	2089	100	349

Table 2 The CTD sections and subsections for Module 3.2.S regarding the API

CTD sections and subsections	Content
3.2.S.1	**General information**
3.2.S.1.1	Nomenclature
3.2.S.1.2	Structure
3.2.S.1.3	General properties
3.2.S.2	**Manufacture**
3.2.S.2.1	Manufacturer
3.2.S.2.2	Description of manufacturing process and process control
3.2.S.2.3	Control of Materials (Restricted part)
3.2.S.2.4	Control of critical steps and intermediates (Restricted part)
3.2.S.2.5	Process Validation and/or Evaluation (Restricted part)
3.2.S.2.6	Manufacturing process development (Restricted part)
3.2.S.3	**Characterisation**
3.2.S.3.1	Elucidation of Structure and other Characteristics
3.2.S.3.2	Impurities
3.2.S.4	**Control of active pharmaceutical ingredient**
3.2.S.4.1	Specifications
3.2.S.4.2	Analytical procedures
3.2.S.4.3	Validation of analytical procedures
3.2.S.4.4	Batch analyses
3.2.S.4.5	Justification of specifications
3.2.S.5	**Reference standard or materials**
3.2.S.6	**Container closure system**
3.2.S.7	**Stability**
3.2.S.7.1	Stability summary and conclusions
3.2.S.7.2	Post approval stability protocol and stability commitment
3.2.S.7.3	Stability Data

or disappearance of a polymorphic form may lead to serious pharmaceutical consequences therefore; control is crucial.

A classic example which showcases the importance of polymorphism is ritonavir which was originally dispensed as an ordinary capsule, with a polymorphic form of form I. [32] During development in 1996, only the polymorph now called form I was found, but in 1998, a lower free energy, more stable polymorph (form II) appeared. [32] This more stable and less soluble crystal form compromised the oral bioavailability of the drug. This led to the removal of the oral capsule formulation from the market.

Table 3 List of API common deficiencies recommended by SAHPRA in the products finalised by the pre-registration unit between 2011and 2017

Subsection	Deficiency	Quantity	% subsection	% overall
3.2.S.1	The documentation must comply with the SA Guide to GMP Chapter 4, Requirements for Documentation, including at least a unique identification, version and date. In addition, a declaration that it is current must be included	55	17.57	4.9
3.2.S.1 (3.2.R.4)*	Include a comparison of the method of synthesis, specifications and batch analysis data to confirm similarity or outline differences between the different API manufacturers	18	5.75	1.6
3.2.S.1 (3.2.R.3)*	Submit an updated CEP as observed from the EDQM website or ensure that the declaration of access to give the applicant access is signed by the CEP holder	24	7.67	2.1
3.2.S.1.3	State the polymorphic form of the API used	14	4.47	1.2
3.2.S.1.3	Provide evidence of occurrence of isomers and chirality where applicable. The absence should also be confirmed	11	3.51	1.0
3.2.S.1.3	The solubility of each API should be stated in terms of a unit part of the substance per number of parts of the solvent, or in unit mass of substance in a given volume of solvent, at a specific temperature. The investigation should include water and the solvent(s) relevant to the product formulation	157	50.16	14
3.2.S.1.3	Include information on the hygroscopicity of the API under physical properties	26	8.31	2.3
3.2.S.1.3	The physical and chemical properties of the API, including e.g. solubility, particle size, hygroscopicity should be included when a CEP has been submitted	8	2.56	0.7
		313		
3.2.S.2.1	The name, business and physical address of each manufacturer of the API being applied for (including any intermediate manufacturer) should be stated	3	3.1	0.3
3.2.S.2.2	A short description of the synthesis and a flow chart which includes the structures and stereochemistry of starting materials and intermediates; reagents, catalysts, solvents, isolation and purification; and any other relevant aspects were not included. This should be submitted	58	59.2	5.1
3.2.S.2.2/3	The starting material proposed is considered complex. Include the tests and specifications as well as the method of synthesis of the starting material or a Certificate of analysis (CoA) to confirm that the starting material is adequately controlled	13	13.3	1.2
3.2.S.2.3	Include the complete name and address of the manufacturer of the starting materials	10	10.2	0.9
3.2.S.2.3	Provide information with respect to control of critical steps and intermediates in the manufacturing process description	7	7.2	0.6
3.2.S.2.3	Briefly describe if there were recovery of materials or solvents (if any) in the method of synthesis and how they were conducted	3	3.1	0.3
3.2.S.2.4	Provide the controls of the critical steps and isolated intermediates used in the manufacturing process of the API	4	4.1	0.4
		98		
3.2.S.3.1	Provide interpretation of spectra, graphs and figures regarding the elucidation of the structure of the API	94	35.1	8.3
3.2.S.3.1	Legible spectra, graphs and figures regarding the elucidation of the structure should be submitted	99	34.0	8.8
3.2.S.3.1	Provide proof of correctness of structure. Spectra, graphs and figures were not submitted to support the correctness of structure	4	1.5	0.4
3.2.S.3.1	Two polymorphic forms have been reported. It should be demonstrated that the one polymorphic form remains unchanged during storage. This is regardless of the fact that the synthetic route yields only one form. State if the identity test can discriminate between the different polymorphs	17	6.3	1.5

Table 3 (continued)

Subsection	Deficiency	Quantity	% subsection	% overall
3.2.S.3.2	Provide a description of impurities, indicating the possible source of impurities and a clear distinction between actual and possible impurities	17	6.3	1.5
3.2.S.3.2	Provide a description of possible degradation products	32	11.9	2.8
3.2.S.3.1	In the case of enantiomers an additional test is required to confirm the identity of the enantiomer and should be controlled in the final API specifications	5	1.9	0.4
		268		
3.2.S.4.1	Include particle size during stability for micronised API to ensure that the API has a well-defined dissolution behaviour	16	6.9	1.4
3.2.S.4.1	Tighten the specifications for individual impurities and total impurities in accordance to ICH guidelines and submitted batch analysis data	10	4.3	0.9
3.2.S.4.1	Include a genotoxic impurity in the final API specifications or provide a justification for its omission	2	0.9	0.2
3.2.S.4.1	The API specifications must be expanded to include a limit for residual solvents including benzene and the relevant validated control procedure must be described	18	7.7	1.6
3.2.S.4.1	Include a specification for the test for polymorphism to ensure that the correct polymorph is consistently formed	10	4.3	0.9
3.2.S.4.1	Include a test for microbial purity/content	6	2.6	0.5
3.2.S.4.1	Include enantiomeric purity in the final specifications to ensure that the enantiomer is consistently controlled	23	9.9	2.0
3.2.S.4.1	Tighten the assay release and stability specification to 95—105% in accordance with the SAHPRA guidelines and include this as a percentage label claim or in mg	7	3.0	0.6
3.2.S.4.1	Include signed and dated specifications by authorised personnel and confirm that they are the same as the FPP's API specifications	9	3.9	0.8
3.2.S.4.1	Bring the API specifications in line with those indicated in a recognised pharmacopoeial monograph and if a CEP is submitted the specifications must be in line with the European Pharmacopoeial monograph	12	5.2	1.1
3.2.S.4.1	Include the specifications for particle size in the FPP manufacturer's API specifications, if applicable	5	2.1	0.4
3.2.S.4.3	Provide details of the reference standards used for validation of related substances	3	1.3	0.3
3.2.S.4.3	Submit validation data for the assay method of the API, residual solvents and related substances including the respective supporting chromatograms	32	13.8	2.8
3.2.S.4.3	The FPP manufacturer must include partial validation or verification for APIs that are pharmacopoeial	13	5.6	1.2
3.2.S.4.3	Include a more stability indicating method than Thin Layer Chromatography (TLC) as the pharmacopoeia includes the use of one, such as High-Performance Liquid Chromatography (HPLC)	5	2.1	0.4
3.2.S.4.3	Indicate the stability of the reference standard solution and the sample solutions	5	2.1	0.4
3.2.S.4.3	Inconsistencies observed in the validation data submitted and clarification required	36	15.6	3.2
3.2.S.4.4	Provide numeric values for the data, "complies should be avoided"	5	2.1	0.4
3.2.S.4.5	Provide justification of the limits set for final API specifications	8	3.5	0.7
3.2.S.4.5	Provide supporting data to prove the justification of the exclusion of certain residual solvents from final specification testing with results tested on six consecutive batches	8	3.5	0.7
		233		

Table 3 (continued)

Subsection	Deficiency	Quantity	% subsection	% overall
3.2.S.5	Provide comparative overlaid IR spectra of the in-house reference standard with the pharmacopoeial reference standard/ qualification of the working standard with the reference standard	26	42.0	2.3
3.2.S.5	Provide the purification method for the in-house reference standard	3	4.8	0.3
3.2.S.5	Provide the CoA of the pharmacopoeial reference standard and/or the in-house reference standard as well as the source of the reference standard	33	53.2	2.9
		62		
3.2.S.6	Provide a description of the container closure system(s) used	52	76.5	4.6
3.2.S.6	Identity of materials of construction of each primary packaging material as well as the identification test used	10	12.3	0.9
3.2.S.6	Submit control procedures, specifications and CoAs of the primary packaging material	9	11.1	0.8
		71		
3.2.S.7.3	Provide additional stability data for the consideration of the requested retest period	42	56.0	3.7
3.2.S.7.3	The out of specification results and justification provided are not accepted and therefore the requested re-test period not granted	2	2.7	0.2
3.2.S.7.3	Indicate the type of batch e.g. pilot/production/experimental as well as the batch size used	12	16.0	1.1
3.2.S.7	Include full stability data for a consideration of the retest of an API. This section should be submitted in compliance with the SAHPRA guidelines	29	25.3	2.6
		85		

(3.2.R.3)* This is a section relating to 3.2.S but has been placed under the regional Sect. 3.2.R.3 on the submission of a CEP

(3.2.R.4)* This a section relating to 3.2.S in cases where more than one API source has been applied for, this is placed under the regional Sect. 3.2.R.4 on multiple API manufacturers

Modules: 3.2.S.1 general properties of the API, 3.2.S.2 manufacture, 3.2.S.3 characterisation, 3.2.S.4 control of the API, 3.2.S.5 reference materials, 3.2.S.2.2 description of manufacturing process and process controls, 3.2.S.2.3 control of materials, 3.2.S.2.4 controls of critical steps and intermediates, 3.2.S.3.1 elucidation of structure, 3.2.S.3.2 impurities, 3.2.S.4.1 specifications, 3.2.S.4.2 analytical procedures 3.2.S.4.3 validation of analytical procedures, 3.2.S.4.4 batch analysis 3.2.S.7 stability, (see Table 2 for further descriptions)

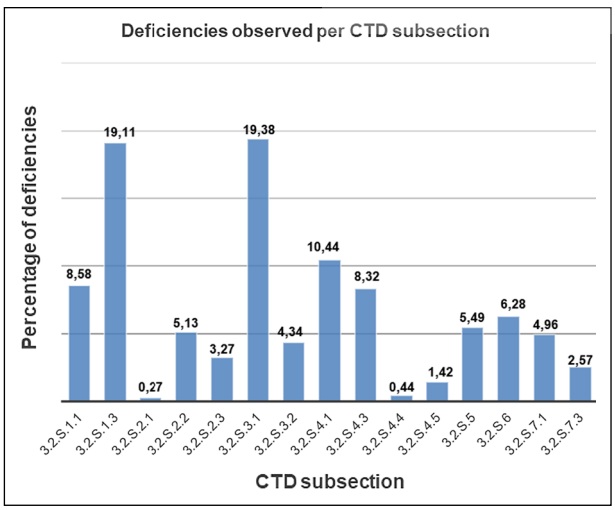

Fig. 2 Distribution of deficiencies per API CTD subsection

Second Highest Common Deficiencies

Figure 2 shows that subsection 3.2.S.1.3 had the second highest number of deficiencies. The recommendations were based on physico-chemical properties of the API. Aspects such as polymorphism, chirality, isomerism, solubility and hygroscopicity of the API were not addressed by the API manufacturer and were therefore requested. Close to 50% of these recommendations were requesting the solubility of the API at physiological pH (1.2–6.8) with several buffered solutions and with solvents relevant to the product formulation and the temperature at which the solubility studies were conducted, to be included. This is critical information that assist in determining the Biopharmaceutics Classification System (BCS) class of the API and hence establish its behaviour during dissolution and bioequivalence studies. Solubility is critical to determine the formulation, the process and the performance of a product, therefore a study is normally required to investigate the solubility of each API. Hygroscopicity on

Table 4 The common deficiencies observed from 20 initial query letters from 31 APIMFs in the restricted part

Subsection	Deficiency	Quantity	% subsection	Request rate (%)
3.2.S.2.3	The API starting materials proposed are complex and form a large part of the backbone of the final API, therefore these require to be well characterised and adequately controlled during the synthesis of this starting material. This therefore requires further redefinition of the starting materials in accordance to the ICH Q7 and ICH Q11 guidelines. In addition, submit the specifications of the starting material to confirm that it is adequately controlled	31	11.3	100
3.2.S.2.3	State the scale of manufacture, the typical batch size, and the maximum batch size (the range) for which the process is described as well as quantities (mass or molar equivalents) of the starting materials and yield ranges for each step of the synthesis	31	11.3	100
3.2.S.2.3	Confirm that no alternative processes are applied during the proposed manufacturing process	30	10.9	96.8
3.2.S.2.3	State if reprocessing or reworking of the API or reaction intermediate occurs. If so, describe this in detail	30	10.9	96.8
3.2.S.2.3	Briefly describe the recovery of materials or solvents (if any), including how the materials or solvents are recovered	31	11.3	100
3.2.S.2.3	Where particle size is considered a critical attribute of the API, the milling/micronisation equipment, process parameters and procedures should be described	23	8.4	74.2
3.2.S.2.3	Provide equipment used during each step of the manufacturing process and operating conditions (e.g. temperature, pressure, pH, time)	27	9.8	87.1
3.2.S.2.3	Confirm that no blending of the final batches is allowed. Should allowance be made for blending then clearly indicate which criteria/tests is/are used to ensure that the individual batch incorporated into the blend meet specifications set for the final product prior to blending	21	7.6	67.8
3.2.S.2.4	Provide the controls of the critical steps and isolated intermediates, including the reaction conditions, completion of individual reaction steps and the identity and purity of the isolated intermediates	25	9.1	80.6
3.2.S.2.6	Indicate any significant changes made throughout the various development stages: these can be changes to the manufacturing process and/ or site of the API since production of earliest batches including non-clinical, clinical batches (e.g. bio-batch supplied to the FPP manufacturer) in comparison to scaled-up pilot and production batches (if applicable)	16	5.8	51.6
	Other	10	3.6	32.2
		275	**100**	

the other hand with 3.0% of the deficiencies will provide insight into the stability of the API and establish whether the API or formulation may be sensitive to moisture. Chirality and stereochemistry (1.7%) of the API are important aspects to be detailed in the structure of the API since other isomers are required to be controlled in the final API specifications if not in the intermediate specifications. The product can have several isomers which may be harmful to the patient even though the structures are similar, therefore isomers serve as impurities and should be controlled as such.

Third Highest Common Deficiencies

The third largest number of deficiencies in the subsections were from tightening specifications in view of the results submitted from batch analysis and stability data of the API. Sixty percent of the responses from applicants stated that the results were within the ICH guideline limites (ICH Q3A (R2)) [33] which was correct, while in other instances the applicant's limits would exceed the ICH limits and they would not provide a sufficient justification for this. ICH Q3A has the following impurity thresholds: identification

threshold (IT), reporting threshold (RT) and qualification threshold (QT). Impurities present that are higher than the IT needs to be identified and impurities higher than QT needs to be qualified for safety. The P&A Committee accepted this justification for reporting, identification and qualification thresholds as SAHPRA is an ICH observer. The second deficiency (1.6%) which led to the back-and-forth communication was applicants who would omit the test of a specific residual solvent, especially benzene which is a class I solvent, without providing supporting data of consecutive production batches to confirm that the solvent is not present in the final API and results being less than 30% of the ICH limit of 2 ppm. The presence of the following solvents in the manufacturing process result in this query being requested since they are known to be potential carriers of benzene; cetone, Toluene, Xylene, Hexanes and Isopropyl alcohol. Depending on where these are used in the manufacturing process, applicants are requested to control benzene in the final API or in the specific solvent specifications.

Fourth Highest Common Deficiencies

The fourth highest deficiencies were from subsection 3.2.S.1. The general information referred to here, is regarding the DMF/APIMF number if a DMF/APIMF is submitted, the CEP validity, if a CEP is submitted and comparison of manufacturing methods if more than one DMF is submitted. These are deficiencies which relate to the API section but do not have a specific location in the CTD and have been placed under regional information but will be discussed in this subsection. The DMF documentation must comply with the SA Guide to GMP Chapter 4 Requirements [34] for Documentation including at least unique identification, version and date. A declaration that it is current should be included. There was 17% of the deficiencies in the subsection relating to the DMF not being submitted as per the above requirements. This is crucial since different FPP manufacturers would source the same API manufacturer who would continually update the DMF/APIMF, therefore it is important for the authority to be informed of the latest version in order to generate a database and avoid duplication of evaluation in cases where the same API source is used by different FPP manufacturers. Also, DMF/APIMFs can be sent to multiple authorities resulting in frequent updates.

Information about the CEP is placed in the regional information Sect. 3.2.R.3 but will be discussed in this section since it relates to the API. Applicants are requested to submit the latest version of the CEP (2.4% of the 3.2.S section). The EDQM generally updates the status of each CEP therefore it is easy to find out if the submitted CEP is valid or not through the Certificate of Suitability database [3].

The section on multiple API manufacturers is also placed under regional information in Sect. 3.2.R.4. In cases where more than one API source is used it is required that the applicant provides a comparison of the method of synthesis, specifications and batch analysis to confirm similarity or outline differences between the API manufacturers which should be conducted by an independent laboratory. Although this may be obtained in the individual DMFs the summary provided assists in the evaluation and makes it easy for the evaluator to notice discrepancies, if any. Only 5.8% of the deficiencies in the subsection were as a result of this.

Fifth Highest Common Deficiencies

The fifth highest CTD deficiency subsection is 3.2.S.4.3. Almost 14% of the deficiencies in the section were due to applicants not submitting the required validation data of the analytical procedures used in specification tests. Other deficiencies were of discrepancies witnessed in the submitted validation data (15.6%) and partial validation data which should be submitted by the FPP manufacturer if they are using the same analytical procedures as the API manufacturer (5.6%).

Sixth Highest Common Deficiencies

Stability deficiencies (Modules 3.2.S.7.1 & 3.2.S.7.3) were the sixth most frequent deficiencies. In most cases, the deficiency was due to inadequate stability data being submitted for the consideration of a full retest period (56% of the requests in the subsection). Another common deficiency in this section was applicants submitting data which shows results that are out of specification with no valid justification for the results, these were only 2.7% of the subsection. For this reason, the retest period would not be allocated and a justification is requested. From the responses it was confirmed that the justifications provided differed per application, some stated that it was due to inaccurate results, others used stability results to insist on a widened specification limit, these were treated on a case-by-case basis depending on the specification. This also led to back-and-forth communication between the agency and applicants resulting in delayed finalisation.

Deficiencies from the Restricted Part

A comparison of the 2020 results was made with those reported on products finalised between 2011 and 2017. Table 3, subsection 3.2.S.2.2–3.2.S.2.4 shows similarity of the common deficiencies with those obtained in Table 4. For example, on the aspect of the complex starting material being submitted in Module 3.2.S.2.3, either the complete method of synthesis of starting material to simpler molecules as well as specifications or the CoA to confirm adequate control of the impurities was requested. This request is similar to that

reported in Table 4 for the redefinition of starting material amongst others. Another similarity amongst others was regarding the confirmation and description of residual solvent recovery. This investigation confirms that the quality of the evaluations has been maintained since critical aspects from the restricted part have always been requested by SAHPRA.

Comparison of API Common Deficiencies with that of Other Authorities

Comparison of API Deficiencies, SAHPRA Versus USFDA

The USFDA reported on how effective the DMF procedure is since it aims to avoid duplication of assessments by the authority. [10, 35] A DMF database was created and updated annually once all the requirements have been addressed. [10, 35] The authority does not quantify the deficiencies per subsection in the reports that have been made thus far.

The first deficiencies outlined under general information by FDA were aspects such as solubility, stereochemistry, hygroscopicity and polymorphism. These were also observed from the deficiencies received in SAHPRA applications which were the most frequent (19.1%) and discussed in detail above. The USFDA also included API characterisation as one of the common deficiencies observed with the applicant not submitting legible copies and analysis to confirm the polymorphic form. These are similar to the frequent recommendations sent to applicants by SAHPRA, making the Sect. 3.2.S.3.1, the highest of common deficiencies.

Another critical deficiency discussed by the USFDA which was the third highest for SAHPRA was the control of impurities (3.2.S.4.1). As discussed in the above section, all impurities in an API which are present at greater than the identification threshold (IT) as described in the ICH Q3A guidance need to be identified, in addition, impurities at levels greater than the qualification threshold (QT) need to be qualified for safety. [33] Thus, setting limits for unknown impurities higher than the IT will invariably lead to a deficiency. Similarly, not providing qualification information for the known impurities set higher than the QT will also not be acceptable. These were the frequent deficiencies observed regarding the individual impurities. This was followed by the request to tighten the total impurities' specifications based on the submitted stability results. Table 5 provides a comparison of the top five deficiencies from all the agencies.

Table 5 Comparison of the top five common deficiencies from the six regulatory bodies listed below

	USFDA	WHOPQTm	EDQM	TFDA	SAHPRA
1	3.2.S.1	3.2.S.2.3	3.2.S.2.3	3.2.S.2.2	3.2.S.3.1
2	3.2.S.2	3.2.S.2.2	3.2.S.3.2	3.2.S.2.3	3.2.S.1. & 3
3	3.2.S.3	3.2.S.7	3.2.S.2.2	3.2.S.4.1	3.2.S.4.1&3
4	3.2.S.4	3.2.S.3.2	3.2.S.2.4	3.2.S.4.3	3.2.S.7.1 & 3
5	3.2.S.5	3.2.S.4.1 & 5	3.2.S.4.4	3.2.S.7	3.2.S.2.2

Modules: 3.2.S.1 general properties of the API, 3.2.S.2 manufacture, 3.2.S.3 characterisation, 3.2.S.4 control of the API, 3.2.S.5 reference materials, 3.2.S.2.2 description of manufacturing process and process controls, 3.2.S.2.3 control of materials, 3.2.S.2.4 controls of critical steps and intermediates, 3.2.S.3.2 impurities, 3.2.S.4.1 specifications, 3.2.S.4.4 batch analysis 3.2.S.7 stability, (see Table 2 for further descriptions)

Comparison of API Deficiencies, SAHPRA Versus EDQM

The reported results on the top 10 deficiencies of new applications submitted to the EDQM are not quantitative and does not provide a thorough comparison. The EDQM reported the deficiencies annually from 2007 to 2016. [11–14] The top five deficiencies are modules; 3.2.S.2.3, redefinition of the starting materials required, 3.2.S.3.2, absence of the discussion of potential mutagenic and genotoxic impurities, 3.2.S.2.3, absence of discussion on the carry-over of impurities and by products from key materials in the process, 3.2.S.2.2, lack of details and poor description of the manufacturing process of the starting materials and 3.2.S.2.3 inadequate or poorly justified specifications to control the quality of starting materials. [11–14] From the above, it is witnessed that most deficiencies are from Module 3.2.S.2 and 3.2.S.3. This information is found in the restricted part of the dossier and SAHPRA only required the information when needed due to the sensitivity of information. Hence, the limited amount of API deficiencies for that section. It was recorded that 98 of the deficiencies (8.2% of the total deficiencies) were from the 3.2.S.2 section with 59% of them due to an insufficient flow diagram detailing the required information and 24% due to the redefinition of the starting materials and request of their specifications. With the introduction of the APIMF procedure, the study on the restricted part queries show that the redefinition of the starting material and other critical aspects of the restricted part are now requested for all applications by SAHPRA.

Comparison of API Deficiencies, SAHPRA Versus WHO-PQTm

WHO-PQTm reported on the common deficiencies witnessed from the 159 products assessed in the period January 2007–December 2012. [17] The qualitative and quantitative information provided allows for comparison of the deficiencies to those observed by SAHPRA. The most frequent subsection was found to be module 3.2.S.2.3 with 69.5% of deficiencies in the 3.2.S.2 section. This is a large difference to SAHPRAs 8.2% observed in the same subsection. The deficiencies included insufficient information provided on the starting material such as the manufacturer of the starting material, specifications of the starting material were either not provided or were unsatisfactory and the request for redefinition of the starting material. [17] API manufacturers have found it cheaper to buy intermediates instead of manufacturing them, hence the frequency of the deficiencies. Redefinition of the starting material is thus not provided or if provided, does not comply with the definition of ICH Q7 [36] and Q11 [37], which makes it difficult for regulatory authorities to assess potential impurities that may arise during preparation. [17] SAHPRA proposed the request of specifications and the CoA of the complex starting material instead of the redefined synthesis method. This gives assurance that the impurities are controlled and removed.

Comparison of API Deficiencies, SAHPRA Versus TFDA

A total of 471 DMF applications were filed between October 2009 and December 2011 by the TFDA and evaluated for common deficiencies. [6] The primary deficiencies observed in the initial assessments were in categories of the manufacturing process (31%) these were data for critical parameters, in-process controls and intermediates being incomplete. These were followed by API specification deficiencies (17%) where proposed limits were not in line with the pharmacopeia, then starting material deficiencies (16%), as redefinition of the starting material does not comply with the definition of ICH Q7 and Q11. [6] Lastly, analytical method validation (11%) where process validation was not included for the purification and sterilisation steps and validation was not conducted on consecutive batches. [6] It was clear that the analysis from the study may assist manufacturers in improving their submission quality and facilitates granting of DMF certificates. The difference and similarity of these with that reported by SAHPRA are highlighted in Table 5.

Conclusion

The study includes a list of common deficiencies observed over a seven-year period and highlighted the top six most common deficiencies identified by SAHPRA. In addition, with the implementation of the APIMF procedure in 2020, the common deficiencies requested from the restricted part were also highlighted. A list of all deficiencies observed was outlined. This study therefore provides transparency to pharmaceutical companies on deficiencies pertaining to Module 3.2.S. to address before dossier submissions are made to SAHPRA, this in turn will reduce turnaround timelines for product registration. Comparisons with other regulatory authorities showed that the evaluation standards employed by SAHPRA are similar to other international regulatory agencies. These findings will guide the API manufacturers and pharmaceutical companies in submitting quality DMFs/APIMFs in future, which will thereby accelerate access to medicine for patients.

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Author Contributions
LM: developed the study design, collected and analysed the data, interpreted the results and wrote the first draft of the manuscript. ML: Developed the study design, assisted in collecting and analysing the data, provided guidance for the data collection and analysis, interpreted the results and reviewed the manuscript. JJ: Developed the study design, provided guidance on the data analysis, interpretation and relevance of the results and reviewed the manuscript.

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Declarations

Conflict of interest
No conflicts of interest that are directly relevant to the content of this article.

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RESEARCH

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Common deficiencies found in generic Finished Pharmaceutical Product (FPP) applications submitted for registration to the South African Health Products Regulatory Authority (SAHPRA)

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Abstract

Background: The aim of the study was to investigate the common deficiencies observed in the Finished Pharmaceutical Product (FPP) section of generic product applications submitted to SAHPRA. The study was conducted retrospectively over a 7-year period (2011–2017) for products that were finalised by the Pharmaceutical and Analytical pre-registration Unit.

Methods: There were 3148 finalised products in 2011–2017, 667 of which were sterile while 2089 were non-sterile. In order to attain a representative sample for the study, statistical sampling was conducted. Sample size was obtained using the statistical tables found in literature and confirmed by a sample size calculation with a 95% confidence level. The selection of the products was according to the therapeutic category using the multi-stage sampling method called stratified-systematic sampling. This resulted in the selection of 325 applications for non-sterile products and 244 applications for sterile products. Subsequently, all the deficiencies were collected and categorised according to Common Technical Document (CTD) subsections of the FPP section (3.2.P).

Results: A total of 3253 deficiencies were collected from 325 non-sterile applications while 2742 deficiencies were collected from 244 sterile applications. The most common deficiencies in the FPP section for non-sterile products were on the following sections: Specifications (15%), Description and Composition (14%), Description of the Manufacturing Process (13%), Stability Data (7.6%) and the Container Closure System (7.3%). The deficiencies applicable to the sterile products were quantified and the subsection, Validation and/or Evaluation (18%) has the most deficiencies. Comparison of the deficiencies with those reported by other agencies such as the USFDA, EMA, TFDA and WHOPQTm are discussed with similarities outlined.

Conclusions: The overall top five most common deficiencies observed by SAHPRA were extensively discussed for the generic products. The findings provide an overview on the submissions and regulatory considerations for generic

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applications in South Africa, which is useful for FPP manufacturers in the compilation of their dossiers and will assist in accelerating the registration process.

Keywords: Finished Pharmaceutical Product (FPP), Common deficiencies, South African Health Products Regulatory Authority (SAHPRA), Non-sterile products, Sterile products

Background

Pharmaceutical companies use data accumulated during discovery and development stages of a pharmaceutical product in order to register and thus market the medicine. Throughout the development stages, they are required to abide by an array of strict rules and guidelines in order to ensure safety, quality and efficacy of the Finished Pharmaceutical Product (FPP) in humans [1]. Inspection of manufacturing plants and laboratory quality control analysis only do not guarantee product quality and safety [2]. All processes involved in the manufacture of the Active Pharmaceutical Ingredients (APIs) and the FPP need to be controlled [2]. Therefore, assessment of the product dossier prior to its acceptance is paramount [2]. Countries possess their own regulatory authority, which is responsible for enforcing the rules and regulations and issue the guidelines to regulate FPP development process, licensing, registration, manufacturing, marketing, labelling and the product life cycle of the FPP. In this highly regulated environment, regulatory affairs play a critical role as the leading department to provide strategic advice on extremely difficult decisions through the life of the FPP [1]. Even with the strict rules and guidelines, very few pharmaceutical companies submit quality dossiers which do not require any additional amendment or additions at initial review. Dossiers possessing a large number of deficiencies will necessitate more interaction between the authority and the manufacturer during the assessment process, thus increasing the turnaround times for registration of medicines [3]. Subsequently delaying patient access to urgently needed medication.

Over the years, a number of regulatory authorities have witnessed and reported on recurring deficiencies observed from the submitted dossiers. Authorities such as United States Food and Drug Administration (USFDA), European Medicines Agency (EMA) and Taiwan Food and Drug Administration (TFDA) have noted how the publication of common deficiencies has resulted in the submission of improved quality dossiers from pharmaceutical companies. The USFDA published a 4-part series citing the common deficiencies observed from the Abbreviated New Drug Applications (ANDA) on the quality aspects of the dossier. Part 1 of the series, dealt with the deficiencies cited in the API section [4]. Part 2–4 of the series was on common deficiencies observed from the FPP part of the dossier [5–7]. The 4-part series was however only qualitative and not quantitative. The TFDA also reported on common deficiencies witnessed in the FPP for applications submitted from June 2011 to the end of May 2012 [8], while the EMA's study focused on applications finalised during the Committee for Medicinal Products for Human Use (CHMP), during 12 consecutive plenary meetings held between 2007 and 2008 [9]. The World Health Organization Pre-Qualification Team (WHOPQTm) reported on the deficiencies observed in the API and FPP sections for products submitted between April 2007 and December 2010 [3]. A guidance document was also published by the WHOPQTm in 2018 to alert manufacturers of the FPP deficiencies witnessed [10]. The studies conducted were aimed at collecting and analysing the quality review issues, which will serve as a reference and a communication medium for applicants to understand the regulatory requirements in the respective countries, which could be useful for compilation of the dossier and to facilitate the approval process.

South African Health Products Regulatory Authority (SAHPRA) has not implemented this transparency since the inception of the authority in 1965. The registration process by SAHPRA involves a scientific evaluation of the dossier submitted by the applicant in the form of a Common Technical Document (CTD). During this evaluation, a list of recommendations is generated related to the quality, safety and efficacy, which are forwarded to the applicant once discussed at the Pharmaceutical and Analytical (P&A) Committee meetings, to be addressed and resolved prior to approval. The P&A Committee managed to conclude and finalise on the scientific assessments of 3148 applications between 2011 and 2017. With SAHPRA receiving approximately 1200 applications annually, by 2016, a backlog of 7902 applications was accumulated. Within the period 2010–2015 only 3779 application were registered or rejected. From the backlog of applications, 4397 applications had not yet been allocated for evaluation while 3505 were in-process in the pre-registration phase. This shows the urgent need to employ measures such as collecting and analysing the quality review issues, thereby accelerating the approval process by the authority.

In order to identify general trends in the quality deficiencies for SAHPRA, we analysed all deficiencies from products finalised during the P&A Committee meetings over a 7-year period (2011–2017). The 3148 applications finalised during this period were considered a large sample to use for the study therefore a statistical sampling approach was employed to obtain a representative sample.

The manufacturing of the FPP is governed by precise requirements and guidelines such as good manufacturing practises and International Conference of Harmonisation guideline, ICH 3QB [11]. This is to ensure that the medicinal products are fit for their intended use and do not pose risks to the patients as a result of inadequate safety, quality or efficacy [12–14]. In the assessment of the medicines for registration by regulatory authorities, deficiencies are frequently observed in the applications, thus a proactive approach is intended in order to promote transparency between SAHPRA and the FPP manufacturers. The investigation undertaken is therefore aimed at identifying common deficiencies in the FPP section of applications submitted to SAHPRA. Publication of these will assist in the submission of quality dossiers which will accelerate the registration process and promote access to medicines for patients.

Methods

Overall 3148 applications were finalised in the 7-year period, of which 2089 were non-sterile products while 667 were sterile products. Veterinary (68), Biologicals (86), Medical Devices (5) and New Chemical Entities (NCEs) (233) were also finalised by the P&A Committee in the period as shown in Fig. 1, but was not included as part of this study. The NCEs were not included because they involve a more extensive evaluation, which required the compulsory submission of the restricted part of the Active Pharmaceutical Ingredient Master File (APIMF). As a result, a set of additional recommendations which are not observed in the generic applications is usually communicated to the applicant. Biologicals were not included due to the same reasons as the NCEs, as well as due to differences in the nature and preparation of the APIs used, this will necessitate a separate study as per the work published by the EMA on Biosimilars [15]. Veterinary products were not included since the P&A Committee was only providing support to the Veterinary Unit and each application requires the submission of Clinical trial data assessed by the Veterinary Clinical Committee, therefore it would be out of the scope of the research study. Lastly, Medical Devices were not included since the sample was too small to render the deficiencies as common. One of the main reasons for exclusively conducting a study for generics is that the generic applications constitutes majority of the applications received by SAHPRA annually and the lessons learnt from the generic products can also be employed for non-generic applications.

Given the large size of the submitted applications, a statistical method was applied to yield a representative sample adequate to use for the study. The calculated sample size obtained was 325 for the non-sterile products and 244 for the sterile products using the equations reported by Israel (1992) [16] and Kadam et al. (2010) [17] as Eqs. 1 to 4:

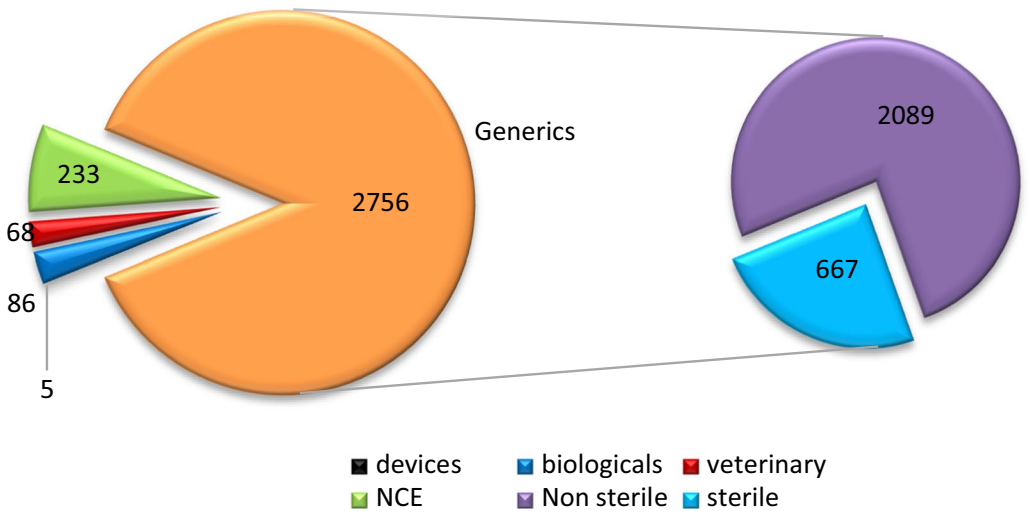

Fig. 1 The distribution and grouping of the finalised products between 2011 and 2017 by the SAHPRA P&A Committee, pre-registration Unit

$$n_0 = \frac{Z^2 pq}{e^2}, \tag{1}$$

$$n = \frac{n.}{1 + \frac{n.-1}{N}}. \tag{2}$$

The equations consist of the following parameters: z = the confidence level corresponds to a z-score, for a 95% confidence level z is 1.96. p = the degree of variability, q relates to degree of variability above, indicated as $1 - p$ depending on the variability of the population, e = level of precision which is ± 5% for the selected confidence level of 95%, n_0 = sample size, n = adjusted sample size for population sizes that are less than 3000, and N = population size [17, 18].

Calculation for the sterile products is stipulated below with a population of 667. The same was applied for non-sterile products with a population of 2089 where the sample size of 325 was obtained:

$$\begin{aligned} n_0 &= \frac{Z^2 pq}{e^2} \\ &= \frac{1.96^2 0.5^2}{0.05^2} \\ &= 384.16, \end{aligned} \tag{3}$$

$$\begin{aligned} n &= \frac{n.}{1 + \frac{n.-1}{N}} \\ &\frac{384.16}{1 + \frac{384.16-1}{667}} \\ n &= 244. \end{aligned} \tag{4}$$

Comparison of the calculated sample size with the table reported by Mohammad [18] for a given population size showed similarity in that the reported value for a population of 650 is 242 with the same confidence interval and level of precision. There are many other tables reported [19–21] with sample size ranging between 240 and 255.

A multi-stage sampling method called stratified-systematic sampling was employed. In this method, the entire population is divided into a number of homogeneous groups usually known as "strata" and thereafter units are systematically sampled from each of these stratums [21].

It is pivotal to ensure that the selection is not random and biased. Stratified systematic sampling allows for this as it ensures that all critical variables are considered. Aspects such as the applicant, the dosage form, the API used, the therapeutic category and finalisation time of the drug product were considered as important variables when sampling is conducted. Out of the above five variables, the most critical is the therapeutic category since we are dealing with pharmaceutical products. The best way to categorise the products is through their therapeutic indications, i.e. function and pharmacological classification of the drug.

Regulation 25 of Act 101 classifies and categorise medicines in South Africa as follows:

- Category A for medicines which are intended for use in humans and which are, without manipulation, ready for administration, including packaged preparations where only a vehicle is added to the effective medicine;
- Category B for medicines which cannot be administered without further manipulation; and
- Category C for medicines intended for veterinary use, which are without further manipulation, ready for administration including packaged preparations where only a vehicle is added to the effective medicine [22].

All medicines in the population are category A. This category is subdivided into 34 pharmacological classifications, some of which are subdivided further. Each therapeutic category is considered a stratum. These are grouped into 19 categories as depicted in Table 1. The sample size in each stratum varies according to the relative importance of the stratum in the population, i.e. percentage contribution. For example, if 16% of the population are antiviral agents, then 16% of the sample should contain drug products in that group. From Table 1, each stratum is now treated as a population with a specific sample size. The strata are arranged in terms of therapeutic category of the applications. Thus, the numbers in the first column Table 1 are the number of finalised applications within that therapeutic category for sterile products. For example, there were 138 applications finalised with a pharmacological classification, central nervous system depressants.

The kth term serves as a constant value used for systematic sampling and is calculated as illustrated in Eq. 5 with N as the population size and n as the calculated sample size [16]. A systematic sample would select the first element and thereafter the kth term on the list afterwards until the required sample has been selected in the whole population. The interval between the selected elements would then be the population size/calculated sample size [16]. The calculated kth term gave the value 2.7.3 (Eq. 6). This therefore makes the value three the kth term for the systematic sampling, i.e. in all strata. This resulted in the sample size of 245. However, 244 was used in accordance to the calculation using Eq. 2. Similarly, this was conducted for the non-sterile products to select the sample size of 325:

Table 1 The different strata (pharmacological classifications) generated for sample selection of sterile products

Pharmacological classification (therapeutic categories)	Population (*N*)	%	Sample (*n*)
Central nervous system depressants	138	21	52
2.1 Anaesthetics			
2.2 Sedatives, hypnotics			
2.5 Anticonvulsants, including anti-epileptics			
2.7 Anti-pyretic or anti-pyretic and anti-inflammatory analgesics			
2.8 Analgesic combinations			
2.9 Other analgesics			
3.2 Non-hormonal preparations	12	1.8	4
4.0 Local anaesthetics	22	3.3	8
Medicines affecting autonomic function			
5.2 Adrenolytics (sympathicolytics)	62	9.3	23
5.4.1 Anti-Parkinson's preparations			
5.7.1 Anti-histaminics			
5.7.2 Anti-emetics and anti-vertigo preparations			
5.10 Serotonin antagonists			
Vasodilators, hypotensive medicines			
7.2 Vasoconstrictors, pressor medicines	33	5.0	12
7.10.3 Other hypotensives			
Medicines acting on blood and haemopoietic system			
8.1 Coagulants, haemostatics	28	4.2	10
8.2 Anticoagulants			
8.3 Erythropoietics (haematinics)			
8.4 Plasma expanders			
Medicines acting on respiratory system			
10.2.1 Inhalants	6	1.0	2
Medicines acting on gastro-intestinal tract			
11.4.3, Antacids, other	10	1.5	4
Ophthalmic preparations			
15.4 Ophthalmic preparations. other	32	4.8	12
Medicines acting on muscular system			
17.1 Peripherally acting muscle relaxants	12	1.8	4
Medicines acting on genito-urinary system			
18.1 Diuretics	29	4.3	10
18.3 Ion-exchange preparations			
18.7 Contraceptive preparations	14	2.1	5
19.0 Oxytocics	22	3.3	8
Antibiotics and antibiotic combinations			
20.1.1 Broad and medium spectrum antibiotics	99	15	37
20.1.2 Penicillins			
20.2.2 Fungicides			
20.2.3 Tuberculostatics			
20.2.8, Antiviral agents			
Hormones, antihormones and oral hypoglycaemics			
21.1 Insulin preparations	59	8.9	22
21.2 Oral hypoglycaemics			
21.4 Parathyroid preparations			
21.5 Cortico-steroids			
21.10 Trophic hormones			
21.12 Hormone inhibitors			

Table 1 (continued)

Pharmacological classification (therapeutic categories)	Population (*N*)	%	Sample (*n*)
26.0 Cytostatic agents	61	9.0	22
28.0 Contrast media	12	1.8	4
32.15 Radiopharmaceuticals	2	0.3	1
34, Other	14	2.1	5
	667	100	245

$$n = \frac{N}{k\text{th}}, \tag{5}$$

$$k\text{th} = \frac{N}{n} = \frac{667}{244} = 2.73. \tag{6}$$

The full history of all products finalised in the 7-year period (2011–2017) were collected. The history comprises all communication between the authority and applicants in order to reach finalisation. The documents include the recommendations sent to the applicant and the responses received, as well as the evaluation reports of responses in the form of amendment schedules. These paper documents were obtained from the committee meeting minutes and the registry files where all documents relating to the product are placed. The investigation process involved obtaining the type and extent of the deficiencies raised in the first deficiency letter following the initial evaluation process, thereafter, extracting all the responses and feedback during multiple rounds of communication. During collection of the deficiencies, those with a frequency that was observed as less than five were categorised under "other" in the tables and calculated in the relevant section or subsection. The understanding was that these would not be classified as common due to the low frequency.

The study focuses mainly on the FPP which is presented as Module 3.2.P part of the CTD structure of the dossier as stipulated in Table 2, Module 3.2.P entails eight sections in which five consists of subsections. The 3.2.P sections are applicable for all types of medicines including sterile and non-sterile products.

The deficiencies obtained were reviewed and the frequency of each listed per section and subsection in 3.2.P together with the percentage frequency of the total deficiencies per section and subsection of the CTD, were calculated as follows:

- Percentage frequency of deficiency identified per section = (frequency of specific deficiency/total number of deficiencies per section of CTD) × 100.
- Percentage frequency of deficiency identified per overall 3.2.P = (frequency of specific deficiency/total

Table 2 FPP (3.2.P) sections and subsections for classification of observations

CTD sections and subsections	Content
3.2.P.1	Description and Composition
3.2.P.2	Pharmaceutical Development
3.2.P.2.1	Components of the Pharmaceutical Product
3.2.P.2.2	Final Pharmaceutical Product
3.2.P.2.3	Manufacturing Process Development
3.2.P.2.4	Container Closure System
3.2.P.2.5	Microbial Attributes
3.2.P.2.6	Compatibility
3.2.P.3	Manufacture
3.2.P.3.1	Manufacturer(s)
3.2.P.3.2	Batch Formula
3.2.P.3.3	Description of Manufacturing Process and Process Control
3.2.P.3.4	Control of Critical Steps and Intermediates
3.2.P.3.5	Process Validation and/or Evaluation
3.2.P.4	Control of Inactive Pharmaceutical Ingredients
3.2.P.4.1	Specifications
3.2.P.4.2	Analytical Procedures
3.2.P.4.3	Validation of Analytical Procedures
3.2.P.4.4	Justification of Specifications
3.2.P.4.5	Excipients of Human Origin
3.2.P.4.6	Novel Excipients
3.2.P.5	Control of Finished Pharmaceutical Product
3.2.P.5.1	Specifications
3.2.P.5.2	Analytical Procedures
3.2.P.5.3	Validation of Analytical Procedures
3.2.P.5.4	Batch Analysis
3.2.P.5.5	Characterisation of Impurities
3.2.P.5.6	Justification of Specifications
3.2.P.6	Reference Standard or Materials
3.2.P.7	Container Closure System
3.2.P.8	Stability
3.2.P.8.1	Stability Summary and Conclusions
3.2.P.8.2	Post-approval Stability Protocol and Stability Commitment
3.2.P.8.3	Stability Data

number of deficiencies per overall 3.2.P section of CTD) × 100.

The deficiencies were collected and illustrated as charts and graphs using Microsoft Office Excel® 2016 (Microsoft Corporation, USA).

Results

Deficiencies from non-sterile products

The 325 applications contained a variety of dosage forms which are: film-coated and uncoated immediate release tablets (48%), immediate release capsules (23%), orodispersible tablets (8.0%), extended release tablets (8.0%), extended release capsules (3.5%), chewable tablets (1.2%), powders for suspensions (5.1%) and other (3.2%). The dosage forms which fall under the "other" category included oral solutions, creams, nasal spray, immediate release granules, gels, ointments, suppositories, lozenges and nose drops. A total of 3253 FPP deficiencies were collected from the 325 deficiency letters. Table 3 shows all deficiencies observed from generic non-sterile products that were finalised in the 2011–2017 period by the P&A pre-registration Unit. Figure 2 shows the distribution of the deficiencies and further highlights the 3.2.P sections in the CTD with the most deficiencies. The sections with the highest deficiencies are Module 3.2.P.3 Manufacture of the FPP, (23%) followed by Module 3.2.P.5 Control of the FPP (21%) and 3.2.P.8 Stability (15%). These three sections are considered the most critical sections in the CTD under Module 3.2.P as observed from reports on common deficiencies by other regulatory authorities while reporting [6–10].

Table 3 specifies all the deficiencies observed in the 3.2.P section of the dossier. The deficiencies were calculated as percentage of the deficiencies in each subsection per overall 3.2.P section. For example, there were 274 deficiencies on the pharmaceutical development section, 3.2.P.2, which is granulated as 3.8% for 3.2.P.2.1 components of the pharmaceutical product, 1.4% for 3.2.P.2.2, final pharmaceutical product, 2.0% for 3.2.P.2.3, manufacturing process development and 1.2% for 3.2.P.2.4 container closure system for each subsection in the table.

The results in Table 3 are depicted as a chart in Fig. 2 to clearly show which subsection exhibits the highest and the lowest number of deficiencies. Subsection 3.2.P.5.1 has the highest deficiency covering 15% (71% of the 3.2.P.5 section). Module 3.2.P.1, Description and Composition of FPP, has the second largest number of deficiencies (14%). Module 3.2.P.3.3, Description of the Manufacturing Process has the third highest percentage of deficiencies (13%) with Module 3.2.P.8.3 on stability data of the FPP at 9.3% (66% of the 3.2.P.8 section).

Deficiencies from sterile products

A similar investigation as for the non-sterile products was conducted for sterile products. The 244 sterile product applications consisted of the following dosage forms: concentrate for injection (35%), powder for injection (17%), lyophilised powder for injection or infusion (42%), ophthalmic solutions (4.8%), irrigation solution (0.8%) and a minority of other comprising the remaining 0.4%. These dosage forms were sterile suspensions and chelating agents. A total of 2742 FPP deficiencies related to sterile products were collected from 244 letters.

The 244 letters were obtained and deficiencies outlined in Table 4. Note that the CTD has different requirements in specific sections depending on the dosage form. For example, the sterilisation method selected for sterile products would need to be clearly indicated and justified in accordance to the decision trees for selection of the sterilisation methods (CPMP/QWP/054/98) [23] under 3.2.P.2.2. This is not a requirement for non-sterile products. There are a number of these sections in the CTD and those deficiencies are listed in Table 4. There are also a number of common sections where the requirements are the same whether a product is sterile or not, for example, 3.2.P.6 Reference Materials, 3.2.P.5.4, Batch Analysis, 3.2.P.5.5 Characterisation of Impurities, etc. Therefore, the deficiencies for sterile products are over and above those listed under Table 3 for non-sterile products depending on their applicability to the dosage form.

Figure 3 highlights the most frequently observed deficiencies from the sterile products. It shows that FPP subsections Module 3.2.P.3.5, Process Validation and/or Evaluation (17%), Module 3.2.P.2.2, Development of FPP (13%), Module 3.2.P.8.3, Stability Data (12.6%), Module 3.2.P.3.3, Description of the Manufacturing Process (12.5%) and Module 3.2.P.5.1, Specifications (11%) fall under the top five most common deficiencies requested by SAHPRA for sterile products.

Discussion

The most frequent common deficiencies observed by SAHPRA in the submitted non-sterile and sterile products are extensively discussed below as depicted Figs. 2 and 3.

Deficiencies in Module 3.2.P.3., manufacture of the FPP

The highest section reported as per Fig. 2 was Module 3.2.P.3. Further analysis (Fig. 3) reveals that 13% of the overall deficiencies were due to Module 3.2.P.3.3—Description of Manufacturing Process and Process Control, 7.4% on Module 3.2.P.3.4—Control of Critical Steps and Intermediates and 2.2% on Module 3.2.P.3.5—Process Validation and/or Evaluation. Concerning sterile product deficiencies, a similar trend is witnessed where

Table 3 List of FPP common deficiencies in the 3.2.P section of the CTD recommended by SAHPRA for non-sterile products finalised by the pre-registration unit between 2011 and 2017

Subsection	Deficiency	Amount	% overall
3.2.P.1 Description and composition of the FPP			
3.2.P.1	Include an indication that water or other solvents are not present in the FPP since they have been eliminated during the manufacturing process	34	14
3.2.P.1	State the polymorphic form of the API(s) used in the unitary batch formula	52	
3.2.P.1	If a potency adjustment for the API has to be made, a statement to the effect that the actual quantity of the active will depend on the potency and the Pharmaceutical ingredients Inactive (IPI) that will be used to adjust the bulk quantity should be made. The manner in which the adjustment will be made should also be specified	48	
3.2.P.1	Include the grades of all the IPIs used in the formulation, or the functionality specification of the IPI, if applicable. Indication that it is a pharmaceutical grade is not sufficient	101	
3.2.P.1	The purpose of each IPI should be stated briefly. If the IPI is used for multiple purposes in the formulation, each purpose should be mentioned	31	
3.2.P.1	The Colour Index Numbers (Foodstuffs, Cosmetics and Disinfectants Act, 1972 Regulation Food Colourants) or the colourant reference number in accordance with the European directive of colourants for those used in the formulation	26	
3.2.P.1	The theoretical quantity of the base of the active pharmaceutical ingredient (API) should be stated if a compound, e.g., hydrate, solvate, salt is used	19	
3.2.P.1	The description of the FPP (including scoring) is incomplete and does not concur with other relevant sections in the dossier such as 3.2.P.5.1 and Module 1.3	32	
3.2.P.1	The theoretical mass must be indicated for uncoated tablets. In the case of coated dosage forms, the theoretical mass of the core, coating material, as well as the total mass of the dosage form/unit should be indicated	48	
3.2.P.1	Fill mass, type of gelatine used as well as the capsule size, composition and mass of the capsule should be indicated	21	
3.2.P.1	The overage used for the active pharmaceutical ingredient (API) should be indicated as a footnote and justified in 3.2.P.2.2	12	
	Other	19	
		443	
3.2.P.2 Pharmaceutical development			
3.2.P.2.1 Components of the pharmaceutical product			
3.2.P.2.1	A Pharmaceutical Development Report (generally of not more than 25 A4 pages) should be submitted with each application	13	3.8
3.2.P.2.1	Provide a brief summary of the synthesis of the API including a brief discussion of the physico-chemical characteristics of the API which are relevant to the final product	23	
3.2.P.2.1	Include a discussion of the stability of the final product formulation and conclusion on stability and shelf-life allocation in accordance with the P&A CTD guideline	10	
3.2.P.2.1	Explain the difference in specific excipients between the test and reference product	11	
3.2.P.2.1	Submit the compatibility studies of the API-IPI used in the formulation to confirm that these are compatible with each other	23	
3.2.P.2.1	Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed	45	
3.2.P.2.2 Final pharmaceutical product			
3.2.P.2.2	The reason for the overage should be stated/justified, e.g., with reference to batch results, in 3.2.P.2.2.2	21	1.4
3.2.P.2.2	Justify the choice and quantity of excipients used in the formulation	23	
3.2.P.2.3 Manufacturing process development			
3.2.P.2.3	The discriminatory nature of the selected dissolution medium should be illustrated	32	2.0
3.2.P.2.3	Provide justification of the selected dissolution quality control (QC) medium with the inclusion of a surfactant	34	
3.2.P.2.4 Container closure system			
3.2.P.2.4	Submit the discussion on the suitability of the formulation with the primary packaging system to confirm the acceptability of the proposed primary packaging	34	1.2
	Other	5	
		274	

Table 3 (continued)

Subsection	Deficiency	Amount	% overall
3.2.P.3 Manufacture of the FPP			
3.2.P.3.3 Description of manufacturing process and process controls			
3.2.P.3.3	The description of the manufacturing procedure must include duration of treatment, manufacturing conditions (temperature and humidity) and specifications for machine settings and capacity	83	13
3.2.P.3.3	No provision has been made to bulk storage before packaging. Indicate the nature of the containers and maximum period the core and/or film-coated tablets may be stored (bulk) before final packaging. Submit information and provide supporting data with regard to holding time studies. This includes bulk holding time for cores prior to coating as well as container used	97	
3.2.P.3.3	The manufacturing process flowchart is inadequate, include the in-process controls, hold times for processing steps and other additional controls to ensure completeness	23	
3.2.P.3.3	The proposed holding times for intermediate products should to be included in the calculation of the shelf-life; they should not exceed 25% of the shelf life and if more than 30 days stability data should be submitted	29	
3.2.P.3.3	Describe the tablet compression procedure and compression speed included as well as coating parameters used	7	
3.2.P.3.3	The leak test, sealing test and adhesiveness for the blister packs must be described	11	
3.2.P.3.3	Drying time must be indicated and moisture content to which the granules are dried must be stated	24	
3.2.P.3.3	State the sieve sizes and mixing/blending speed during manufacture of the product as well as duration of stirring and drying temperature	76	
3.2.P.3.3	A brief description of the packaging procedure must be provided	33	
3.2.P.3.3	Fluid bed drying conditions must include inlet and outlet air temperature	6	
3.2.P.3.3	The manufacturing process outlined is inaccurate in comparison to the description and validation report	17	
3.2.P.3.4 Control of critical steps and intermediates			
3.2.P.3.4	The in-process control tests and frequency must be included as well as expansion of specifications for the granulate to include moisture content	88	7.5
3.2.P.3.4	Specification for uniformity of content of the divided tablet must be included and blend uniformity as an in-process test	41	
3.2.P.3.4	The limit for tablet hardness must be included as an in-process test and limits should be expressed in Newton and inclusion of the friability test	43	
3.2.P.3.4	Include the test for friability for uncoated tablets as an in-process control or in the final specifications	24	
3.2.P.3.4	Confirm that Batch Manufacturing records and packaging documents will be available upon request or during inspection	10	
3.2.P.3.4	Limits proposed on the critical steps were not accepted and further justification is required	32	
	Other	6	
3.2.P.3.5 Process validation and/or evaluation			
3.2.P.3.5	Submit a bulk formula for each batch size for each strength as three master manufacturing batch records were submitted with different batch sizes	4	2.2
3.2.P.3.5	Include validation report for three commercial batches to confirm reproducibility and batch to batch consistency of the manufacturing process	43	
3.2.P.3.5	Provide validation protocol and/or report for the proposed batch size	25	
		722	
3.2.P.4 Control of inactive pharmaceutical ingredients			
3.2.P.4.1 Specifications			
3.2.P.4.1	Quantitative and qualitative composition of the colourant must be included	26	6.2
3.2.P.4.1	Provide a declaration that the IPI, e.g., talc is asbestos free	7	
3.2.P.4.1	Submit the certificate of analysis for each of the IPIs used	32	
3.2.P.4.1	Include specifications and control procedures of the IPIs used in the formulation for non-pharmacopoeial	32	
3.2.P.4.1	Provide evidence that the IPIs are transmissible spongiform encephalopathies/bovine spongiform encephalopathies (TSE/BSE) free	44	
3.2.P.4.1	The related substances controlled in the IPIs should be quantified	45	
3.2.P.4.1	Provide the identification used for the colourant or dye, for example a UV spectrum	16	
3.2.P.4.1	Confirm that the colourant complies with purity criteria of the Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972 or with directives of the European countries or the register of the USFDA	32	

Table 3 (continued)

Subsection	Deficiency	Amount	% overall
3.2.P.4.3 Validation of analytical procedures			
3.2.P.4.3	Validation data were not submitted for analytical testing methods of non-pharmacopoeial substances. Submit	16	0.9
	Other	13	
		263	
3.2.P.5 Control of FPP			
3.2.P.5.1 Specifications			
3.2.P.5.1	The dissolution specification must be brought in line with the profiles of the biostudy and reference products for this parameter. All the strengths of both test and reference products demonstrated very rapid dissolution whereas the specification is not in line with the definition of rapid dissolution	139	15
3.2.P.5.1	The dissolution specification for release and shelf-life must correspond	16	
3.2.P.5.1	Tighten the assay release and stability specification to 95–105% in accordance with the PA guidelines and include this as a percentage label claim	80	
3.2.P.5.1	The final product specification must be expanded to include a limit for residual solvents and the relevant validated control procedure must be described	16	
3.2.P.5.1	The FPP specifications should include an additional identification test	23	
3.2.P.5.1	Include the leak test to confirm that the product is protected from moisture in the final FPP specifications or as an in-process control	11	
3.2.P.5.1	Include all the parameters to be controlled for the Final product, i.e. FPP specifications at release and shelf life	9	
3.2.P.5.1	Tighten the specifications for water content taking into consideration the increased formation of impurities by water hydrolysis and the fact that the stability results do not justify the proposed specification	22	
3.2.P.5.1	Include authorised documentation code and date of authorisation for release and stability specifications (version control)	19	
3.2.P.5.1	Bring the degradation/related impurity limits of the FPP in line with the ICH guideline Q3B	16	
3.2.P.5.1	Tighten specifications for Total impurities to be in line with the stability and batch analyses results	48	
3.2.P.5.1	Tighten the shelf life specification limits of the specified and unspecified impurities, as they appear to be wider	45	
3.2.P.5.1	Tighten specifications for disintegration time since the final product is highly soluble	11	
3.2.P.5.1	Include a test for microbial purity in the FPP specifications	9	
3.2.P.5.1	Bring the FPP specifications in line with those indicated in a recognised pharmacopoeial monograph	15	
3.2.P.5.2 Analytical procedures			
3.2.P.5.2	The pore size of the filter must be stated in the dissolution method description or justified	21	1.8
3.2.P.5.2	Dissolution method should specify inline filtration or filtered immediately. The method for withdrawal and filtration of samples must ensure that dissolution of undissolved particles does not occur after sampling	38	
3.2.P.5.3 Validation of analytical procedures			
3.2.P.5.3	Submit validation data for the assay method of the API, residual solvents and related substances/degradation products	28	2.9
3.2.P.5.3	The following inconsistencies were observed in the submitted validation data which required clarification: nature of stress used in stress samples used in validation not confirmed, reference standard not calibrated against an internal standard; linearity of potency assay not conducted, detection limit for some specified related substances/residual solvents, acceptance criteria for system suitability tests and other parameters not justified	32	
3.2.P.5.3	Representative chromatograms should be submitted for validation of analytical methods	21	
3.2.P.5.3	Submit validation data of forced degradation studies in the assay method	12	
3.2.P.5.4 Batch analysis			
3.2.P.5.4	Submit a complete analysis data of at least two batches	23	0.7
3.2.P.5.6 Justification of specifications			
3.2.P.5.6	Justification of specifications was not submitted and requested	11	1.3
3.2.P.5.6	The proposed justification of specifications is inadequate and not accepted. An amendment is proposed in 3.2.P.5.1	21	
	Other	11	
		697	

Table 3 (continued)

Subsection	Deficiency	Amount	% overall
3.2.P.6 Reference standard or materials			
3.2.P.6	Supply information on the primary reference standard used to confirm traceability if pharmacopoeial and describe how the secondary reference standards were established	19	3.7
3.2.P.6	Provide certificate of analysis (CoAs) of the reference standards used	32	
3.2.P.6	Provide the CoAs showing the results of the identification, purity and content of the reference standards used	43	
3.2.P.6	Characterisation of the reference and impurity reference standards not complete or inadequate	12	
	Other	14	
		120	
3.2.P.7 Container closure system of the FPP			
3.2.P.7	Include an identification test, e.g., IR of the immediate container closure system	31	7.1
3.2.P.7	Give a specification and demonstrate the integrity for the heat seal bond strength as well chemical nature and identification test for this heat seal lacquer in the aluminium foil	27	
3.2.P.7	Specify the printing details on blisters and give a control test for the quality of the printing	7	
3.2.P.7	The chemical nature of the desiccant must be disclosed	13	
3.2.P.7	Identification, chemical nature and density of the container closure must be included as well as specifications and the relevant control procedure included. This includes colour, dimensions and thickness	38	
3.2.P.7	The manufacturers of the primary packaging materials should be included	23	
3.2.P.7	Information included in the packaging insert/patient information leaflet (PI/PIL)/label is not in accordance with the packaging presentations contained in this section. Correct	21	
3.2.P.7	The certificates of analysis (CoAs) for the immediate container closure(s) used were not provided	43	
	Other	28	
		231	
3.2.P.8 Stability of the FPP			
3.2.P.8.1 Stability summary and conclusions			
3.2.P.8.1	Provide a justification for the out of trend assay results	28	4.5
3.2.P.8.1	The shelf-life specifications are incomplete or have missing criteria or parameters. Include these or provide a justification for not including the parameters listed in 3.2.P.5.1	32	
3.2.P.8.1	Indicate the date of initiation of the stability studies	15	
3.2.P.8.1	Include the minimum and maximum size of the batches placed under stability study	32	
3.2.P.8.1	Submit stability data for an alternative local packer for final products manufactured in a different country to the manufacturer, on the product packed in bulk containers over a suitable period covering the relevant transport conditions	29	
3.2.P.8.1	Indicate the type of batch, e.g., pilot/production/experimental as well as the batch size. For pilot batches, a provisional shelf life of up to 24 months is allocated	11	
3.2.P.8.2 Post-approval stability protocol and stability commitment			
3.2.P.8.2	The proposed post-approval stability study did not include the batches being placed on stability annually or how many batches per strength are annually put on stability testing	34	1.7
3.2.P.8.2	The proposed stability programme commitment is not in accordance with the stability guideline; Summary tables with test results from stability studies conducted under accelerated and stressed conditions were not submitted	21	
3.2.P.8.3 Stability data			
3.2.P.8.3	Correct the container closure system to correspond with that indicated in the container closure section, Module 3.2.P.7	36	9.3
3.2.P.8.3	Impurity/degradation shelf-life limits should be tightened from a quality perspective in view of the results observed for commercial batches	56	
3.2.P.8.3	Critical stability indicating parameters such as related substances and dissolution are not included in the stability testing. These should be included	54	
3.2.P.8.3	The proposed shelf life is not supported by the submitted studies, provide additional data to support the proposed shelf life, which should now be reasonably available	98	
3.2.P.8.3	Stability studies for different manufacturing sites were not provided, confirming similar stability. Submit	34	
3.2.P.8.3	Submit photostability data under normal conditions which show that secondary packaging protects the ultraviolet ray (UV)-sensitive API and that unrelated impurities did not increase with exposure to light and UV	14	
	Other	9	
		503	

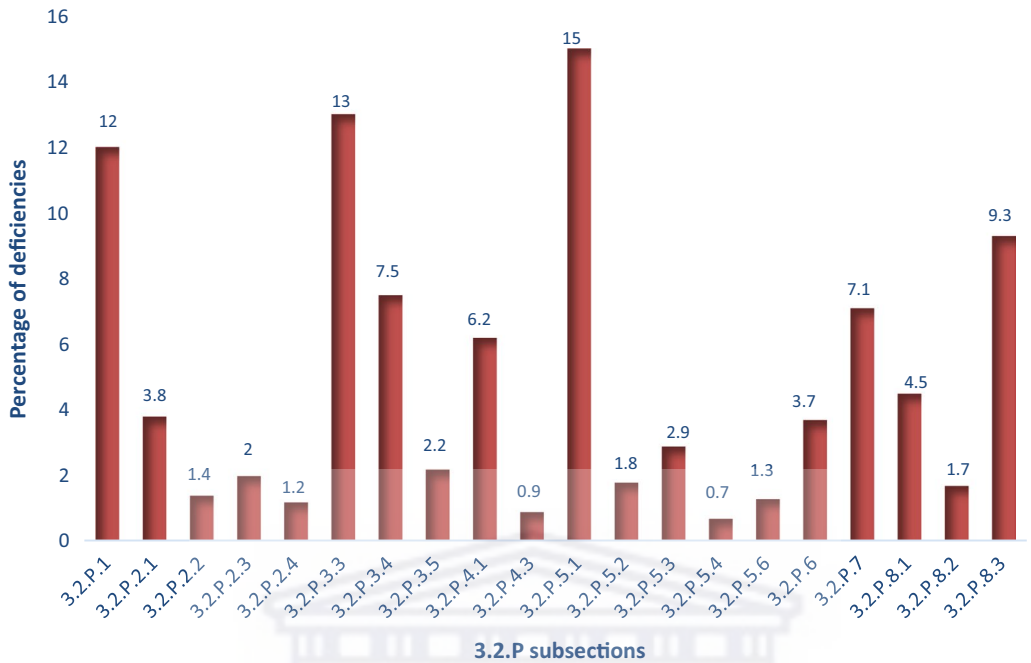

Fig. 2 The distribution of all deficiencies found in the 3.2.P sections and subsections for non-sterile applications submitted to SAHPRA. Modules: 3.2.P.1 Description and Composition, 3.2.P.2.2 Final Pharmaceutical Product, 3.2.P.2.3 Manufacturing Process Development, 3.2.P.2.4 Container Closure System, 3.2.P.3.3 Description of the Manufacturing Process, 3.2.P.3.4 Control of Critical Steps and Intermediates, 3.2.P.3.5 Process Validation and/or Evaluation, 3.2.P.4.1 Specifications of IPIs, 3.2.P.4.3 Validation of Analytical Procedures of IPIs, 3.2.P.5.1 Specifications of the FPP, 3.2.P.5.3 Validation of Analytical Procedures of FPP, 3.2.P.5.4 Batch Analysis of the FPP, 3.2.P.5.6 Justification of Specifications, 3.2.P.6 Reference Materials, 3.2.P.7 Container Closure System, 3.2.P.8.1 Stability Summary and Conclusions, 3.2.P.8.2 Post Approval Stability Protocol and Stability Commitment, 3.2.P.8.3 Stability Data

the highest reported section is Module 3.2.P.3, manufacture of the FPP. Module 3.2.P.3.5, Process Validation and/or Evaluation, constitutes 17% of the deficiencies, followed by 12.5% from Module 3.2.P.3.3, Description of the Manufacturing Process and lastly, 2.2% from Module 3.2.P.3.4, Control of Critical Steps and Intermediates.

The common deficiencies observed in the manufacturing process of non-sterile products included: insufficient information being provided on the manufacturing process such as duration of treatment; manufacturing conditions (temperature and humidity); specifications for machine settings; capacity of equipment compression procedure and speed; sieve sizes used; duration of stirring and drying temperatures. These and more are critical parameters that should be included in the process to provide the evaluator with a comprehensive description of the manufacturing process. The second deficiency was on the hold time period not being indicated as well as the bulk containers used for the intermediates and final product before packaging. The proposed holding time is dependent on the shelf life, whereby a holding time exceeding 25% of the shelf life [24] should be supported by accelerated and long-term stability data for approval. There were a large number of deficiencies where applicants did not indicate the proposed period, did not provide a hold time study report in Module 3.2.P.3.5, process validation and/or evaluation and supporting data in 3.2.P.8.3, stability data, if the proposed period exceeds the acceptable conditions as indicated above.

The common deficiencies witnessed from the sterile products in this prevalent section was on subsection, Module 3.2.P.3.5 Process Validation and/or Evaluation. The deficiencies included issues on the validation and outstanding summary report on validation of; the sterilisation method used, media fill procedures, depyrogenation of glass containers and sterilisation for rubber stoppers and autoclaving of production equipment. These are a requirement and should normally be submitted by the manufacturer when the product is considered sterile using aseptic processing or terminal sterilisation. It is imperative that the container used, the excipients, the FPP and container closures be sterile or sterilised for these products, therefore, summary reports on how the validation is conducted is vital. Media fill simulations are also of importance as they assess the performance of an aseptic manufacturing procedure using a sterile microbiological growth medium, in place of the FPP solution, to test whether the aseptic procedures are adequate to

Table 4 List of FPP common deficiencies in the 3.2.P section of the CTD recommended by SAHPRA for sterile products finalised by the pre-registration Unit between 2011 and 2017

Section/subsection	Deficiency	Amount	% overall
3.2.P.1 Description and composition of the FPP			
3.2.P.1	Nitrogen is used as pressure source for filtration it must be indicated in the list of excipients and controlled in 3.2.P.5	74	3.1
	Other	12	
		86	
3.2.P.2 Pharmaceutical development			
3.2.P.2.2 Final pharmaceutical product			
3.2.P.2.2	The product development report is insufficient. It does not address the development of the buffered blend for filling, neither does it address aspects such as choice of container closure system, filter media, sterilisation methods	39	13
3.2.P.2.2	It is stated that sterile filtration is chosen as method of sterilisation without justification. The choice of sterilisation by filtration as the method of sterilisation must be scientifically justified in terms of the decision tree for sterilisation choices for aqueous products (CPMP/QWP/054/98). Terminal sterilisation should normally be the method of choice if the product is expected to be heat stable	106	
3.2.P.2.2	Discuss the selection and effectiveness of preservative	34	
3.2.P.2.2	Include the pore size of the filter used for the method of sterilisation	67	
3.2.P.2.2	The volume of overfills were unjustified in pharmaceutical development. Provide data to support that the indicated total fill volume sufficient to administer nominal dose	34	
3.2.P.2.2	Provide results of tests on extractable volume and the API content after reconstitution of the FPP with the selected solvent	76	
3.2.P.2.3 Manufacturing process development			
3.2.P.2.3	Justify sterilisation by filtration. Heat instability during autoclaving has been determined at 121 °C/20 min. Have studies been done at reduced F_o – values to confirm that terminal sterilisation is not possible	45	1.6
3.2.P.2.4 Container closure system			
3.2.P.2.4	Submit in-use stability testing method and results in this section to confirm integrity of the container closure system to prevent microbial contamination	32	1.9
3.2.P.2.4	The consistency for droplet size for the dropper used should be conducted to ensure that the same API/FPP is ejected at each drop	21	
3.2.P.2.6 Compatibility			
3.2.P.2.6	Extractability and leaching studies of the selected filter should be submitted	45	6.3
3.2.P.2.6	The studies to confirm the compatibility of the product with the recommended intravenous (IV) solutions was not conducted	54	
3.2.P.2.6	Provide compatibility studies of the formulation with the equipment used in the manufacturing process	31	
3.2.P.2.6	Compatibility and leaching studies of the formulation with the coated rubber stoppers to demonstrate that these do not cause leaching should be submitted	23	
	Other	19	
		626	
3.2.P.3 Manufacture of the FPP			
3.2.P.3.3 Description of manufacturing process and process controls			
3.2.P.3.3	The information must include an inspection flow diagram describing both processes, the batch manufacturing formulae, a comprehensive flow diagram and a comprehensive description detailing the various stages of both steps in the manufacturing process including environmental classification of areas, sterilisation methods and conditions of containers and equipment	54	13
3.2.P.3.3	Nitrogen is used as pressure source for filtration, it must be indicated in 3.2.P.3.3 and should be indicated in the formula and controlled in 3.2.P.5. In addition, the method of sterilisation used for nitrogen should be stated	43	
3.2.P.3.3	Confirm that the filter integrity is confirmed before and after filtration. Reference to the process procedure only to conduct filter integrity test is inadequate	23	
3.2.P.3.3	State the type and size (porosity) of the filters used for filtration of the solution	45	
3.2.P.3.3	Describe the grades of clean areas for manufacture and filling process of water for injection/diluent	82	
3.2.P.3.3	Provide lyophilisation conditions of the cycle used and confirm that the lyophiliser is sterilised after each cycle	68	
3.2.P.3.3	Proof of efficacy of the sterilisation of the dead space in the connecting tube and twist off ports of the bags must be provided	27	

Table 4 (continued)

Section/subsection	Deficiency	Amount	% overall
3.2.P.3.4 Control of critical steps and intermediates			
3.2.P.3.4	Bioburden testing and the acceptance criteria for bioburden must be included as an in-process control measure	59	2.2
3.2.P.3.5 Process validation and/or evaluation			
3.2.P.3.5	Provide summary reports on the validations for the sterilisation of the rubber closures and for the lyophilised powder	76	17
3.2.P.3.5	The validation of sterilisation and depyrogenation processes with conditions and determination of maximum holding/processing times must also be included	83	
3.2.P.3.5	The hold time validation data should include hold time before and after filtration of final product bulk or hold time within lyophiliser chamber after cycle completion	34	
3.2.P.3.5	Provide summary reports on the validations of depyrogenation of the glass vials and sterilisation of the rubber closures and for the water for injection/diluent	23	
3.2.P.3.5	Submit a summary report of the validation (qualification) of the sterilisation cycle of the final product including the loading patterns	23	
3.2.P.3.5	Submit a summary report of the validation of the selected filter	16	
3.2.P.3.5	Provide a protocol or report of the validation of autoclaves and sterilisation/depyrogenation tunnels	23	
3.2.P.3.5	Provide a protocol or summary report of the media fill procedures and validation of holding times	43	
3.2.P.3.5	Include a summary report on autoclaving of production equipment	45	
3.2.P.3.5	A number of issues on the media fill validation including; Media fill validation not covering all product volumes and container types, details of the media fill conditions were not described, Aseptic process not validated by media fill to name a few	65	
3.2.P.3.5	The validation process should contain storage and shipping conditions linked to process validation results	25	
	Other	16	
		873	
3.2.P.4 Control of inactive pharmaceutical ingredients			
3.2.P.4.1 Specifications			
3.2.P.4.1	Nitrogen is used as pressure source for filtration. Provide specifications and control procedures	56	4.5
3.2.P.4.1	Indicate the leak test performed on the container closure system during filling	45	
	Other	23	
		124	
3.2.P.5 Control of FPP			
3.2.P.5.1 Specifications			
3.2.P.5.1	Seal integrity testing (leak testing) of ampoules must be included as a final product control	23	11
3.2.P.5.1	Visible particulate matter should be included as a specification either as final product release specification or as in-process control	54	
3.2.P.5.1	Bacterial endotoxin test (BET) should be included as a specification either as final product release specification or as an in-process control	80	
3.2.P.5.1	In view of the batch release data and stability data provided for related substances the justification of the specifications for total impurities based on batch release data is not accepted and should be reconsidered	34	
3.2.P.5.1	Include a specification for preservative effectiveness. The test is not required for routine analysis provided that the preservative effectiveness has been established at the lowest limit specified, however, the specification should be retained as a skip test	43	
3.2.P.5.1	The following were missing from the specifications and should be submitted: preservative efficiency testing at the end of shelf life; active content in reconstituted solution; product-related impurities in specifications considered as too wide; acceptance and extractable volume after reconstitution as well as uniformity of mass	22	
3.2.P.5.3 Validation of analytical procedures			
3.2.P.5.3	Provide validation data for the sterility test method. If a pharmacopoeial method from a recognised pharmacopoeia is used partial validation data will suffice	23	2.5
3.2.P.5.3	Provide validation data for the bacterial endotoxin test method	45	
3.2.P.5.6 Justification of specifications			
3.2.P.5.6	There were unjustified items: bacterial endotoxin limits; pH specification limits; active salt selection; omission of impurities in specifications and missing container closure test	54	2.8
	Other	22	

Table 4 (continued)

Section/subsection	Deficiency	Amount	% overall
		400	
3.2.P.7 Container closure system of the FPP			
3.2.P.7	Consistency of the droplet size should be confirmed	45	7.2
3.2.P.7	Coating composition of the stoppers used was not included	27	
3.2.P.7	The CoAs for glass and rubber stoppers used were not provided	17	
3.2.P.7	Sterilisation of primary packaging components was not satisfactorily described	13	
3.2.P.7	Compatibility of the stopper material with the final product was not demonstrated on potential extractables. Extractability and leaching study is therefore requested	39	
3.2.P.7	Leachability study of the leachables originating from the container closure system should be investigated	34	
	Other	21	
		196	
3.2.P.8 Stability of the FPP			
3.2.P.8.3 Stability data			
3.2.P.8.3	Provide results of the stability studies on the diluted solution in selected diluent for infusion confirming the recommendations in the PI	28	13
3.2.P.8.3	The results of the photo stability studies showing no effect to impurity values and thus no requirement for protection from light during storage of the product should be provided	45	
3.2.P.8.3	The results of the in-use stability study confirming stability of the product at a specific temperature for specified amount of time as indicated in the PI and in accordance with the guidelines should be provided	38	
3.2.P.8.3	The results of the transportation stability test at specified elevated storage condition for a sufficient amount of time should be submitted	23	
3.2.P.8.3	Provide stability results to confirm the effectiveness of the preservative	43	
3.2.P.8.3	Stability studies should be conducted in upright and inverted positions, the results were only submitted for samples stored in an upright position. Submit for the inverted position	34	
3.2.P.8.3	There were missing tests during stability studies, for example, volume in container, sterility and BET. This should be conducted in the next testing and submitted	44	
3.2.P.8.3	Missing or insufficient data for aspects such as vacuum stress for container closure ingress testing; supporting storage out of Refrigeration; potency test performance during stability control; chromatograms from final product long-term, accelerated, and stressed stability studies and sterility tests on preservative efficiency	38	
3.2.P.8.3	Stability studies for temperature excursions at the end of the shelf-life should be submitted	36	
	Other	15	
		344	
3.2.R.1 Pharmaceutical and biological availability			
3.2.R.1*	Data to substantiate efficacy have been provided in Module 3.2.P.2 where essential similarity of the innovator and test product was proven however, a request for exemption from submitting proof of Biological availability based on the Biostudies Guidelines was not stipulated. Exemption will only be considered when motivation and comparative data have been submitted in Module 3.2.R.1	93	3.4
		93	

Note that there are deficiencies applicable to sterile products already included in Table 3, these were not included in this table to avoid duplication and quantified as other in the table due to the low frequency

*A regional requirement for sterile and liquid dosage form to request exemption from submitting proof of efficacy studies, only essential similarity with an SA innovator product is required in such cases

prevent contamination during actual FPP production [25–27]. The section comprised 54% of these deficiencies.

A common deficiency in the section, 3.2.P.3, Manufacture of the FPP, is the lack of inclusion of environmental classification of areas in the manufacture of sterile products. The classified rooms help the sterile pharmaceutical industry to manufacture products that are free from particulate and microbial contamination [27, 28]. The areas have a controlled contamination level, which is specified regarding the number of particles for every cubic meter for a specified particle size. These restricted areas are constructed with strict humidity, temperature and pressure control conditions to minimise the generation, introduction and retention of particulate matter inside the rooms [28, 29]. The classifications are either A, B, C and D with sterile environments normally using Class A or B or a combination of both. This requirement is therefore very critical in the manufacture of a sterile product

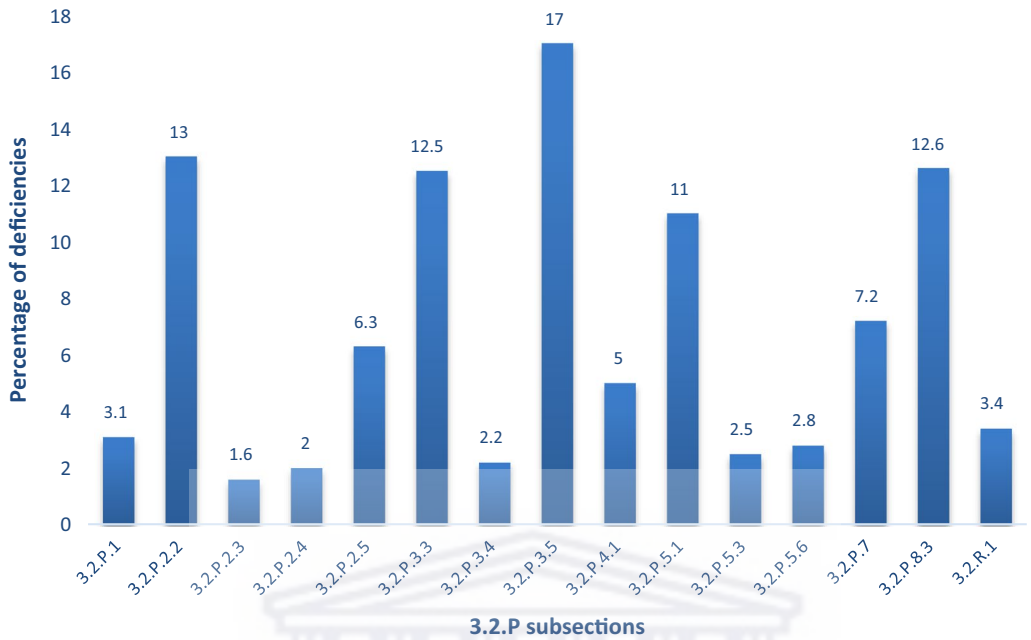

Fig. 3 The distribution of deficiencies relating to sterile products. Modules: 3.2.P.1 Description and Composition, 3.2.P.2.2 Final Pharmaceutical Product, 3.2.P.2.3 Manufacturing Process Development, 3.2.P.2.4 Container Closure System, 3.2.P.2.5 Compatibility, 3.2.P.3.3 Description of the Manufacturing Process, 3.2.P.3.4 Control of Critical Steps and Intermediates, 3.2.P.3.5 Process Validation and/or Evaluation, 3.2.P.4.1 Specifications of IPIs, 3.2.P.5.1 Specifications of the FPP, 3.2.P.5.3 Validation of Analytical Procedures of FPP, 3.2.P.5.6 Justification of Specifications, 3.2.P.7 Container Closure System, 3.2.P.8.3 Stability Data, 3.2.R.1 Pharmaceutical and Biological Availability

and should be specified in the process. These deficiencies comprised 16% of the section.

Deficiencies in Module 3.2.P.5., control of the FPP

The section with the second highest deficiencies is Module 3.2.P.5, control of the FPP, (21%) as depicted in Fig. 2. Figure 3 further shows that subsection 3.2.P.5.1, Specifications, had the most deficiencies in the whole 3.2.P reported for non-sterile products. Missing dissolution profiles and/or unacceptable dissolution limits were observed from nearly all the applications. Multimedia dissolution profile data on the biostudy test product is critical and used as reference data set that is used to support and assign dissolution limits in accordance to the EMA reflection paper [30]. The reports indicate that manufacturers often assign dissolution limits that are wider than the biostudy test product. This leads to back and forth communication between the applicant and the authority. Applicants often justify the widened limits based on the results of the stability results, however, this is not accepted since the acceptance criterion set should be based on the biostudy product. The behaviour should not change during stability as any deviation confirm deterioration of product quality. This is also part of the reason why the proposed dissolution specifications for release and shelf life should not differ as the product quality is expected to remain the same throughout shelf life as per the biostudy test product.

Module 3.2.P.5.1, Specifications, contains a number of deficiencies (58%) involving the request to tighten the proposed specifications based on batch analyses data, stability results and limits as indicated in ICH guidelines. For degradation/related impurities, manufacturers are required to ensure that the proposed specifications are in line with the recognised pharmacopoeia or that the limit is in accordance with ICH guidelines Q3B (R2) [11]. The limit should be below the calculated qualification threshold or reporting threshold. It was also observed that the acceptance criteria set for any other unknown impurities did not conform to ICH requirements. Impurities that are structural alerts for genotoxicity need to be controlled at the Threshold of Toxicological Concern (TTC) of 1.5 mcg/day, as found in the European Medicines Agency (EMA) [31, 32] and draft FDA guidance [33]. However, a higher limit may be proposed based on safety studies demonstrating that the proposed limit does not pose a safety concern. Other limits such as water content, assay, disintegration time are based on the batch analyses and stability results observed. A reasonable proposed limit would need to be justified by supporting data for

acceptability if not already indicated in the pharmacopoeia or guidelines.

The most frequent deficiency observed for sterile products in this subsection is the request to include the limit for bacterial endotoxin in the FPP specifications. Endotoxins released from Gram-negative bacteria are the main reason of contamination in pharmaceutical products and as a result of this, an endotoxin test is required to be performed on sterile products especially those which are to be injected in the body so as to avoid bringing adverse effects to human [34].

Deficiencies in Module 3.2.P.8, stability

The section with the third highest deficiencies is Module 3.2.P.8, Stability of the FPP, (15%) for non-sterile products. It comprises Module 3.2.P.8.1 (7.6%), -Stability Summary and Conclusions, Module 3.2.P.8.2 (1.8%) Post-Approval Stability Protocol and Stability Commitment and Module 3.2.P.8.3 (9.3%)—Stability Data. The frequent deficiencies in subsection 3.2.P.8.3, Stability Data, were on the limits proposed on degradation impurities and total impurities being too wide and applicant requested to tighten them in reference to the stability results, this relates to subsection 3.2.P.5.1, Specifications, as discussed above. The other deficiency was on the applicant omitting critical stability indicating parameters such as dissolution, total impurities or degradation impurities in the stability testing. Acceptance of a product cannot be granted if the stability testing does not include these critical parameters which determine the behaviour of the product throughout its shelf life.

There were 12.6% of the additional deficiencies specific to sterile products witnessed in subsection 3.2.P.8.3, Stability Data. The deficiencies were on the request for results of the in-use stability study confirming stability of the product at a specific temperature for a specified amount of time as indicated in the Professional Information (PI). Since the products are sterile, there is a requirement that if the product is not for single use such as ophthalmic solutions, lyophilised powders for infusion, etc., stability results should be conducted to confirm that the product quality is not compromised while in-use. Another list of stability data required involved studies to confirm compatibility of the selected diluent used for infusion solutions, photostability studies to confirm the effect of light on the final product and transportation stability test at specified elevated storage conditions.

Deficiencies in Module 3.2.P.1, description and composition of the FPP

There is 14% of deficiencies attributed to Module 3.2.P.1, Description and Composition of the FPP, from the whole 3.2.P section. The deficiencies in the section comprised requests for the potency adjustment calculation to be included. This equation clearly outlines the quantities required for the API depending on the assay of the API batches used. It also factors the water content present in the API and corrects to provide the acceptable quantity to be used. This should be included as a footnote under the composition table in 3.2.P.1. The other common deficiency in this section was on the indication of the polymorphic form used. The FPP manufacturer has to include the type of polymorphic form used in the batch formula as well as studies conducted to confirm the polymorphic form. They are required to provide the physico-chemical properties of the API in Module 3.2.P.2, pharmaceutical development, which will include polymorphic form investigation, particle size distribution and solubility. It should be noted that these parameters are not critical and may not be controlled by the final product manufacturer if the manufacturing process employs the following techniques which enhance the solubility as a result of the formation of the amorphous form of the product:

- Complete dissolution of the API in a diluent—results in the formation of an amorphous form [35].
- Hot melt extrusion which forms a solid dispersion of the API resulting in the formation of an amorphous polymer with enhanced solubility and bioavailability [36, 37].

The most common deficiency witnessed from sterile products in this section is on the request to include the pressure source used for filtration in the batch formula or composition list. The pressure source commonly used is nitrogen gas. It is also imperative that the pressure source used be sterile, this can be indicated in Module 3.2.P.4.

Deficiencies in Module 3.2.P.7, container closure system of the FPP

The most common deficiencies in the section included the request for the following regarding the immediate container closure system:

- CoAs of the immediate container closure system (CCS),
- Identification, chemical nature and density of the container closure as well as specifications and the relevant control procedures,
- Colour, dimensions and thickness of the container closure system,

- The integrity for the heat seal bond strength (see Table 3).

Manufacturers are required to include the testing parameters used for the container closure system as well as analytical procedure used to do the test. Further description of the CCS is also frequently requested such as colour, dimensions and thickness. This needs to concur with the description in the PI and Patient Information Leaflet (PIL). This section also relates to Module 3.2.P.2.4 where developmental studies on the CCS should be conducted and the most common deficiency is that the manufacturers do not provide or poorly documenting the suitability of the container with the final product. This should include performance studies, suitability, compatibility and safety of the CCS. The common deficiency is frequently cited for sterile products in the section since compatibility studies with all components the final product is in contact with should be provided. For non-sterile products, a frequent response normally refers to the stability data provided in 3.2.P.8.3 or the confirmation that the reference product also uses the identical CCS. SAHPRA accepts these justifications.

Comparison with other authorities

The reported deficiencies listed in Tables 3 and 4 have been compared with those published by other authorities and discussed below.

Comparison of deficiencies, SAHPRA vs USFDA

The USFDA published a four-part series on common deficiencies witnessed in the ANDA applications they received before 2010. Part 2–4 includes the common deficiencies found in the 3.2.P section of the CTD with Part 2 covering Module 3.2.P.1 and 3.2.P.4 on description, composition and excipients [5]. Part 3 covers Module 3.2.P.5 and 3.2.P.8 [6] while Part 4 covers the common deficiencies in Module 3.2.P.2/3 and 3.2.P.7, Manufacture and Container Closure System [7]. A quantitative comparison cannot be made since USFDA did not quantify the frequency of deficiencies. Some of the common deficiencies highlighted in 3.2.P.3 were on the in-process controls and tests (3.2.P.3.4, control of critical steps and intermediates) which is also 37% of deficiencies in the subsection by SAHPRA. Queries on granulation process was also reported to be significantly high and manufacturers were requested to provide a definitive quantitative end-point. A deficiency is included if no control or justification is provided by the applicant and the sole control proposed is a subjective, visual observation. For high shear processes, suitable controls may be related to the change in power consumption with respect to the granulation equipment (e.g., amperage). For fluid bed processes, moisture content can be a suitable control for end-point of the desired granules [7]. There were 5.9% of the deficiencies in the subsection requesting this by SAHPRA. For sterile products, the reported common deficiency was on excess fill volume and studies on extractable volume. A justification should be provided under manufacturing development based on data of multiple containers demonstrating that the intended volume can be extracted. Large overfills exceeding the required limit according to the USP 1151 general chapter [37, 38], should be appropriately justified as this may pose potential safety concerns. There were 9.6% of these deficiencies reported by SAHPRA for the applicable dosage forms. The most prevalent deficiency from Part 3 was on the control of the final product, specifications (3.2.P.5.1) which is also one of the highest common deficiency observed by SAHPRA at 58% in the subsection. The reported deficiencies are confirmed to be similar to those included in this study by SAHPRA.

Comparison of deficiencies, SAHPRA vs TFDA

A report by TDFA was made for applications submitted between June 2011 and May 2012 [8]. Deficiencies in the specification of the final product were the most prevalent in the final quality assessment reports. Issues regarding the specification of the final product were mainly related to the test item, related substances, or degradation products [8]. The second deficiency was for the validation of analytical procedures and mainly related to the validation for related substances/degradation products. The issues were mainly about the inadequate range/linearity and incomplete information about the characteristics (specificity, accuracy, precision, etc.) [8]. These deficiencies comprised 46% of subsection Module 3.2.P.5.3 for SAHPRA submissions. The other deficiency witnessed was regarding the manufacturing process which included

Table 5 Comparison of the top five common deficiencies from the five regulatory bodies listed below

SAHPRA[#]	TFDA	USFDA*	EMA	WHOPQTm
3.2.P.5.1	3.2.P.5.1	3.2.P.3.3	3.2.P.5	3.2.P.3
3.2.P.3.3	3.2.P.5.3	3.2.P.5.1	3.2.P.3	3.2.P.4
3.2.P.1	3.2.P.3.3	3.2.P.8	3.2.P.2	3.2.P.5
3.2.P.8.1/3	3.2.P.3.4	3.2.P.2.2	3.2.P.8	3.2.P.8
3.2.P.7	3.2.P.6	3.2.P.4	3.2.P.4	3.2.P.7

*USFDA did not report on the deficiency quantitatively

[#] Sequence included is for non-sterile products, the sequence is different for sterile products. Modules: 3.2.P.1 Composition and Description, 3.2.P.2 Pharmaceutical Development, 3.2.P.3.3 Description of the Manufacturing Process, 3.2.P.3.5 Process Validation or Evaluation, 3.2.P.8 Stability Data, 3.2.P.2.2 Pharmaceutical Development, 3.2.P.5.1 Specifications, 3.2.P.4 Control of the IPIs, 3.2.P.7 Container Closure System (see Table 2 for further descriptions)

inappropriate overages applied, an unjustified change in the manufacturing process, unclarified batch sizes, and others. These are similar to those reported by SAHPRA as seen from Tables 3 and 4 above. The top five deficiencies reported by SAHPRA are very similar to those reported by the TFDA (Table 5).

Comparison of deficiencies, SAHPRA vs EMA

The study by the EMA was conducted on applications finalised by the CHMP, during 12 consecutive plenary meetings held in 2007 and 2008. The concerns raised by the Committee were on control of FPP (32% for 3.2.P.5.1), followed by concerns on the manufacturing (21% for 3.2.P.3), product development (17% for 3.2.P.2) and stability (17% for 3.2.P.8) [9]. This is similarly observed by SAHPRA as shown in Table 5, which compares the frequent deficiencies with what other authorities and organisations reported.

With respect to stability (3.2.P.8), 32% of concerns were regarding the lack of data submitted by the applicant to substantiate the proposed shelf-life of the FPP. For pharmaceutical development (3.2.P.2), 16% of concerns had to do with the results from comparative in vitro studies (for example the dissolution) or comparative in vivo studies (e.g., bioequivalence) requiring further discussion as well as a lack of information on the discriminatory power of dissolution method used [9]. These deficiencies were also observed by SAHPRA in the respective sections. The EMA also published a recent study reporting on common deficiencies witnessed for biosimilar submissions [15] Although these are different to orthodox medicines with respect to the API synthesis in most cases, there is similarity of these products with sterile products since most biosimilars are sterile. There were a number of similar deficiencies reported with those reported by SAHPRA. The deficiencies are; variety of media fill validation issues, validation of depyrogenation of glass vials and hold time validation issues in 3.2.P.3.5 (47% in the section), filter material and filter pore size not included in 3.2.P.3.3, lyophilisation conditions of the cycle used not indicated in 3.2.P.3.3 (28%) and compatibility studies of the FPP with the equipment not indicated in 3.2.P.2.4 (17%) [16]. Table 4 on the additional sterile product deficiencies also highlights these in the respective sections thereby confirming similarity.

Comparison of deficiencies, SAHPRA vs WHOPQTm

The WHOPQTm published FPP deficiencies observed in applications submitted between April 2007 and December 2010. The deficiencies reported were on missing executed and blank manufacturing records (BMRs), inadequate description of equipment, process parameters and end-point determination, inadequate description of sterile processes, unsatisfactory in-process tests and their frequency or acceptability of intermediate product specification, for Module 3.2.P.3 [3]. All the above have also been requested by SAHPRA as observed in Tables 3, 4 and 5. Previously, SAHPRA only requested the BMRs and packaging records when the need arose from the evaluations since they were the principle requirement during inspections. However, this condition was amended in 2020 by SAHPRA and is now a requirement during evaluations. Inadequate or poorly defined end-point for wet granulation process was another common deficiency as well as hold time related deficiencies from the guidance document [10]. These were also observed by SAHPRA and discussed in previous sections.

Conclusion

The main objective of this study was to provide a comprehensive list of common deficiencies encountered by SAHPRA from the submitted 3.2.P section of CTD dossiers. The issues raised stem from product development, production and control of FPPs. The list is aimed at assisting manufacturers and applicants who submit future products to anticipate and avoid common pitfalls in regulatory affairs. Thus, as a result, this study will help pharmaceutical companies and manufacturers in reducing unnecessary and avoidable delays in the registration of these products to the benefit of accelerated access of medicines to patients. Comparisons with other regulatory authorities showed that other international regulatory agencies also observe similar common deficiencies as SAHPRA. This confirms the similarity in the extent of scientific assessments by the authorities, thus ensuring that quality, safe and efficacious medicines is available to patients.

Limitations and future work

The study could not be conducted for applications finalised between 2018–2020 due to the following: the authority transitioned from the Medicine Control Council (MCC) to SAHPRA in 2018. In that time, SAHPRA staff continued to be housed in Civitas building in Pretoria with the National Department of Health employees. From April 2018, the department employees working in the Civitas building embarked on a protest action because of concerns about working conditions in the building. In the medium term, SAHPRA as a section 3A public entity, moved into new premises at the end of 2018. In addition, a backlog project was initiated in 2020, which required SAHPRA evaluators to implement, induct and train new evaluators involved in the project. As a result, information for 2018–2020 is not included in this study due to the disruptions caused by the protesting

action, the move to the new premises and the initiation of the backlog project.

Further investigations will be conducted on other sections within the CTD to provide additional assistance in informing manufacturers and research organisations partaking in pharmaceutical development with the intent to obtain approval/registration from regulatory authorities.

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Authors' contributions
LM, ML and JJ were involved in the development of the study design. LM collected and analysed the data. LM and ML co-wrote the first draft of the manuscript. JJ reviewed the manuscript and added suggestions. All authors read and approved the final manuscript.

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Availability of data and materials
Data not available due to privacy and confidentiality restrictions.

Declarations

Ethics approval and consent to participate
This study did not require any specific ethical approval. The study was approved by the University of the Western Cape Senate Research Committee.

Consent for publication
Not applicable.

Competing interests
No conflicts of interest that are directly relevant to the content of this article. The views expressed in this article are the personal views of the authors and may not be used or quoted as being made on behalf of, or reflecting the position of SAHPRA.

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DIA

ORIGINAL RESEARCH

Bioequivalence Common Deficiencies in Generic Products Submitted for Registration to the South African Health Products Regulatory Authority (SAHPRA)

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Abstract

Background The cost of healthcare has become expensive globally, of which the greater part of the money is spent on buying innovator medicines. In order to make medicine affordable, the development of generic medicines has become paramount. The science of bioequivalence studies of generic products to demonstrate therapeutic equivalence with innovator products has been developed over the last 50 years. These studies cost far less as compared to innovator products thereby reducing the cost of medicines. Accelerating access to medicines has become an increasing challenge due to insufficient resources from regulatory authorities, while pharmaceutical industry continues to expand. An investigation on the deficiencies identified during scientific assessments by SAHPRA in submitted bioequivalence studies is therefore paramount. Identification and publication of these deficiencies will assist in accelerating the access of medicines to patients.

Objective The aim of the study is to investigate the types and frequency of the common deficiencies observed in the bioequivalence section of generic submissions to SAHPRA. The study was conducted retrospectively over a 7-year period (2011–2017) for generic products that were finalised by the Pharmaceutical and Analytical pre-registration Unit. A more recent analysis on common deficiencies witnessed for applications assessed between 2020 and 2021 was also done to illustrate the consistency in the evaluation practises adopted by SAHPRA.

Methods There were 3148 applications finalised between 2011 and 2017, and to attain a representative sample for the study, statistical sampling was conducted. The multi-stage sampling called stratified systematic sampling was selected as the method of choice. The sample size was obtained using the statistical tables found in the literature and confirmed by a sample size calculation resulting in the selection of 325 applications (Fig. 2a). Additionally, 300 master applications were assessed between 2020 and 2021 for up-to-date data (Fig. 2b). All the deficiencies were collected and categorised according to the ICH E3 guideline and components relevant to biostudies.

Results A total of 2458 deficiencies were collected from the selected sample size for applications finalised between 2011 and 2017 where a biostudy was submitted. The majority of the identified deficiencies were from the following categories; in vitro dissolution testing and specifications (18%), study design (17%), details on the test and reference products (16%), issues on sample analysis (16%), and statistical analysis (10%) (Fig. 3). From the applications assessed in 2020–2021, 492 deficiencies were identified with a similar trend compared to those finalised between 2011 and 2017. Comparison of the deficiencies with those reported by the USFDA and WHO PQTm is discussed with similarities outlined.

Conclusions The five most common deficiencies observed were extensively discussed. The outcomes of this study will guide pharmaceutical companies, sponsors, and Clinical Research Organisations (CROs) in submitting quality biostudies which will reduce turnaround times for registration and accelerate access to medicines for patients. In addition, the deficiencies identified will assist assessors from the different regulatory authorities to improve on their bioequivalence assessment.

Keywords South African Health Products Regulatory Authority (SAHPRA) · Common deficiencies · Bioequivalence · Bioavailability · Biostudies · Generic products

Introduction

Innovator pharmaceutical products are New Chemical Entities (NCEs) that have received a patent on the chemical formulation or manufacturing process and obtained registration

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from a regulatory authority after extensive testing [1]. Innovator and generic products are both available on the market, but innovator products are usually more expensive compared to the generics due to extensive research conducted from discovery and development to marketing and promotion of the product [2]. For example, clinical trials which are the primary tool to assess safety, efficacy and clinical benefits of new Finished Pharmaceutical Products (FPPs) in humans tend to be time consuming, expensive, and burdensome for subjects. These can be replaced by the cost-saving bioequivalence studies which ensure the progression of future therapeutic development. In 2017 alone, the United States of America (USA) government was able to save $265.1 billion due to the use of generic products, and an overall of $1.67 trillion was saved in the last decade [2]. In South Africa, the domestic manufacturing pharmaceutical industry almost exclusively produces generic products, and the South African pharmaceutical sector is import dependent [3]. In 2013, generic medicines accounted for 63% of the private pharmaceutical market and 80% of the market share in the South African government's pharmaceutical use [3].

Bioavailability refers to the rate and extent to which the Active Pharmaceutical Ingredient (API), or its active moiety, is absorbed and becomes available at the site of action [4]. When two formulations of the same API or two FPPs are claimed bioequivalent, it is expected that they are therapeutically equivalent [4–8]. The generic products submitted to regulatory authorities must be both pharmaceutically equivalent and bioequivalent to the corresponding innovator product to establish that the two products are therapeutically equivalent. A biowaiver may also be requested instead of submission of the biostudies, when justified, in line with the Biopharmaceutics Classification System (BCS) [7] .

The South African Health Products Regulatory Authority (SAHPRA) receives approximately 1200 applications per annum from pharmaceutical companies for registration into the market, and 90% of these are generic products. Direct demonstration of therapeutic equivalence through a comparative clinical trial is rarely a practical choice, as these trials tend to be insensitive to formulation differences and usually require a very large number of patients [7]. Further, these studies in humans can be financially limiting, often unnecessary and may be unethical [5]. As a result, the science of bioequivalence testing has been developed over the last 50 years [7].

Data from biostudies are received and evaluated by the Pharmaceutical Evaluations and Management (PEM), Pharmaceutical and Analytical (P&A) pre-registration Unit. SAHPRA mostly relies on external evaluators to execute biostudy evaluations. The P&A pre-registration Unit utilised five to eight external experts as biostudy evaluators. The experts formed part of the Pharmaceutical and Analytical (P&A) Committee, which provide the necessary support to the Unit and the meetings served as a quality assurance measure for all products. Committee members provide technical and scientific advice for evaluations in the pre-registration Unit. This meant that each biostudy report on the evaluation of the data provided in the dossier was discussed in the meeting before it can be communicated to the applicant. Due to the resultant backlog of applications over the years, SAHPRA embarked on a project called the Backlog clearance programme aimed at clearing the existing backlog over a specified time. Inherited processes and practices from the former Medicine Control Council (MCC) were re-assessed, and the backlog project was initiated to support new methodologies required to achieve the goal of clearing the backlog of applications [9]. All applications received by SAHPRA prior to February 1, 2018 were considered to be part of the backlog project and ~ 8000 applications were in the pre-registration phase [9]. The authority, therefore, implemented a process that allows applicants to re-submit the dossiers, as some information may be required to be updated since the backlog applications were initially submitted as far back as 2008. Re-submission windows (RW) were created based on the importance of therapeutic categories of medicines to the country. Re-submission window one (RW1) consisted of medicines in the therapeutic category of Human Immunodeficiency Virus (HIV), Tuberculosis (TB), Vaccines and Hepatitis, while re-submission window two (RW2) was for medicines in the therapeutic category, oncology medicines [10]. Re-submission window five (RW5) was for medicines targeting Diabetes, Malaria, maternal and newborn health as well as all the priority APIs [10]. The inclusion of the backlog applications in this study is to identify the biostudy deficiencies and establish if there are any differences in the outcomes from the newly developed biostudy assessments practices.

The four major study report components for biostudies and evaluations are as follows: in vitro dissolution testing, bioanalytical validation and analysis, clinical study reports, and details of the test and reference products used as illustrated in Fig. 1. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use (ICH) E3 guideline provides the structure and content of the clinical study reports [11]. In an effort to improve the quality of biostudy submissions by the applicants, different regulatory authorities developed additional guidelines [4–8]. The United States Food and Drug Administration (USFDA) published guidance documents on General Bioavailability and Bioequivalence (BA/BE) Guidance [6], Statistical Approaches to Bioequivalence Guidance [12], and creation of the online Dissolution Methods Database (November 2005) to name a few. The USFDA noted that although there has been an improvement in the overall quality of the submissions with the employment of the guidelines and the Dissolution Methods Database

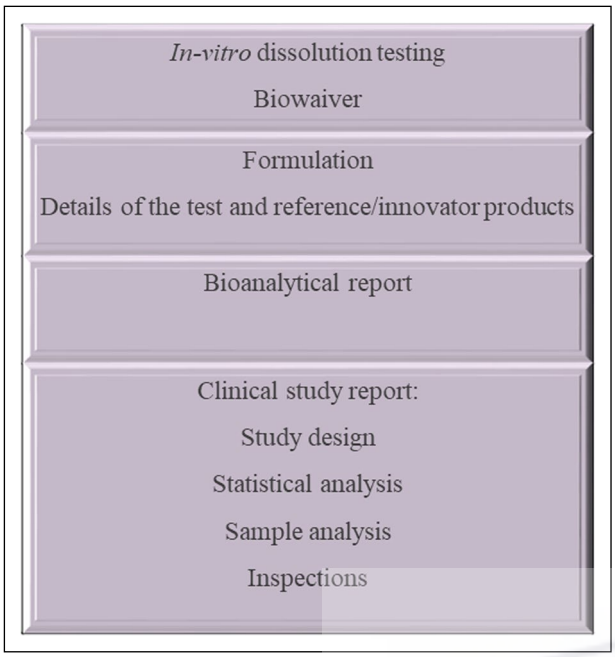


Fig. 1 Four groups of bioequivalence study components with nine categories for the deficiencies observed in biostudy submissions

[13], there were still some recurring deficiencies that may be associated with one or more of the components of the biostudy reports of the applications. This resulted in authorities publishing common deficiencies observed in biostudy evaluations to the industry in order to avoid future delays in submissions and promote access of medicine to patients. Thus far, reports on common deficiencies were published by the USFDA [14] and the World Health Organisation Prequalification Team: Medicines (WHO PQTm) [15]. This current study therefore aims to identify and quantify common deficiencies in the biostudy section of generic products finalised by SAHPRA's PEM pre-registration Unit between 2011 and 2017. In addition, deficiencies identified in applications assessed between 2020 and 2021 were also investigated. The transparency between the authority and industry on common deficiencies in the biostudy section will assist in reducing the scientific review process and thereby accelerating the access of medicines to patients.

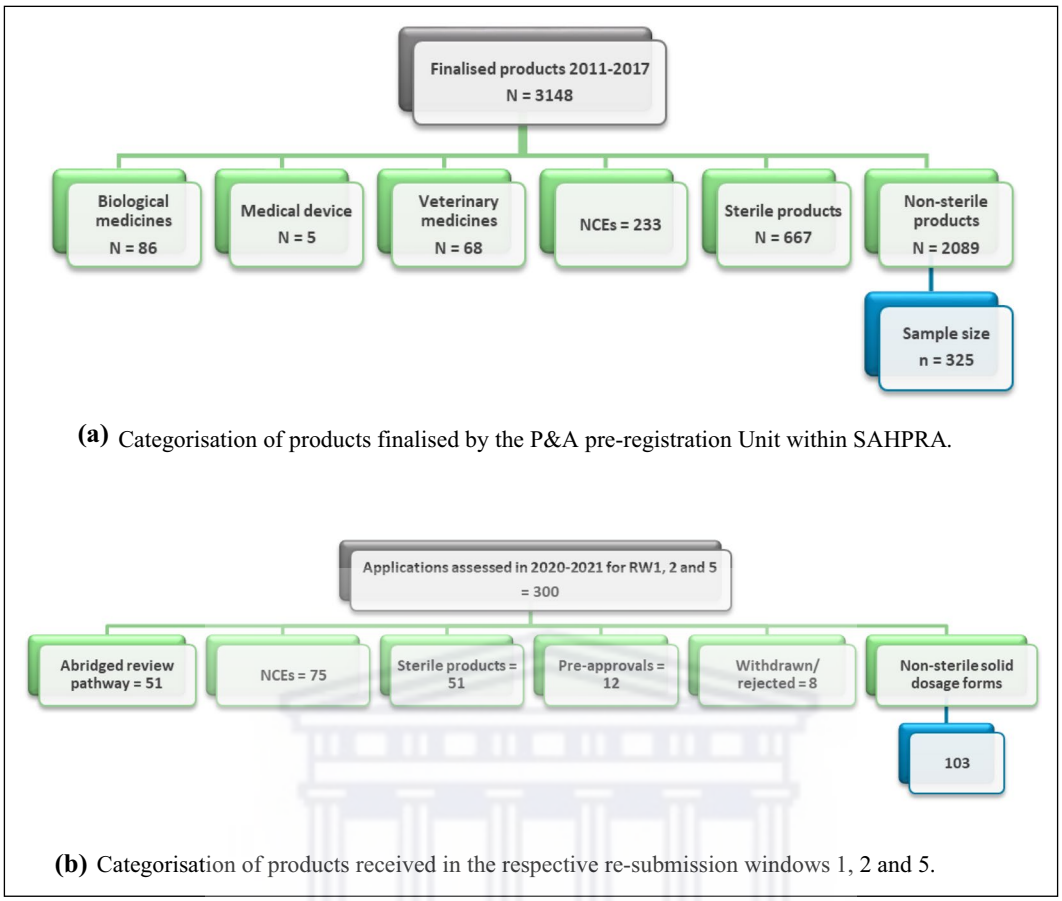
Method

Over the 7-year period (2011–2017), 3148 applications were finalised by the P&A pre-registration Unit within SAHPRA. The sterile products (667), Veterinary (68), Biologicals (86), Medical Devices (5), and New Chemical Entities (NCEs) (233) were also finalised by the P&A Committee in the period as shown in Fig. 2 but were not included as part of this study. NCEs require the submission of clinical trial data assessed by the Clinical Evaluation Unit within SAHPRA. Solutions for oral use, aqueous solutions administered by parenteral routes, powders for reconstitution, otic, ophthalmic, nasal, topical, and cutaneous products containing the API in the same molar concentration as the reference product are considered to be equivalent without further documentation of equivalence [5]. The applicant should demonstrate that the excipients in the pharmaceutically equivalent product are essentially the same and in comparable concentrations as those in the reference product [5]. Sterile products are normally classified in the above dosage forms, thus, biostudies are not required and not submitted for these. The biological products also use sterile preparations due to the criticality and nature of the active moiety. The veterinary products were not included in the study since the P&A Committee only provided support to the veterinary Unit on each application in terms of quality assessments only. The veterinary applications require the submission of clinical trial data due to the diversity across animal species' physiology and the numerous dosage forms used in veterinary practice resulting in unique formulations and dosage routes [16]. As such, technical requirements for registration of veterinary medicines are constantly evolving as a result of scientific developments [16]. Lastly, medical devices were not included in this study because the sample size was too small to render the deficiencies common.

The distribution clearly shows that SAHPRA receives a large number of generic products since 90% of the finalised products are generic products and 66% of those are non-sterile (Fig. 2a).

Due to the large population size of the non-sterile products, a statistical sampling method became a requirement for this research. The sample selected needs to be a true representation of the population, and the results of the study can be generalised to the population as a whole. Selection of the sampling method is crucial as different sampling techniques are used for specific research problems since one technique may not be appropriate for all problems [17]. The sample size determination and sample selection for the non-sterile products have been well described in the findings on common deficiencies in the Active Pharmaceutical Ingredient section by SAHPRA [18]. Stratified systematic sampling is the selected sampling method, and a sample size of 325 non-sterile applications was obtained (Fig. 2a) [18].

For the study investigating applications assessed between 2020 and 2021, all applications received in re-submission windows one, two, and five (300) (Fig. 2b) where a



(a) Categorisation of products finalised by the P&A pre-registration Unit within SAHPRA.

(b) Categorisation of products received in the respective re-submission windows 1, 2 and 5.

Fig. 2 **a** Categorisation of products finalised by the P&A pre-registration Unit within SAHPRA. **b** Categorisation of products received in the respective re-submission windows 1, 2 and 5

biostudy was submitted were used. An overall of 84 (RW1), 143 (RW2), and 73 (RW5) applications were received in the respective windows. Table 1 and Fig. 2b illustrate the distribution of the pathways the applications undertook in the three windows. Abridged review pathway is an external reliance mechanism employed by the authority wherein reports from other authorities are received and comparison of the scientific content conducted instead of full scientific review. In addition, there were applications that were pre-approved by the PEM before the 1st of February 2018, these have been assessed and finalised by the Unit previously although not yet registered. Lastly, the first two windows consisted of NCE submissions as these are high priority and require the submission of clinical trial data. Thus, biostudy

Table 1 The illustration of applications received in re-submission windows 1, 2 and 5

	Re-submission window 1 (RW1)	Re-submission window (RW2)	Re-submission window (RW5)
Total applications received	84*	143*	73*
Abridged review pathway	8	22	21
Liquid dosage forms (biostudy not required)	5	29	17
Non-sterile solid dosage forms (biostudy required)	31†	48†	24†
Pre-approvals (already assessed)	1	4	7
NCEs	39	36	–
Withdrawn/rejected	–	4	4

*Total number of applications received in each category

†Total number of non-sterile applications in each RW with biostudies, used in the study

submissions were for a total of 103 applications between the three windows.

Collection of Deficiencies

The full history of all the products finalised between the 7-year period (2011–2017) was collected which comprises of all communication between the authority and applicants in order to reach finalisation. The documents include the recommendations sent to the applicant and the responses received, as well as the evaluation reports of responses in the form of amendment schedules. These paper documents were obtained from the committee meeting minute documents and the registry files where all documents relating to the product are placed. The investigation process involved obtaining the type and extent of the deficiencies raised in the first deficiency letter following the initial evaluation process, thereafter, extracting all the responses and feedback during the multiple rounds of communication. For applications assessed between 2020 and 2021, the full history was obtained in the electronic database for SAHPRA applications. The deficiencies in the initial query letters were collected and quantified. The selected nine categories for the deficiencies are as illustrated in Figs. 1 and 3.

The deficiencies obtained were reviewed and the frequency of each biostudy component was listed with the percentage frequency calculated as follows:

- Percentage frequency of deficiency identified per biostudy component = (frequency of specific deficiency/Total number of deficiencies biostudy component) × 100.

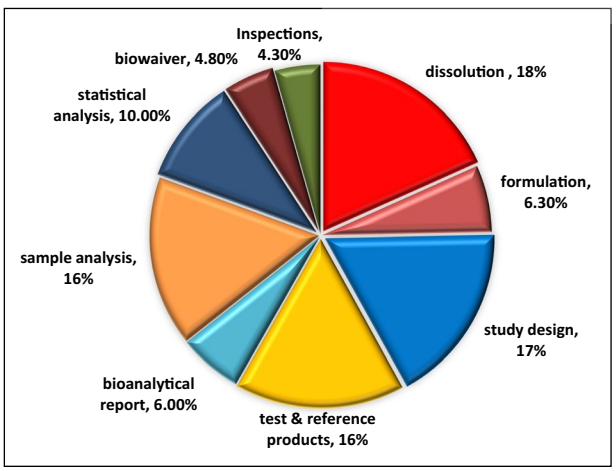


Fig. 3 Distribution of deficiencies from biostudies finalised between 2011 and 2017 by the PEM pre-registration Unit

All charts, graphs, and analyses were carried out with Microsoft Office Excel® 2016 (Microsoft Corporation, USA).

Results

From the stratified systematic sampling, a sample size of 325 non-sterile applications was obtained, and of those, nine were non-sterile products which do not require the submission of a biostudy such as oral liquids, topical products, etc., classified under "other" as indicated in the types of dosage forms below. The applications contained a variety of solid dosage forms, which are film-coated and uncoated immediate-release tablets, (48%), immediate-release capsules (23%), orodispersible tablets (8.0%), extended-release tablets (8.0%), extended-release capsules (3.5%), chewable tablets (1.2%), powders for suspensions (5.1%), and other (3.2%). There was an overall of 2458 deficiencies collected from the 316 initial letters from the biostudy sections.

For the applications assessed between 2020 and 2021, there were 103 applications where a biostudy was submitted as outlined in Table 1. Of the 103, 50 were film-coated and uncoated immediate-release tablets (49%), 25 were immediate-release capsules (24%), 10 were powders for suspension (13%), eight were extended-release tablets and capsules (10%) and other (4.0%). This is a similar trend of the types of dosage forms received between 2011 and 2017 as indicated above. There were 492 deficiencies obtained as stipulated and discussed in the following section.

The deficiencies observed in the four components are expanded on in Tables 2, 3, 4 and 5.

Discussion

Figure 3 clearly depicts the distribution of the deficiencies observed in the biostudies. It shows that the highest deficiencies, 18%, were from dissolution testing. This component is followed by study design (17%), queries on the test and reference products (16%), sample analysis (16%), and statistical analysis (10%). The common deficiencies observed in the categories are further discussed below.

In Vitro Dissolution Testing and Biowaivers

Dissolution testing is an essential part of product development and serves as a quality control measure once the composition and the manufacturing process are defined for the scale-up of production batches to ensure batch-to-batch consistency [5, 6, 19–22]. It is also used in support of a biowaiver of bioequivalence testing to demonstrate the similarity between different product formulations of an active

Table 2 List of common deficiencies observed in in vitro dissolution testing and biowaivers identified by SAHPRA between 2011 and 2017

Deficiencies In vitro dissolution testing	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
Comparative dissolution studies must be conducted per the requirements in the guideline to include the purpose of study, products batch information, full dissolution conditions, and method validation, as well as numbers of units per the study, how units were filtered, and any problem with pH related stability of the samples should be indicated and discussed in terms of preventative handling measures, analysis and interpretation of data, analytical method or reference to part of the dossier, results (API dissolved): tabulated, graphically, similarity determination/f2 calculation if necessary	64	15	2
The calculation of similarity factor values (f2) for profiles is not appropriate and should be corrected	13	2.9	
The calculation on the similarity factor for the two profiles was not conducted and should be submitted	10	2.3	
The submitted individual dissolution data are not accepted. There should be 12 units used for the comparative dissolution studies between the test and reference products	21	4.8	5
Include the dissolution data for the innovator reference product (foreign and/or South African) as this was not submitted	15	3.4	
Bring the final product release and stability dissolution specifications in Module 3.2.P.5.1 in line with the profiles of the biostudy test (and reference) products. A specific specification is proposed based on the results observed	33	18	33
The dissolution profiles in the selected quality control medium were not included and should be submitted	30	6.8	19
Describe the method for withdrawal and filtration of samples and how this ensures that dissolution of non-dissolved particles does not occur after sampling Include in-line filtration for drawing the dissolution samples in the dissolution method in 3.2.P.5.2 to ensure that the dissolution of the sample is stopped immediately on withdrawal of the sample (USP "Test specimens are filtered immediately upon sampling unless filtration is demonstrated to be unnecessary"). If the method states that the samples should be drawn and filtered this does not necessarily imply or ensure that the dissolution of undissolved particles in the sample is stopped at the time of sampling	46	11	19
Demonstrate the similarity of the dissolution profiles of the reference and corresponding test product or SA innovator in three of the physiological media and justify the use of other buffers apart from those in the guideline or the addition of a surfactant	30	6.8	4
The sample withdrawal times and other aspects do not comply with the requirements stipulated in the dissolution guideline	29	6.6	
Provide a statement on whether in vivo and in vitro correlation from the data were obtained	09	2.0	
Indicate where the dissolution studies were conducted as well as the dates when the studies were conducted	10	2.3	6
The submitted dissolution data are incomplete for the extended-release products as it is lacking dissolution data in multimedia and alcohol dose dumping data for extended-release products	10	2.3	
Consider including an additional dissolution specification for the extended-release products with a longer release rate	06	1.4	
Demonstrate the discriminatory nature of the dissolution method in 3.2.P.2 to ensure that it is sensitive to changes in manufacturing processes and /or in grades and/or amounts of critical excipients. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters	59	13	24
Other	09	2.0	
	442		112
Biowaiver			
Provide evidence to show the proportional similarity of the different strengths. Fully address biowaiver requirements for the lower strength(s) by including confirmation that all strengths are manufactured using the same process, similar equipment, similar dissolution profiles, linear pharmacokinetics, etc	38	32	15
The BCS classification of the API has not been identified and all requirements according to the guideline regarding the appropriateness of the BCS biowaiver have not been addressed, evidence that the API is fully absorbed upon oral administration is also required	31	26	

Table 2 (continued)

Deficiencies In vitro dissolution testing	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
According to pharmacopoeial monograph, the API is poorly soluble and poorly permeable therefore BCS II/IV. Therefore, the API will not be considered by SAHPRA for biowaiver			10
Provide permeability studies to confirm the indicated BCS classification of the API	41	34	5
A biowaiver for the additional strength cannot yet be granted until data for dissolution at pH 1.2 is also provided, or the omission justified			10
For a BCS-based biowaiver application, comparison should have been demonstrated for each strength of the test product with the corresponding strength of the foreign reference product. In addition, the following documentation for the reference products should have been submitted: a. Copies of product labelling (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate b. Copies of the comparator products carton outer boxes. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling c. Copies of CoAs for the comparator products			3
A volume of 1000 ml was used for the dissolution comparative dissolution studies for biowaiver purposes. This volume may be acceptable for release testing; however, this is not acceptable for biowaiver purposes. You should submit new comparative dissolution data in 900 ml of media (pH 1.2, 4.5 and 6.8) and at release conditions			6
Other	09	7.6	
	119		49

substance and the reference medicinal product and to indicate potential problems with bioavailability. Thus, issues regarding comparative dissolution details between the test and reference products used in the biostudy are assessed in this component as well as the appropriateness of the proposed dissolution specifications.

For biowaivers, the Biopharmaceutics Classification System (BCS) waiver is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the API and is intended to reduce the need for in vivo bioequivalence studies [21]. This is confirmed by comparison of the proportional additional strength(s) and similarity of the dissolution profiles in the three physiological media with the reference product [4, 5]. The deficiencies observed in the biowaiver requests are therefore investigated in this component.

The dissolution of a product is important for its bioavailability and therapeutic effectiveness and is therefore considered a critical parameter in biostudies [23]. The deficiencies observed in these components are listed in Table 2, and Fig. 4 further highlights the five most frequent deficiencies observed in the sections. Dissolution testing requires the development of a robust and rugged dissolution method that is adequately discriminating to distinguish any changes that could affect the product [22, 23]. As depicted on Table 2, there was 13% of deficiencies relating to the discriminatory nature of the selected dissolution method not having been demonstrated and was therefore requested. The choice of an adequate medium that can discriminate between critical manufacturing variables is crucial in such cases [24, 25]. The changes may include quantitative formulation, material specifications, and/or using slightly modified process parameters [25] .

When a dissolution test is not defined in the monograph of the product, or if the monograph is not available, a comparison of product dissolution profiles is recommended in three different dissolution media at physiological pH ranges, that is, 0.1 N Hydrochloric acid—pH 1.2, Acetate buffer—pH 4.5 and phosphate buffer—pH 6.8 [21, 22]. Table 2 clearly shows that there were 6.8% of these deficiencies from the dissolution testing category. If the API is poorly soluble, appropriate concentrations of a surfactant are recommended, and therefore, comparative dissolution results should also be submitted in the selected medium with the surfactant [21]. A clearly described justification is required for these products since this is not encouraged. The comparative dissolution study results should be submitted in accordance with the SAHPRA dissolution guideline which is in the three media as described above, specified dissolution vessel, media volume and agitation speed between the test product and reference product [24, 26, 27], there were 15% of the deficiencies requesting this. The 15% also comprised of deficiencies such as lack of submission of the method validation, inadequate numbers of units used for performing the study, how the units were filtered, similarity determination (f2) calculation

Table 3 List of common deficiencies in the bioequivalence clinical study reports identified by SAHPRA for non-sterile products finalised by the pre-registration Unit between 2011 and 2017

Deficiencies Clinical study report Study design	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
3.0. Include a comprehensive table of contents (ToC) for the Overview. General information guideline 3.1.2 and Biostudies guideline 3.9. (currently not relevant since SAHPRA allows only electronic submissions)	30	7.1	
5.1. Submit the ethical approval letter by the Ethics Committee or Institutional review board (IRB) for the approved protocol and the subject consent forms	26	6.1	
9.1. The meal composition employed in fed studies should be consistent with the description in the labelling i.e. Profession Information (PI)	23	5.4	
9.1. The Summary of product characteristics (SmPC) of the reference product indicates that the product should be taken with food, therefore submit the appropriate biostudy i.e. fed study	09	2.1	
9.1. Justify the inclusion / explain/clarify the relevance and appropriateness of the proposed pharmacokinetic information in the professional information with reference to the results of the bioequivalence study, by a comparison of the results (including mean values, inter- and intra-individual variability, of this study with published results (literature, product information of reference product (innovator), WHOPARs). Copies of these references should be provided as well). The submitted fasting study does not appear to support the pharmacokinetic values for plasma concentration in the proposed PI, and no statement regarding the effect of food on the bioavailability of the final product is included	09	2.1	2
9.1. Evidence of food effect must be included for fed studies. Alternatively: The biostudy employed an open label, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study in healthy adult male human subjects under fed conditions, because the comparator product in the European Union is taken with food. However, the claim that it can be taken with and without food requires that the biostudy should be conducted in fasting conditions	34	8.0	13
9.2. Include the complete dates of the treatment schedules, ensure that the washout period is not excessively larger than five times the largest expected half-life	32	7.5	
9.3.1/2. The inclusion and exclusion criteria could not be located in the protocol	14	3.3	
9.4.5 The proposed sampling times are found inadequate and not sufficient to cover the Cmax	10	2.4	
9.4.5 Provide clarity on the dates of the study reports and analytical reports	27	6.4	
9.4.5 The lowest Cmax is at a specified time based on the submitted concentration–time data. This means that there is only one post dose time point before the Cmax. Provide evidence to show that no Cmax happened between the 1st sampling time and the lowest Cmax			2
9.7.2. Ensure that the number of additional subjects added to the sample size to compensate for potential dropouts or withdrawals are realistic and consistent with the study design	12	2.8	
9.7.2. Provide the parameters and method that were used to determine the sample size	25	5.9	
9.7.2. Provide justification for the proposed sample size as it is lower than the minimum requirement	12	2.8	
10.2. Insufficient information provided on the protocol e.g. address deviations in the submitted and approved protocol	35	8.2	
14.1. Submit individual subjects' demographic profiles i.e. age, race, ethnicity, gender, and body mass	25	5.9	9
14.1. Submit the number of females and males participating in the study	25	5.9	
16.1.1. Provide the protocol for the study which includes the protocol final version number	19	4.5	
16.1.1. The protocol should indicate the software that will be used for the statistical calculations and factors to be included in the Analysis of Variance (ANOVA) should be well defined	24	5.6	
16.1.2 Confirm that case report forms will be available upon request or for inspection. (this is now a requirement by SAHPRA, case report forms should be included in the submissions) 2011–2017	21	4.9	
16.1.2 Provide copies of Case report forms (CRFs) completed at screening for the volunteers recruited for inclusion in the fasting study. A blank copy of the CRF was found in 16.1.2 for all studies, this is noted but not adequate to address this requirement. 2020–2021			2

Table 3 (continued)

Deficiencies Clinical study report Study design	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
16.1.2 Tabulate the respective laboratory results against the normal ranges for any results that were outside of study site normal values. Further, the case report form for respective study participants must also be provided			4
Other	13	3.1	
	425		32
Sample analysis			
9.5.4. Provide the temperature of the water bath in which the samples were defrosted before testing	46	11	
9.5.4. Demonstrate the long-term stability of the plasma samples in the study under the correct study conditions for the period between centrifuging and analysis	59	15	20
9.5.4. Provide a description of the sample transportation, transport temperature recording from the clinical site to the analytical site	39	9.7	10
9.5.4. Provide or justify why no definitive time, temperature, and speed is given for the centrifuging of samples after receiving the blood samples	25	6.2	15
9.5.4 Calibration data, i.e. raw data and back-calculated concentrations for standards, as well as calibration curve parameters, for the entire study should be provided	11	2.7	7
12.2. Provide a discussion on the selection of samples for repeat analyses as these could not be located	15	3.7	5
12.2 Provide the SOP specifying the criteria for reanalysis and reporting of reanalysed samples			2
12.2. Plasma samples from subjects who dropped out or were withdrawn due to an adverse event should be analysed for a complete safety analysis of the data	31	7.7	
14.2. Submit 20% of chromatograms in accordance with the SAHPRA biostudies guideline 3.9.2.e. The chromatograms must have a table of contents indicating the subject and page numbers. The legend or sample coding system must be included and clearly identified and sampling time given	76	19	10
14.2. Submit the mean and all individual plasma concentration versus time profiles presented on a linear/linear as well as log/linear scale	40	10	9
14.2 Provide evidence that the analytical method used was able to detect and resolve the primary analyte from possible metabolites			3
14.2 A discussion of sensitivity in terms of signal-to-noise ratio determined at Lower limit of quantification (LLOQ) concentrations including the signal-to-noise ratio values should be provided for the methods used to analyse the APIs in the plasma			4
14.2. Provide legible concentration vs time plots and Certificates of Analysis (CoAs)	29	7.2	8
14.2. Submit complete documentation with respect to subject sample analyses	26	6.5	6
Note that samples from all dosed subjects should be analysed for safety evaluation			20
Other	06	1.5	
	403		119
Statistical analysis			
11.4.1. Comment on the high standard deviation (SD) of the area under the curve (AUC)	25	9.9	
11.4.1. The submitted pharmacokinetic/statistical calculations are incorrect and require revision and re-calculation	27	11	
11.4.1. The criteria for selection of samples for reanalysis are not objective, unscientifically sound or potentially biassed towards a favourable bioequivalence outcome. Provide adequate justification for the selection of samples used for reanalysis	19	7.5	
11.4.1. The biostudy submission consists of missing data files required for statistical analysis. Submit the missing data files	12	4.7	
11.4.1. Indicate how sampling deviations were handled in the statistical analysis	11	4.3	
11.4.1. Correct/justify the statement in the PI under pharmacokinetic properties where it is stated that peak plasma is reached after a specified time, while data presented in the biostudy show peak plasma is reached well within a different time	19	7.5	
11.4.1. Address and justify for the high point estimates that have been obtained on the results	21	8.3	

Table 3 (continued)

Deficiencies Clinical study report Study design	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
11.4.1. Provide a justification of the extended bioequivalence criteria of 80–125%	22	8.7	
14.2. Provide adequate justification for subjects that are excluded from the statistical analysis	48	19	
14.2 The matrix effect should be evaluated by analysing at least 3 replicates of low- and high-quality controls (QCs), each prepared using a matrix from at least 6 different sources/lots. The accuracy should be within ± 15% of the nominal concentration and the precision (percent coefficient of variation (%CV)) should not be greater than 15% in all individual matrix sources/lots as per International Council for Harmonisation (ICH) acceptance criteria			11
14.2 Provide the complete statistical software printouts of the analysis made on log transformed data for AUC0-t and Cmax to help justify your findings reported in the ANOVA table			4
14.2 The statistical output of Statistical Analysis Software (SAS) system in appendix 16.1.9.2 does not include the calculation of the 90% Confidence interval (CI) for the ratio test/reference of the primary pharmacokinetic parameters when the conventional ANOVA with subject, sequence, period, and subject (sequence) factors are analysed. Provide new statistical analysis including the raw SAS output taking into account the recommendations above			8
14.2. Submit the calculated point ratios of the AUC0-t, AUC0-inf, and Cmax	23	9.1	
16.1.11. Provide a discussion of the study results with available literature references	12	4.7	10
Other	14	5.5	
	253		33
Inspections			
16.1.8 Provide a GMP/GLP compliance declaration by the laboratory, including reference to the availability of validation records of test methods and procedures for and records of calibration of instruments and maintenance of equipment	24	23	
16.1.8 Provide auditing and monitoring activities that took place in relation to the studies undertaken	25	24	15
16.1.8 Confirm that the Sponsor and investigational sites, facilities and laboratories, and all data (including source data) and documentation and reports concerning the data including participant files are available for verification by the Inspectorate and indicate the facility where all the relevant study documentation is available for inspection by the Good Clinical Practice (GCP) inspectors	47	44	10
16.1.8 Submit a declaration that all the biostudy documents are available for inspection by the Inspectorate and indicate the facility at which they may be inspected	17	16	7
Provide the executed Batch Manufacturing Records (BMR) for the biobatch used in the biostudy			9
Ensure that the Bioequivalence Trial Information Form (BTIF) is adequately and accurately completed to reflect the same data as on the submitted dossier			15
Ensure that all documents are adequately bookmarked with appropriate titles/document names			10
Other	10	9.4	
	106		66

where necessary. The complete list of deficiencies for this component is included in Table 2. In the case where the reference product used in the biostudies is not procured in South Africa (SA), SAHPRA requires a comparative dissolution study report between the foreign reference product and the SA innovator product to confirm equivalence [21]. The results of the biostudy test product are therefore used to determine the dissolution specification for the product in Module 3.2.P.5.1. The deficiency where an incorrect or unacceptable dissolution specification is proposed (18%) for the final product is very common and leads to the back and forth communication between the applicants and the authority thus delaying registration. The dissolution specifications should be based on the results of the biostudy test product since the manufacturer needs to ensure that the manufacture of the proceeding batch continues to meet the standard of the biostudy test product. If the product is unable to meet these specifications in the stability results, it illustrates the deterioration of the quality of the product which should therefore be addressed by

Table 4 Common deficiencies witnessed in aspects relating to the reference and test product including formulation comparisons

Deficiencies Formulation	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
Confirm that the formulation being applied for is the same as that of the biostudy test product. The data should include unit formula, manufacturing procedure, equipment, site of manufacture, source of raw material, overall product specifications, and other relevant information	41	26	6
Provide a comparison of the qualitative formulation of the test and reference products	21	13	2
Provide justification for the major differences observed in the formulation for the test and reference products	22	14	
For studies five years and older, submit data to confirm that the product being applied for is identical to the test product used in the bioequivalence study. The data should include but not be limited to the following: •Unit formulation, manufacturing procedure, and equipment •Site of manufacture of final product and manufacturer of the API •Overall product specifications and •Other relevant information	67	42	6
Other	07	4.4	
	158		14
Details of the reference and test products			
Provide a justification for the use of the biostudy reference product fully complying with the requirements stipulated in the SAHPRA guideline	48	12	5
The potency and/or content uniformity data for the test product were not submitted	33	8.5	
Provide further literature information to support the proposed reference product	13	3.4	
Provide a justification for the proposed batch size, which is smaller than the recommended batch size in accordance to the biostudy guideline	33	8.5	6
Provide detailed CoAs for the biostudy reference and the corresponding innovator product in South Africa which include the dissolution, assay, and impurity results	13	3.4	20
Evidence to show that the reference product used in the study is equivalent to the innovator product registered by SAHPRA must be submitted	54	14	4
Submit the corrected complete overview 3.2.R.1 according to the guideline	25	6.4	
The biostudy test batch and that used in the validation and stability batches are from two different manufacturing sites. The equivalence or essential similarity of the two products manufactured by the stated final product manufacturers has not been adequately addressed and is not accepted. Demonstrate essential similarity between the product manufactured by manufacturer 1 and the product manufactured by the final product manufacturer being applied for, i.e. manufacturer 2	15	3.9	
Provide certified copies of invoice/ purchase documents as proof of receipt of the reference product and South African (SA) innovator product used in the bioequivalence study as well as copies of immediate container label and carton which visibly includes the name of the product, name and address of the applicant, batch number, and expiry	19	4.9	2
The shipment and storage of the reference product should be submitted and properly documented	34	8.8	6
Ensure and confirm that the final product release and stability specifications for total impurities are in line with the impurity profile of the reference product	19	4.9	
Batch size, manufacturing date (test product), and expiry date of the biostudy reference and test products must be included	39	10	
Submit CoAs of the foreign reference and the SA innovator products	33	8.5	
Other	10	2.6	14
	388		57

investigating the product development. The justification of changing the dissolution specification based on the stability results is therefore not acceptable.

Dissolution testing can also be used to support the bioavailability of a new pharmaceutical product in which case a biowaiver is requested. The frequent deficiency on the

Table 5 Deficiencies observed by SAHPRA on the bioanalytical report submitted for the bioequivalence studies

Deficiencies Bioanalytical report issues	Frequency (2011–2017)	% in the respective component (2011–2017)	Frequency (2020–2021)
The bioassay validation report must be submitted	12	8.2	
Submit the analytical method report and bioanalytical method standard operating procedure (SOP) which could not be located	36	25	10
Submit the detection and quantification limits of the parent and metabolites of the analytical methods	34	23	
The biological matrix used was not clearly indicated in the report	12	8.2	
The reasons for the high rate of failures of control samples could not be located. This should be justified	23	16	
Provide a discussion of the preparation of the calibration curve standards and the quality control samples	20	14	
Other	10	6.8	
	147		10

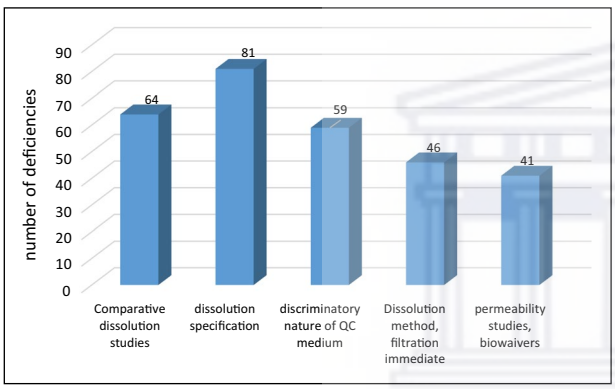


Fig. 4 Distribution of the five highest deficiencies observed in the in vitro dissolution testing and biowaivers section

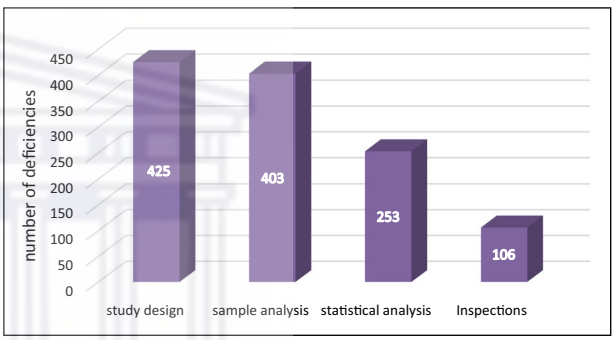


Fig. 5 Categorisation of the deficiencies in the bioequivalence clinical study reports

biowaivers was on the request of permeability studies to confirm BCS class I or III. Class I and III APIs are considered highly soluble, while Class II and IV have low solubility. With regard to permeability, Class I and II have high permeability, while III and IV have low permeability. Thus, when a BCS-based biowaiver is requested, it is imperative to support the classification of the API with solubility and permeability studies.

Clinical Study Reports

The conduction of bioavailability studies in humans requires that the FPP be administered to a group of individuals and that the time-course of the concentration of the API in the blood be evaluated [28]. The clinical study reports provide a summary of this scientific data. The clinical study report section is divided into four sub-categories based on the common deficiencies observed. These are further described in detail below and the quantification is depicted in Table 3 and Fig. 5.

Study Design

Study design involves the adequacy and appropriateness of the bioequivalence study design selected covering aspects such as the following:

Selection and appropriateness of single-dose, multiple dose or steady-state studies.
Selection and appropriateness of a two-period, two-sequence, crossover design or a parallel design.
Appropriateness and acceptability of the dose selected to conduct the biostudy.
Selection and appropriateness of the study selected to investigate food effects, if relevant, thus whether under fed or fasting conditions depending on the molecule and medicine under investigation.

Acceptability of the number of subjects proposed to conduct the study.

The study design selected for 91% of the 316 applications was simple single-dose, randomised, two-treatment, two-period, crossover biostudies. The most common experimental plan for comparing the bioavailability of two products is a simple crossover study as outlined above [5–8]. In this design, each individual in a group of subjects receives both FPPs at different times so that there is a direct comparison of the absorption of each product in the same individual. Special care must be taken to allow sufficient time to elapse (washout period) between the administration of the first and second final product so that there are no carryover effects [5]. In order to minimize the influence of such effects on the outcome of the study, good experimental design requires that each final product be administered initially to half of the subjects, hence this being the most common study design selected. There are however special cases where this study design cannot be employed depending on the behaviour of the API under investigation, in such cases a different study design such as parallel design, steady-state studies, multiple dose studies are selected [5]. The study design deficiencies as depicted in Table 3 included deviations witnessed in the protocol which differ from the approved protocol (8.2%). The protocol should be approved by a reputable ethics Committee or Institutional Review Boards (IRB) before the study commences, should there be any amendments or deviations to the protocol these should also await approval by the Committee. The deficiencies noted were not stated in the approved version of the protocol, and therefore, the latest protocol was required. Other deficiencies also involved applicants not including the Ethics approval letter (6.1%). Ethical approval is an integral part of the research process and aims to protect both researchers and participants who should have enough details to make informed and autonomous decisions [29]. The details on the study design also did not include critical aspects such as demographic details of the subjects i.e. age, race, ethnicity, body mass and description of the gender of subjects used in the study (12%), the inclusion and exclusion criteria employed (3.3%), and instances where an incorrect study has been included between the fed- and fasting study (7.5%). If the reference product's labelling instruction includes that the product should be taken with food or an extended-release product is applied for, a fed study should be submitted [30] .

Sample Analysis

The third component with the highest deficiencies is sample analysis comprising 16% as seen in Fig. 3 with the deficiencies listed in Table 3. This covers issues observed relating to the sample analysis procedure such as the appropriateness of the sample collection and sampling times selected, stability of the plasma sample, assurance that the Clinical Research Organisation (CRO) follows Good Clinical Practice in the sample collection and storage, and appropriateness of the bioanalytical analysis of the samples [5] .

The most frequent deficiencies in the Sect. (41.9%) are on sample handling before the analysis. This is a critical aspect in biostudies since during storage the final product may undergo chemical degradation, adsorption on the walls of the container, etc., thus, storage of plasma samples is important [5, 6]. Complete information on the long-term stability data of the samples was either not included or insufficient (15%), or details on the transportation and transport temperature recordings of the sample from the clinical site to the analytical site (9.7%), or the details of centrifugation of the blood samples (6.2%) or the details of the treatment of the frozen samples before testing (11%) were not provided. These are critical parameters that need to be safeguarded and adequately documented to ensure that the quality of the samples is maintained throughout the biostudy. Other deficiencies witnessed include the submission of chromatograms which should be 20% of consecutive subjects involved in the study. There was also a deficiency observed on the request to analyse samples for subjects who initiated the study and dropped out or were withdrawn due to adverse events (7.7%). This remains a requirement in order to obtain a complete safety analysis.

Statistical Analysis

This involves assessment of the issues associated with the statistical calculations of the pharmacokinetic parameters used to deduce bioequivalence. The statistical method for testing relative bioavailability is based on the 90% confidence interval for the ratio of the population means (Test/Reference) for the parameters under consideration. The pharmacokinetic parameters should be analysed using statistical software called Analysis of variance (ANOVA) to attain an acceptance criterion for the main bioequivalence [4, 5]. The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80–1.25 (80–125%) for the investigated parameters in order to confirm bioequivalence.

Deficiencies in statistical analysis accounted for 10% of the biostudies investigated. The most common deficiency was from the lack of justification for the exclusion of subjects from the statistical calculation which constituted 19%. It is important to include the results of all subjects that were dosed from the study to avoid bias. The calculation of the pharmacokinetic (PK) parameters should be accomplished from observed data instead of fitted data. Some deficiencies included incorrect calculations on the PK parameters noted

by the evaluator which required correction. These constituted 11% of the deficiencies in the category.

For the biostudy to be established, 90% confidence interval for the ratio of the geometric least-square means of peak plasma concentration, AUC of test, and reference products should be within 80–125%. [5, 24, 31] Closer limits are considered for products that have a narrow therapeutic index, serious dose-related toxicity, steep dose effect curve, and nonlinear pharmacokinetics within the therapeutic dose range. European guidelines also provide a tightened acceptance interval of 90.00–111.11% for narrow therapeutic index drugs (NTIDs) as well as highly variable products which SAHPRA has adopted [24, 31]. A wider acceptance range is admissible if it is based on a sound clinical justification [6]. This justification was not included in some biostudies submitted with the extended range (10%) and this was requested.

Inspections

Deficiencies on inspection reports of the CRO conducting the biostudy as well as any outstanding audit and monitoring reports for the biostudy are required in order to confirm that the biostudy was conducted in line with Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) requirements. Confirmation that the sponsor, investigational sites, facilities, laboratories, all data (including source data), documentation and reports concerning the biostudy including participant files must be available for verification by the Inspectorate Unit. This was queried and comprised of 44% of the deficiencies in this section as illustrated in Table 3. Over and above the biostudy information being submitted to the authorities, it is critical that the raw and complete data sets for the study be archived for the Inspectorate Unit to request upon inspections.

Aspects Relating to the Reference and Test Products

One of the critical aspects in selecting a reference product is ensuring that the assay content and dissolution data are similar to the test product. For example, the assayed content of the batch used as a test product should not differ by more than 5% from that of the batch used as the reference product [7]. Acceptability of the source of the reference product is also assessed, this should be sourced from an authority SAHPRA aligns itself with, thus all supporting documentation and testing of the test and reference product should be included [5]. Deficiencies relating to outstanding documentation or details regarding the test, foreign reference, and SA innovator product were investigated in this component.

The common deficiencies in this category as highlighted in Table 4 include the request to justify the proposed reference product in accordance with biostudy guidelines and available decision trees on the selection of the appropriate reference product. These comprised 12% of the deficiencies identified in this category. In the case where the reference product is not procured in SA, the following supporting information on the foreign reference product is required:

- The name and address of the manufacturing site where the reference product is manufactured.
- The qualitative formulation of the reference product. (3.9%)
- Certificate of Analysis of the reference product. (8.5%)
- Shipment and storage details of the reference product to the sponsor. (8.8%)
- Copies of the immediate container label as well as the carton or outer container label of the reference product. (4.9%)
- The method of manufacture of the reference product is claimed by the applicant to be the same.
- Procurement information of the reference product:
  - Copy of licensing agreement/s if relevant
  - Distribution arrangements/agreement/s if relevant
  - Copy of purchase invoice (to reflect date and place of purchase) (4.9%) [5]

The above deficiencies were the largest observed in this category and were quantified as 31%.

The bioequivalence study aims to confirm the similarity of two formulations of the test and reference product. Formulation comparison is imperative, as there may be formulation effects, which alter the bioavailability of the test product, and therefore, qualitative comparison with the reference would need to be assessed. There was 42% of the deficiencies depicted in Table 4 requesting the confirmation of similarity between the formulation of the test and reference products as well as any changes which have been made to the biobatch if the submission received was older than five years. The data requirements are confirmation of the following to ensure no significant changes occurred: unit formulation, manufacturing procedure and equipment, site of manufacture of final product and manufacturer of the API, and overall product specifications. This is to ensure that there were no major amendments made to the product which may negatively impact on the quality of the product compared to the biobatch.

Comparison with RW1, RW2, and RW5 Applications (2020–2021)

Tables 2, 3, 4 and 5 also illustrate the similarities on the common deficiencies witnessed in applications finalised between 2011 and 2017 and those assessed between 2020 and 2021. The additional row indicating the frequency of deficiency in 202–2021 shows all the deficiencies that were

identified. This confirms that the standards of assessment have been maintained as the identified deficiencies comprised of more than 80% of the deficiencies already identified in the 2011–2017 sample. The distribution of deficiencies is also similar to that observed in Fig. 3 with dissolution as the highest category (23%) and sample analysis (24.2%) followed by inspections (13.4%). The deficiencies that were observed only in the 2020–2021 applications are largely on the request of Case reports forms and the Statistical Analysis Software (SAS) report for raw data as well as the executed BMR (batch manufacturing records) of the biobatch. These were previously not a requirement. The Case report forms were assessed during inspections as well as the executed BMRs and therefore not incorporated in the quality and bioequivalence assessments; however, these are now requirements by SAHPRA and relevant documents should be included in the dossiers.

Comparison of the Deficiencies with Those of Other Well-Known Regulatory Authorities

Only a few reports have been published on biostudy common deficiencies from other regulatory authorities. The USFDA reported on these in 2012 using Abbreviated New Drug Application (ANDA) applications received between 2001 and 2008 to identify the most commonly occurring biostudy deficiencies [14]. The two most common deficiencies related to dissolution are method and specifications which constitute 23.3% of the applications and bioanalytical method validation and/or report found in 16.5% of the applications [14] .

The USFDA noted that the establishment of an online dissolution method database has helped greatly in improving the quality of the ANDA submissions. Reducing the deficiencies to 15.5% in 2006–2008, thus accelerating the approval of generic products [14]. The observed deficiency on in vitro dissolution testing is comparable to the deficiency recorded as the highest in SAHPRA applications at 18%.

On bioanalytical method validation and/or report, the USFDA found the most frequent deficiencies include a lack of SOPs, no data showing long-term stability of API in frozen samples of biological fluid, and incomplete sets of bioanalytical raw data [14]. These are similar to those observed in Tables 3 and 5 for sample analysis and bioanalytical report issues witnessed by SAHPRA. Issues relating to the lack of inclusion of relevant SOPs in the bioanalytical report and the raw data of the bioanalytical report were observed as 23% by SAHPRA. The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP) and Good Clinical Practice (GCP). The Bioanalytical methods used must have adequate sensitivity and accuracy, as well as selectivity that will make it possible to quantify the API in the presence of its metabolites or of endogenous compounds that may interfere with the determination of the compound in biological fluids [28]. The samples should be well characterised, fully validated, and documented to yield reliable results that can be satisfactorily interpreted [6]. This section, therefore, covers this aspect to ensure the appropriateness of the bioanalysis and reliability of the validated methods.

The other components reported by the USFDA were potency and formulation, unjustified exclusion of subjects, analytical issues, and long-term stability [14]. This confirms the similarity in the quality of evaluation of the submitted biostudies between SAHPRA and the USFDA.

WHO PQTm also conducted a study for applications submitted between April 2007 and December 2010 [15]. The deficiencies observed were categorised as follows: clinical study information, subject sample analysis, audit and monitoring information, statistical calculation, analytical method validation issues, and an unacceptable reference product [15]. The deficiencies were quantified according to the therapeutic category of the submission, for example, 15% of the dossiers on reproductive health (treatment category) included incorrect pharmacokinetic/statistical calculations that required revision and re-calculation. The deficiencies observed from the components mentioned were very similar to those reported in Tables 2, 3, 4 and 5 confirming the similarity of the quality of evaluations. The similarity is also witnessed in the work published by WHO PQTm in 2020 which stipulates an update on the qualitative common deficiencies in the biostudy reports submitted [32] .

Conclusion

The study included the collection of a list of common deficiencies on biostudies from applications finalised over a seven-year period and highlighted the most common deficiencies requested by SAHPRA. In addition, a recent study was conducted which confirms that the standards of assessments have been maintained as the deficiencies reported between 2011 and 2017 are similar to those observed in the 2020–2021 assessments. This, therefore, provides transparency to pharmaceutical companies on deficiencies to address before biostudy submissions are made to SAHPRA. The findings also show that the evaluation standards employed by SAHPRA are similar to other international regulatory agencies such as the USFDA and WHO PQTm. These findings will guide pharmaceutical companies, manufacturers, and CROs in submitting quality biostudies in the future which will thereby allow accelerated access to medicine for patients. This in turn will reduce the turnaround product registration timelines for SAHPRA. Moreover, the deficiencies identified will assist assessors from the different countries to improve on their bioequivalence assessments.

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Author Contributions
LM developed the study design, collected and analysed the data, interpreted the results, and wrote the first draft of the manuscript. ML developed the study design, assisted in collecting and analysing the data, provided guidance for the data collection and analysis, interpreted the results, and reviewed the manuscript. JJ developed the study design, provided guidance on the data analysis, interpreted the results and relevance of the results, and reviewed the manuscript.

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Declarations

Conflict of interest
No conflicts of interest that are directly relevant to the content of this article.

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ORIGINAL RESEARCH ARTICLE

The Implementation of a Risk-Based Assessment Approach by the South African Health Products Regulatory Authority (SAHPRA)

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Abstract

Background An extensive backlog of pending regulatory decisions is one of the major historical challenges that the South African Health Products Regulatory Authority (SAHPRA) inherited from the Medicine Control Council (MCC). Revising and implementing new regulatory pathways is one of the strategic mechanisms that SAHPRA employs to circumvent this problem.

Objectives To alleviate the backlog, the use of a new review pathway termed the risk-based review on the scientific quality and bioequivalence assessments was explored. The objective of the study was to articulate the risk-based assessment (RBA) pathway, to determine robust criteria for the classification of the levels of risk for medicines, and to define the improved process to be followed in the assessment and approval of medicines.

Methods In 2015, an extensive exercise was conducted by SAHPRA to identify the unknown status of in-process applications. The RBA pilot project commenced in 2016 and further piloted in 2021 using the knowledge gained from the 2016 study for optimisation of efficiency.

Results By 2015 the backlog was quantified as 7902 applications in the pre-registration phase. The 2015 project entailed two phases. The initial phase was conducted to identify the status of 3505 in-process applications, which resulted in the registration of 198 applications. The second phase commenced in 2016 on 4397 applications not yet reviewed whereby the RBA approach was explored. With the developed criteria for risk classification and refined end-to-end registration process, the pilot resulted in a finalisation time with a median value of 90 calendar days and a median approval time of 109 calendar days. The throughput of the RBA pilot study conducted in 2021 was 68 calendar days finalisation time for the 63 applications used. These finalisation times are lower in comparison to the 501 calendar days for the current process employed by SAHPRA for the backlog clearance programme initiated in 2019. Both the 2016 and 2021 studies had similar approval times calculated from the date of allocation of scientific assessments. The reported evaluation timelines for both studies were within 6–7 h for a low-risk quality assessment, 9–10 h for a high-risk quality assessment, 7–8 h for a bioequivalence assessment, and 2–3 h for a biowaiver and initial response assessment.

Conclusions The refined processes used in the risk-based pilot studies to alleviate the SAHPRA backlog are described in detail. The process managed a reduction of the finalisation time to 68 calendar days in comparison to 501 calendar days for the current process that was employed by SAHPRA for the backlog clearance programme initiated in 2019. The RBA approach, therefore, reduces the finalisation and approval times for quality and bioequivalence assessments for regulatory authorities without compromising on the quality, safety and efficacy of the medicinal products. In addition, the approach provides a prototype solution to counteract the influx of medicinal product applications received by the regulatory authorities.

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Key Points

The South African Health Products Regulatory Authority (SAHPRA) had accumulated a backlog of 7902 medicinal product applications in the system in 2016, and by 2018, this had escalated to 8220. In addition, a median approval time of 1622 calendar days was reported between 2015 and 2018. The growing application backlog in SAHPRA demonstrates the need for drastic interventions; hence the development of the risk-based assessment approach aimed at alleviating the current and continuously forming backlog by reducing overall approval timelines.

The risk-based assessment approach is a robust end-to-end registration process, which would be a new alternative regulatory review pathway that has been developed to alleviate the backlog and reduce overall approval times. This process includes a risk classification applied before assessments, improved overall registration process, improved evaluation tools, and amended peer-review process. The pilot studies conducted using this new regulatory review pathway confirmed the reduced approval timelines.

1 Background

In the effort to protect public health, access to free or affordable essential medicines is one of the main obligations by Governments to fulfill the right to health [1]. The World Health Organization (WHO) has reported that one-third of the world's population does not have timely access to such medicines and has encouraged countries to amend their national legislation or constitutions to provide for this right [2]. Regulatory authorities are established by Governments with a mandate to safeguard the patients by ensuring that safe, efficacious, and quality medicine is accessible at an accelerated rate [2]. The median approval times by several regulatory authorities are outlined in Table 1 for the period of 2015–2019 [3–6]. The table illustrates the median approval times reported with the lowest as 247 calendar days for 48 applications by the US Food and Drug Administration (FDA) [3], and the highest with a median approval time of 1622 calendar days for 121 New Chemical Entity (NCE) applications by the South African Health Products Regulatory Authority (SAHPRA) [6]. In 2020 a study was conducted by SAHPRA and a median approval time of 790 calendar days was reported for 244 generic applications [7]. Table 1, therefore, demonstrates that SAHPRA has significantly longer approval times compared to other Authorities. The large influx of medicines from pharmaceutical companies due to the emerging pharmaceutical market as a result of the increasing disease burden and the growth of the pharmaceutical generic sector amongst others has made access to medicines a challenge to regulatory authorities in low- to middle-income countries [4, 8].

Regulatory authorities in developing countries such as SAHPRA face a number of resource constraints, with the main one being insufficiently skilled individuals for dossier assessments and manufacturing site inspections. The delays were also attributed to deficient operational processes and increased volume of applications for registration. The long regulatory decision timeframes have serious public consequences, as these delay access to life-saving medicines. In addition, the Medicines and Related Substances Act, 1965 (Act 101 of 1965), Section 22F [9], did not prevent or state how many generics the regulatory authority should register per active pharmaceutical ingredient (API). This Act encouraged 'dossier farming' within the industry, which created a significant backlog within the Regulator [10, 11]. SAHPRA received an average of 1200 applications annually between 2006 and 2015 and the authority could therefore not evaluate all the applications received within the period due to resource constraints and other factors as mentioned above. This resulted in the formation of a backlog of applications, delaying access to medicines for patients.

1.1 South African Health Products Regulatory Authority (SAHPRA)'s Organisational Structure

SAHPRA, with internationally recognised standing, is aimed at facilitating the availability, evaluation and approval of the quality, safety and efficacy of medicinal products and related substances intended for humans and animals. In the years in which SAHPRA (formerly Medicine Control Council, MCC) has been in effect, over 20,000 medicinal products have been registered [12]. SAHPRA assumed the roles of both the MCC as well as the Directorate of Radiation Control (DRC) which were housed at the South African National Department of Health (NDoH) [13]. Subsequently, SAHPRA was constituted as an independent entity that reports to the National Minister of Health through its Board [13]. The organisation is headed by the Chief Executive Officer (CEO) with support from the Chief Financial Officer (CFO), Chief Operating Officer (COO), Chief Regulatory Officer (CRO), and the Human Resource Executive, who all form part of the Executive Committee of the organisation (see Supplementary Online Material (OSM) Resource 1). Within the office of the CRO lies the programmes: Pharmaceutical Evaluation Management (PEM), Clinical Evaluation

Table 1 Median approval times: The reported median approval times from various regulatory authorities between 2013 and 2019

Authority, years	Country	Median approval times (calendar days)	Number of applications
US Food and Drug Administration, 2017–2019	USA	247	48
Health Canada, 2015–2019	Canada	347	30
Australian Therapeutic Goods Administration (TGA), 2015–2019	Australia	351	25
European Medicines Agency (EMA), 2015–2019	European countries	433	27
Swiss Medic, 2015–2019	Switzerland	527	28
Agência Nacional de Vigilância Sanitária (ANVISA), 2013–2016	Brazil	795	138
South African Health Products Regulatory Authority (SAHPRA), 2015–2018	South Africa	1622	121

Management, Inspectorate and Regulatory Compliance, and Medical device and Radiation control as illustrated in the OSM (see OSM Resource 2).

The programmes are in turn subdivided into units responsible for coordination and execution of various activities. Within the PEM programme lies the Pharmaceutical and Analytical (P&A) Pre-Registration Unit. The work of the Unit involves the evaluation of the quality and efficacy (bioequivalence) aspects of products submitted as a dossier in the Common Technical Document (CTD) format by pharmaceutical companies. The clinical aspects, i.e., to confirm that the labelling of the generic products is in accordance with the registered innovator products and efficacy of the NCEs is evaluated by the clinical evaluations' pre-registration unit. Inspection of manufacturing sites is conducted by the Inspectorate Unit. Appropriate naming and scheduling status of the products is conducted by the Names and Scheduling Unit (OSM Resource 2) [14]. The PEM, P&A Pre-Registration Unit has proven to be the rate-limiting part of the registration process since the bulk of the evaluations that include quality and bioequivalence assessments are conducted in the unit. The growing application backlog in SAHPRA demonstrates the need for mechanistic interventions such as the RBA approach to alleviate the backlog by reducing the scientific evaluation timelines.

1.2 Risk-Based Assessments

Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm [15, 16]. The evaluation of risk requires the identification of a hazard and the likelihood of its occurrence [17, 18]. In pharmaceuticals, managing risk is of prime importance to ensure that the patient gets medicines/products of acceptable safety, efficacy and quality, according to WHO standards, as set out in WHO guidelines [15, 16, 18]. Risk assessment is applied on the diseases to be treated as well as in the technology involved in the development and manufacture of the pharmaceuticals. The technology level affects the feasibility of the manufacturing process, including packaging and quality control testing, the overall quality assurance system of the manufacturer, as well as the capacity of the local National Regulatory Authority (NRA) to effectively assess the resultant dossier [19]. Thus, one of the main factors that affect the quality of the product is the quality of the manufacturing process that produces both the API and the Final Pharmaceutical Product (FPP). Hence, sound and reliable processes produce quality products. Quality cannot be tested into the product, but it is to be built into the product during its manufacturing.

In order to expeditiously provide the public with access to quality, safe and efficacious medicines, a risk-based approach to the assessment of a pharmaceutical product should be explored. This approach is discussed in the publication by the Centre for Innovation in Regulatory Science (CIRS), which describes measures that regulatory authorities should consider to apply in the risk-based approach [20]. The review highlights the importance of the level of experience of the evaluators used and the assessment tools employed during assessments to ensure that there is no compromise in the quality and that all critical components are appropriately detailed in the assessments. The component of the level of experience of the evaluators used in the assessments of the dossiers is supported by the results of the project previously undertaken by SAHPRA. In July 2009–September 2010, the Regulator had a backlog of 2114 applications and initiated a project aimed at alleviating the backlog of applications. Only 16.6% of the products were registered while 1.6% were rejected and 6% were cancelled or withdrawn [21]. The reason for the unsatisfactory results were due to substandard reports that were submitted by inexperienced evaluators, which required re-assessment by the PEM, P&A Pre-Registration Unit. This, therefore, illustrates the importance of experienced evaluators who are well knowledgeable with vast experience in the field of regulatory science and scientific assessments with a

thorough scientific understanding of the benefit and risk involved [22].

The second component mentioned in the CIRS article is the scientific review tools, which play a major role in the efficiency and effectiveness of the authority and could result in delayed registration, depending on the tools and strategies used to conduct scientific assessments [20]. In the effort to attain shorter registration turnaround times, authorities need to incorporate the benefit-risk factors at the assessment stage. This entails adopting and implementing a systematic process of assessment of the dossier that builds quality into the assessment. Understanding what critical information is needed to reach an acceptable level of certainty to resolve scientific questions and meet regulatory standards for registration is important [22]. Therefore, identification of critical aspects in the Common Technical Document (CTD) and International Conference for Harmonisation (ICH) E3 bioequivalence structures is paramount.

Risk-based assessments, involving the thorough evaluation and reporting of only critical sections in the dossier that affect the quality of the specific product, are now commonly applied by a number of regulators [23, 24]. By applying a risk-based assessment, the following are questions to be considered:

- What is the risk to the user and how serious is it?
- What is the weight of evidence that supports that a risk exists?
- What is the expected and the actual benefit for a specific patient?
- Will the risk intensify over time?
- Does the risk outweigh the benefit? [25]

Both practical and theoretical knowledge of regulatory assessment is desirable to achieve a good understanding of the issues likely to be associated with the product under review and identify the risk and the critical aspects [16, 17, 26].

1.3 Objectives

The objectives of the study were fourfold:

- quantification of the backlog that developed within SAHPRA,
- defining risk and developing robust criteria for risk classification of products,
- developing a new robust mechanistic review pathway called the risk-based approach and evaluating the review process based on the results of the pilot study conducted,
- providing a detailed description of the implementation of the RBA process aimed at reducing the scientific evaluation timeframes and thereby reduce the overall registration turnaround time within SAHPRA.

2 Methods

2.1 The 2015 Backlog Project

The backlog project undertaken in 2015 was divided into two phases. The initial phase entailed the identification of the status of in-process applications and the second phase was on applications not yet allocated for review. The extensive planning of the backlog project required the collaboration of all units involved in the registration process, which resulted in the formation of a backlog working group. The status of most of these applications by the different units was unknown and required an extensive investigation in order to obtain the exact status of the products. The list was created, and the documents were titled in the backlog spreadsheet (Microsoft Excel® 2016, Windows 10), which consisted of all the in-process applications in the pre-registration phase.

2.1.1 Obtaining the Status of In-Process Applications

SAHPRA initiated an overtime project during weekends to allow for the extraction of the information from the registry files, brown files, dossiers, Committee meeting minutes, applicants, etc. For instance, if the product status is unknown, obtaining the information involved the following sequential order, and if it is not obtained in one document area, it moves to the next:

- the brown files, which should consist of the communications sent to the applicant;
- the Committee meeting minute documents, which consist of the history and dates of each application discussed and the outcome thereof;
- registry files, which contain the full history of documents received from applicants were checked to see the available history;
- if no information is obtained from the above, the applicant was contacted for a re-submission.

It was discovered from this process that a number of units were not aligned when it comes to evaluations, i.e., one unit would have finalised an application while another unit was only at the initial evaluation stage. Therefore, although there might be finalisation in one

unit, registration cannot be executed because another unit has not finalised the application. When documentation was obtained from the above four areas, it was promptly shared or communicated with the applicant to facilitate review and accelerated the registration process.

2.2 New Applications—Risk-Based Review

The pilot project was initiated with the available new applications on a first-come first-served basis. During this time, the Authority was allocating applications received in 2011, while those received prior were either registered or in the pre-registration phase under review. There were 208 line-item applications, which equate to 150 master applications that were received towards the end of 2011–2012 that were not yet reviewed. These were used in the pilot study as they were next in the queue to ensure fairness to all applicants. The intent of the pilot study was to observe the effects of the proposed process with the aim of implementing it to all applications upon assessing the results. There were two separate phases within the project, the first one for the in-process applications that was initiated in 2015, and the second phase for the new applications initiated in 2016. For the 2021 pilot study, the applications that were next in line for allocation were in re-submission window eight (8), and were therefore used for further optimisation and efficiency of the process.

3 Results

3.1 The 2015 Backlog Project

For quantification of the backlog, Figs. 1 and 2 illustrate how the backlog resulted within SAHPRA in the period 2006–2015. For example, in 2010, SAHPRA received 1204 applications and could only register 425, resulting in 779 backlog applications. The collective backlog by May 2016 was 7902 applications and only 3779 were registered between 2006 and 2015 [27]. There were 3505 in-process applications in the initial phase for identification of their status and 4397 applications not yet allocated for review in the second phase [27]. The results from these two phases were investigated and the outcomes are detailed below.

The backlog pilot project on the in-process applications succeeded in the registration of 198 products, while 189 products were withdrawn by applicants after analysis of the business need. For the 2015/2016 cycle, in quarter one (April–June 2015), 34 products were registered, in quarter two (July–September 2015), 43 products were registered, in quarter three (October–December 2015), 88 products were registered, and in quarter four (January–March 2016), 33 products were registered. The project achieved the clearance of 387 products in 2015 as well as obtaining the status of all the applications that were pending registration (see Fig. 3). The 448 registered applications include 250 registrations via the normal process that were not part of the pilot project.

Figure 3 shows the grouping of the status of applications obtained during the 2015 project. The exercise managed to identify and classify the status of all pending applications, a task that was historically difficult for the authority. The authority did not have a central database or tracker for applications and relied on individual units to monitor the applications, which led to misalignment within the units as they were not communicating with one another on evaluations of applications. As a result, there were 707 applications with P&A finalised status, and 519 applications with Clinical finalised status. There were also 244 applications with P&A and Clinical finalised status; however, these could not be approved since the Inspectorate and Names and Scheduling Units had not finalised the applications. These applications were classified as 'the low hanging fruits' since they were near registration and only required finalisation by one or two units. For the P&A finalised applications, it meant that other units needed to focus on those products to attain registration and vice versa for the other finalised groups.

3.2 Risk-Based Assessment Process

3.2.1 Registration Process

Once the status of the pending applications was concluded, the authority moved on to reviewing the evaluation pathways for the new applications. Strategic planning over a 2-year period between 2014 and 2016 was employed in order to alleviate the backlog by improving the existing registration process. It was important that the process be revisited to ensure that the proposed process is seamless and avoids the

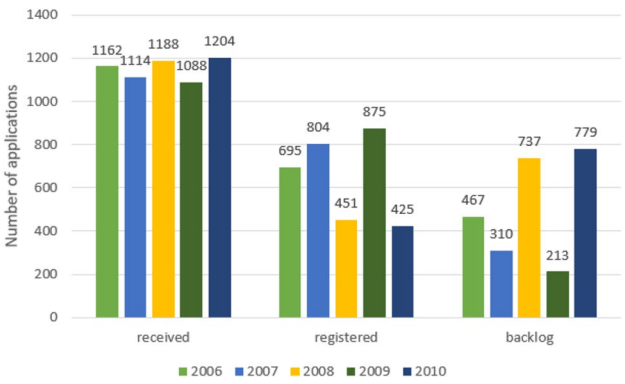

Fig. 1 A depiction of the registered products within South African Health Products Regulatory Authority (SAHPRA) between 2006 and 2010 resulting in the backlog

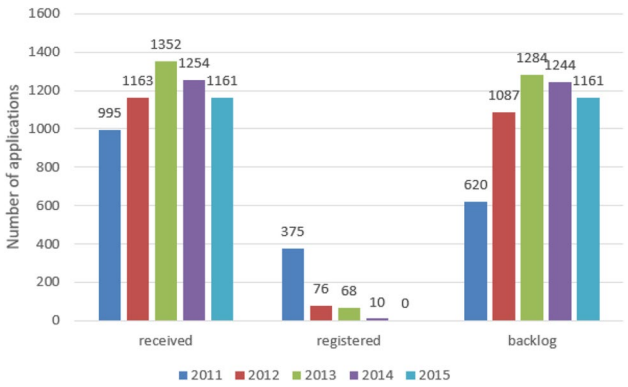

Fig. 2 A depiction of the registered products within South African Health Products Regulatory Authority (SAHPRA) between 2011 and 2015 further exacerbating the backlog

formation of a backlog in future. The overall developed and refined process as detailed in Fig. 4 involved changes to the previous practices, thereby promoting efficiency and timely access of medicines to patients.

3.2.2 Risk Classification

Upon re-assessment and refining of the two pilot studies for scale-up and implementation in the BAU section of SAHPRA, the risk classification template was refined through consultation with numerous experts and extensive literature review [19, 28–46]. This resulted in the developed risk classification template (Table 2) used for determining the risk of generic products including essential medicines that qualify to be included in this pathway. The model and structure detailed in the concept paper by the WHO was used, in which a scoring is assigned for each aspect to consider and the overall scores was used to determine the risk class of the product using Table 2 [19]. Table 3 indicates the risk classification matrix employed to deduce the overall outcome. Note that before the 2021 pilot study, it was decided that NCEs, biologicals medicines or biosimilars will not be reviewed using this pathway; a full review would be conducted for these applications.

For the products that were part of the pilot studies, the overall risk classification of products was deduced using Table 3 and overall classification identified.

From the findings reported, evaluation templates were designed according to the level of risk for evaluators, clearly identifying critical sections for the different risk classifications. The templates are included as OSM Resources 3 and 4. The sections that are critical are identified in the Discussion section.

3.2.3 Summary of Results on the Risk-Based Approach

Table 4 provides a summary of the results from the backlog pilot project conducted in September 2016 and September 2021 by SAHPRA. There were ten evaluators used in both pilot studies; for the 2016 pilot, seven were external evaluators and three were internal evaluators, while for the 2021 pilot study eight were external and two were internal evaluators. The reported finalisations times and approval times for both studies are depicted in Fig. 5, which illustrates the median values for the finalisation times in both pilot studies as well as the reported minimum and maximum times. A number of outliers are witnessed in the depictions for applications that took longer to finalise than the other applications due to applicants not addressing the queries as required. Delays in approval times after finalisations are attributed to other units not yet finalising the products, hence delaying registration. This also illustrates how the rate-limiting PEM, P&A pre-registration unit managed to finalise applications before other units, which has always been a historic problem.

Table 5 provides the outcomes of the risk classification of the products that were in the two risk-based assessment pilot studies. This shows that the classification largely depends on the dosage form of the product and the manufacturing process of the final product as stated by Tran et al. [32].

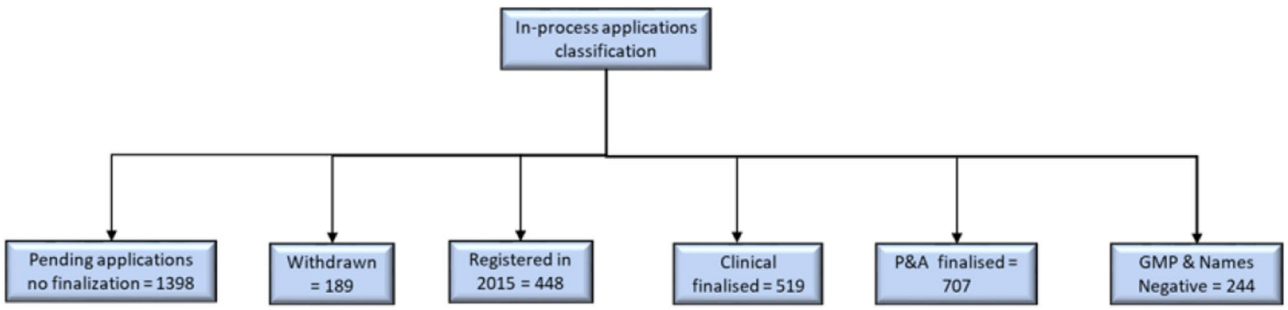

Fig. 3 Status classification and quantification of the in-process applications once Phase 1 of 2015 project was concluded. *GMP* Good Manufacturing Practice, *P&A* Pharmaceutical and Analytical pre-registration Unit

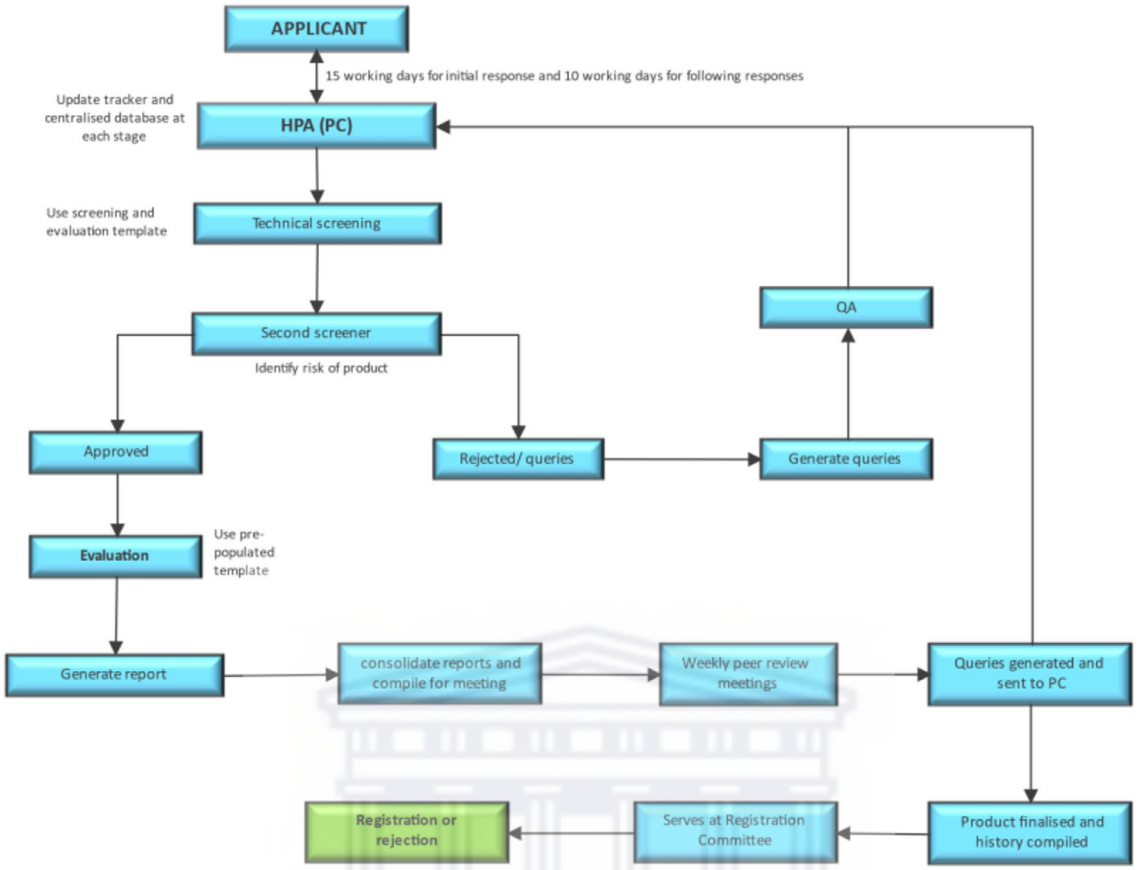

Fig. 4 Proposed risk-based assessment end-to-end registration process in the Pharmaceutical Evaluation Management, Pharmaceutical and Analytical Pre-Registration Unit for quality and bioequivalence assessments. The process is repeated for the response cycle and only 10 working days are allocated for the second response cycle. *HPA* Health Products Authorisation, *PC* Portfolio Coordinator

3.2.4 Assessment Timelines

The assessment times were recorded for each application. Figure 6 illustrates the median times obtained for assessment of a simplified low-risk application, high-risk application, bioequivalence assessment, biowaiver assessment and a response assessment. For the 2021 pilot study, four of the applications were omitted from the calculations since two were clones of already registered products and two had pre-approvals by the PEM, P&A pre-registration unit before February 2018, and only minor variations were submitted for review. Hence, the total n value was 59, which is 38 low-risk applications and 21 high-risk applications (Fig. 6). It should be noted that a Phase 2 pilot study was conducted in 2022 in order to monitor upscaling of the number of applications to 156; a different template was used and is included as OSM Resource 5. This was pre-populated by the applicant and used as an evaluation template for quality assessments. The reported evaluation times for the second phase in 2022 was a median time of 14 h for high-risk and 10 h for low-risk applications. The BE, biowaiver and response assessments remained the same as the templates in the 2021 pilot study results.

4 Discussion

4.1 2015 Backlog Project

For the initial phase of the project, the identification of the status of each pending application proved to be a success as it allowed for better coordination and management of applications. In addition, obtaining the status of the finalised products from each unit provided a list of applications that each unit can focus on (Fig. 3). Although allocation was conducted at the same time by the Health Products Authorisation (HPA) section, the units did not initiate the evaluations at the same time. With the improved process this

Table 2 Risk classification template: The designed risk classification template used to determine the overall risk class of a generic medicinal product

Item no.	Aspects to consider	Dosage form affected	Risk assessment guide	Comments
	RELIANCE			
	API			
RA1.	CEP/CPQ submission, internal and external reports	All	CEP/CPQ submitted = 1 if not, are reports from the Authority's database available = 1 if not, is external reliance claimed = 1 if not, go to RA2	
RA2.	Specifications	All	CEP/CPQ submitted = 1 if not, are reports from the Authority's database available = 1 if not, is external reliance claimed = 1 if not, is pharmacopoeial monograph claimed = 1 if not, is pharmacopoeial monograph available and not claimed = 2 if not, is pharmacopoeial monograph not available = 3	If a monograph is available and not claimed, limits for degradants should be pharmacopoeial and process-related impurities should be according to ICH Q3A (R2) guideline. Applicant to provide cross-validation data to demonstrate equivalence
	FPP			
RF1.	Internal and external reports	All	Are reports from the Authority's database available = 1 if not, is external reliance claimed = 1 if not, go to RF2	
RF2.	Specifications	All	If the above is not applicable, are reports from the Authority's database available = 1 if not, is external reliance claimed = 1 if not, is pharmacopoeial monograph claimed = 1 if not, is pharmacopoeial monograph available and not claimed = 2 if not, is pharmacopoeial monograph not available = 3	If a monograph is available and not claimed, limits for degradants should be pharmacopoeial and process-related impurities should be according to ICH Q3B (R2) guideline. Applicant to provide cross-validation data to demonstrate equivalence
	BE			
RB1.	Internal and external reports	All	Are reports from the Authority's database available = 1 if not, is external reliance claimed = 1 if reports not available = 2	
Decision point	If full internal or external reliance is identified, the risk assessment is herewith concluded If partial reliance, such as in RA1, RA2, RF1 and RF2, is identified and reliance pathways are not identified, then move to non-reliance mechanisms below			

Table 2 (continued)

Item no.	Aspects to consider	Dosage form affected	Risk assessment guide	Comments
	NON-RELIANCE			
	API			
A1.	Solubility BCS class	Solid oral dosage forms	BCS Class 1/3 = 1 BCS Class 2/4 = 4	If bioequivalence is submitted for BCS class 2/4 and equivalence is proven, then score = 2
A2.	Hygroscopicity	Solid oral dosage forms	Slightly to not hygroscopic = 1 Highly hygroscopic = 2	CCS is critical. If Alu-Alu or any blisters are used = 1 When bottles (e.g. HDPE) are used as CCS = 2
A3.	Particle size	Solid oral dosage forms	No micronisation necessary = 1 If micronisation is conducted and specifications included = 1 If micronisation is required but not controlled (this will be requested) = 2	To check if micronisation is required, refer to ICH 3QA decision tree #3 (Only if API is BCS class 2/4); Not applicable if API is fully dissolved during FPP manufacture
A4.	Polymorphism	Solid oral dosage forms	Amorphous form = 1 Consistent polymorphic form manufactured and controlled = 1 Different polymorphic forms produced as a ratio = 2	Only if API is BCS class 2/4, Not applicable if API is fully dissolved during FPP manufacture
A5.	API load (concentration)	Solid oral dosage forms and semisolids	High API load (more than 5% of the total mass) = 1 Low API load (less than 5 % of the total mass) = 2	For low API load, if the manufacturing process involves wet granulation, uniformity is assured = 1 If manufacturing process involves direct compression, in-process controls should be checked for content uniformity = 1 If content uniformity is not conducted, it should be requested and proven = 2
A6.	Therapeutic index	All	Wide therapeutic index = 1 Narrow therapeutic index, high load = 4 Narrow therapeutic index, low load = 5	Examples of narrow therapeutic index APIs = chloramphenicol, lithium, carbamazepine, phenytoin, digoxin, warfarin, rifampicin, phenobarbital, theophylline.[b]
	Repeat for different APIs, if present			
	FPP			

Table 2 (continued)

Item no.	Aspects to consider	Dosage form affected	Risk assessment guide	Comments
F1[a]	Type of dosage form as per dosage form classification (Tran *et al.* [32])	All	Non-sterile solutions = 1 Immediate release solid oral dosage forms = 1 Powders for suspension, not sterile = 1 Semi-solids (ointments and creams) = 1 Sublingual = 2 Buccal = 2 Modified release solid oral dosage forms = 4 Solid oral, immediate release dosage forms for treatment of chronic illnesses = 3 Transdermal = 4 Sterile products = 4 Injectables (products injected directly into the systemic circulation) = 4 Metered-dose inhalation (applied directly to the site of action) = 5	
F2[a]	Complexity of the manufacturing process	All	**Non-sterile solutions** Measuring; mixing blending = 1 **Immediate release solid oral dosage forms**, Compression (tablet); granulation (dry and wet); milling; measuring; mixing blending; coating; drying; encapsulation (hard gel) = 1 **Powders for suspension, not sterile** Milling; mixing blending; measuring = 1 **Semi-solids (ointments and creams)** Emulsification; mixing blending, Deaeration; heating, cooling; measuring = 1 **Sterile products, injectables** Aseptic filling-traditional method; form-fill seal, isolation, filtration; lyophilisation, mixing blending, terminal sterilisation, validation, in-process and testing conditions = 4 **Modified release solid oral dosage forms** Compression (tablet); granulation (dry and wet); milling; measuring; mixing blending, rate-controlling materials, release system; coating; drying; encapsulation (hard gel) = 4 **Transdermal** Active deposition; coating; extrusion, mixing blending, drying; measuring, primary packaging is critical to dose delivery = 4 **Metered-dose inhalations** Assembly; filling, Micronisation = 5	

Table 2 (continued)

Item no.	Aspects to consider	Dosage form affected	Risk assessment guide	Comments
F3.	Composition in relation to the reference product	All	If qualitative composition of the reference product is the same = 1 If qualitative composition differs from reference product = 2	For qualitative composition that differs from the reference product, assess API-excipient compatibility studies for excipients not in the reference product
F4.	Excipients	All	Well-known and pharmacopoeial = 1 Novel = 5	A DMF is required for a novel (non-pharmacopoeial) excipient
F5.	Container closure system (CCS)	All	If CCS is the same as the reference product = 1 If the CCS is critical to accurate dosing = 5 (e.g. metered-dose inhalers) If the manufacturer cannot use the CCS as required by reference or other generic products = 2	For CCS that is not identical to the reference or other generic products, assessment of the stability data will prove suitability of container = 1
	Repeat for other FPP manufacturers, if present and different			
	BE			
B1.	Bioequivalence and comparative dissolution with the reference products	Solid oral dosage forms	Biowaiver submitted = 1 BE and dissolution submitted and bioequivalence proven = 2 If the API(s) is known for bio-inequivalence problems = 4	To confirm equivalence check section under results on the BE template to confirm a confidence interval of 80 – 125 %

Five-point risk scoring scale: 1–very low, 2–low, 3–medium, 4–high, 5–very high

API Active Pharmaceutical Ingredient, *BCS* Biopharmaceutics Classification System, *CEP* Certificate of Suitability, *CPQ* Certificate of prequalification, *DMF* Drug master file, *ICH Q3A* International Conference for Harmonisation Q3A, *ICH Q3B* International Conference for Harmonisation Q3B, *HDPE* high-density polyethylene.

[a]If F1 and F2 are scored as 4, then application is high risk as these aspects carry more weight

[b]For the comprehensive list see reference[47]

[c]The scores for all rows are assessed once template is completed and Table 3 used to obtain overall classification

RA# reliance for API section, *RF#* reliance for FPP section, *RB#* reliance for BE section, *A#* aspect to consider under API section, *F#* aspect to consider under FPP section, *B#* aspect to consider under BE section

Table 3 Deduction of overall risk classification: The risk classification matrix employed to deduce the overall outcome

Outcome of risk assessment	Risk classification
Any one aspect scoring 5	High risk
Any three aspects or more scoring 4 or more	High risk
Any four aspects or more scoring 3 or more	High risk
Any three aspects scoring 3, rest 2 or below	Low risk
Any two aspects scoring 3, rest 2 or below	Low risk
All aspects scoring 2 or below	Low risk

would be alleviated as communication to the applicant will be synchronised for all the applications.

4.2 New Applications—Risk-Based Assessments

The planning of Phase 2 of the 2015 backlog involved engagements with other stakeholders for the success of the project. The stakeholders, such as the applicants and the Expert Committees, held a wealth of knowledge regarding processes, historical information, industry insight, and in the planning and execution of the project for new applications. It was therefore imperative that they were consulted in the decision-making of the project to allow for a seamless process to occur. The proposed process was outlined, and modifications were made where necessary until a consensus was reached to initiate the pilot project.

The proposed process was communicated with all stakeholders involved, which included the CEOs of the pharmaceutical companies in the pilot study, the P&A Expert Committee Members and Unit, the Clinical Evaluations Expert Committee Members and Unit, the members of the MCC Registration Committee, and the Industry Technical Group (ITG). It was agreed that all new applications not yet reviewed should be resubmitted to facilitate review. This is because the submission for these products were between 2011 and 2012, thus the information in the dossiers was outdated. It was observed that the frequent recommendations for the old applications, since 5 years had lapsed, were on updates of the stability data, updated Certificate of Suitability (CEP), changes in the methods of synthesis, changes in the API manufacturers, changes in the FPP manufacturers, etc. This meant that several changes had occurred to a product over time, and in some instances, the product was considered non-existent as the final product manufacturers were no longer in business or were no longer manufacturing it. Thus, after registration, the applicant would apply for post-registration amendments, and by registering the products that essentially no longer exist, MCC was shifting the work to the Post-Registration Unit without eliminating the burden the authority faced. Hence, applicants were requested to uplift, update and re-submit the paper documents. Uplifting of the paper dossiers was conducted 2 months prior to the re-submission date, which gave applicants enough time to update their applications.

Consultation with the applicants resulted in withdrawal of 31% of the applications due to the lack of a business need for the product and only 99 master applications were left for the pilot study. The dossiers were re-submitted between 12 and 16 September 2016, distributed to the respective units, and evaluated by the PEM, P&A Pre-Registration Unit during the evaluation week held on 19–23 September 2016.

Even with the two phases as detailed above, by 2018 the backlog of applications had increased to 8,220. In 2018, the authority embarked on a project called the Backlog Clearance Programme aimed at clearing the existing backlog over a specified time. The planning and development of the project was initiated in February 2018 through the assistance of a project consulting firm, which assisted in the quantification of the backlog. Inherited processes and practices from the former MCC were re-assessed and the backlog project was initiated in August 2019 to support new methodologies required to achieve the goal of clearing the backlog of

Table 4 Pilot study summary results: The summary results of the backlog Phase 1 pilot projects conducted by SAHPRA in 2016 and 2021

	2016 risk-based approach in P&A Pre-Reg Unit	2021 risk-based approach in Backlog Clearance Program
Time received to time when application was allocated	1,542 calendar days	431 calendar days
Product total (master applications)	150	63 (RW 8)
Withdrawn (opted out)	51	6
Product used in the pilot project	99	57
Number of evaluators used	10	10
Evaluation week (products evaluated)	54	Weekly meetings for 10 weeks
Finalisation time (median)	90 calendar days (3 months)	68 calendar days (2.3 months)
Approval time[a] (median)	109 calendar days	110 calendar days

P&A Pre-Reg Pharmaceutical and Analytical Pre-Registration

[a]The approval time is calculated from date of initial allocation

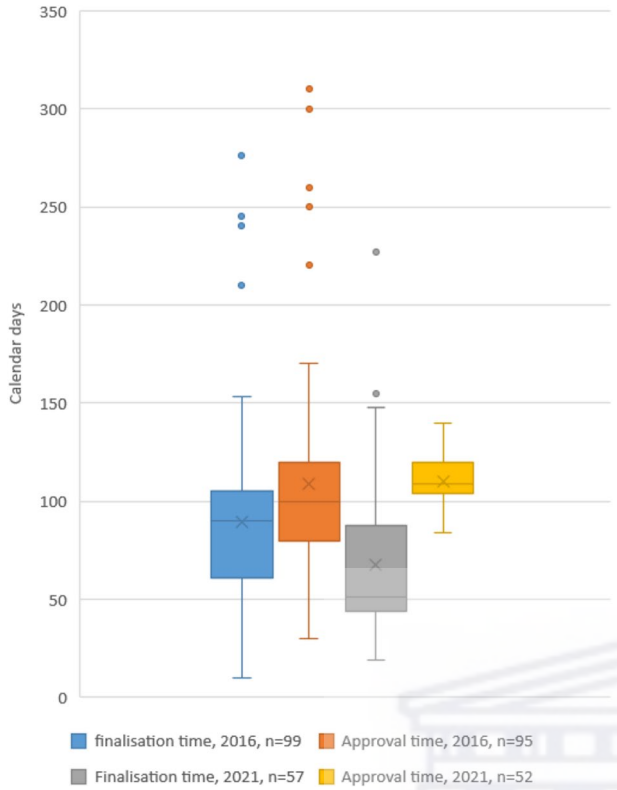

Fig. 5 The distribution of finalisation times and approval times for applications in the backlog Phase 1 (2016) and 2021 pilot studies. Box: 25th and 75th percentiles. Whiskers: 5th and 95th percentiles

applications [7]. The project was initiated through the assistance of funding from government, development partners and donors [48].

The applicants were initially requested to indicate if they would like to include their applications in the Backlog Clearance Project. Upon analysis of the business need and proposed timeframe to submit there were 4,610 applications that opted out of the project and 99 applications were withdrawn. Not being part of the backlog project meant once the dossier was ready for resubmission with the new requirements, it would be submitted to the BAU section of SAHPRA. The in-process applications that were near finalisation, by either unit, were assessed in the BAU and concluded. Thus, SAHPRA initiated the Backlog Clearance Project in August 2019 with 3,343 applications, which translates to 1,364 master applications.

The Backlog Clearance Project utilised 56 external domestic and international evaluators to conduct the scientific assessments as well as the internal evaluators from the BAU section working overtime to assist with the project. By May 2021, 34% of the applications had been cleared. This was nearly 2 years after the initiation of the project where the intent was to eliminate the backlog in 2 years. The program was extended by 1 year and 5 months to December 2022 and the delay in the clearance was attributed to the assessments conducted within the PEM, P&A Pre-Registration component due to the bulk of the work being done in this unit [49]. Hence, the necessity for the refinement of

Table 5 Risk classification outcomes of products: The risk classification outcomes for the products used in the pilot studies

Dosage form	Number of applications, 2016 pilot study	Risk classification	Number of applications, 2021 pilot study	Risk classification
Immediate-release tablets	27	All were low risk	30	All were low risk
Immediate-release capsules	21	All were low risk	2	All were low risk
Modified release tablets	10	All were high risk	4	All were high risk
Enteric-coated tablets	0		1	High risk
Non-sterile powders	4	All were low risk	2	All were low risk
Eye drop solutions	5	All were high risk	2	All were high risk
Sterile IV or IM solutions	13	All were high risk	12	All were high risk
Syrup	3	All were low risk	4	All were low risk
Topical gel	8	All were low risk	1	Low risk
Transdermal patch	1	High risk	1	High risk
Mouth wash	0		1	Low risk
Throat spray	0		1	Low risk
Suppository	3	All were low risk	1	Low risk
Nasal spray	1	Low risk	0	
Anaesthetic inhalation, solution	0		1	High risk
Medical device with API inside device	1	Low risk	0	
NCEs	2	All were high risk	0	

API Active Pharmaceutical Ingredient, *IM* intramuscular route, *IV* intravenous route, *NCE* New Chemical Entity

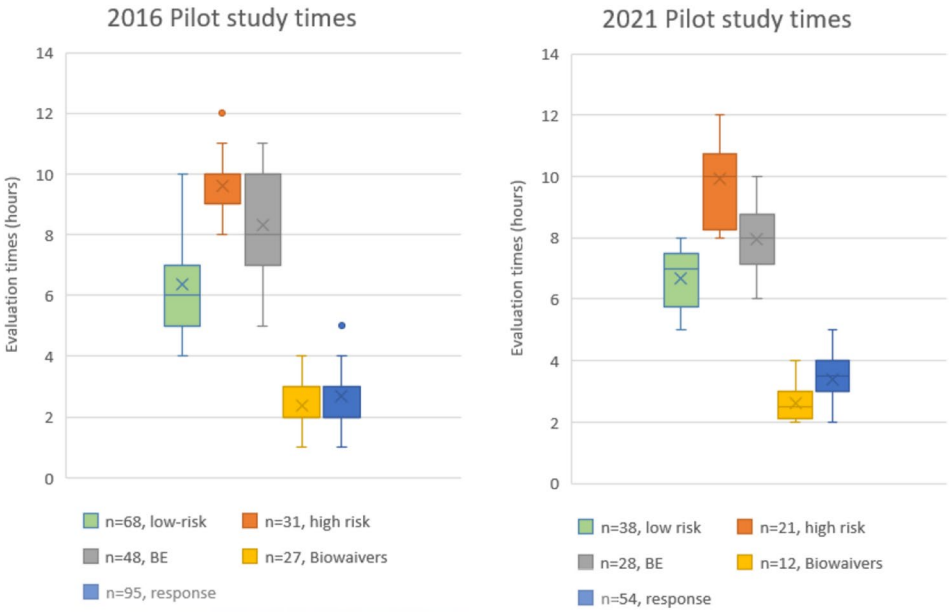

Fig. 6 Median evaluation times reported in the two risk-based assessment pilot studies for low-risk, high-risk, bioequivalence (BE), biowaiver and responses. (*n*) = number of product applications. Box: 25th and 75th percentiles. Whiskers: 5th and 95th percentiles

the risk-based assessment in September 2021 in an effort to conclude the Backlog Clearance Project in the set time. The 63 applications that were next in line for allocation were in re-submission window eight (8) and were therefore used in the 2021 pilot study.

In 2019 when the backlog clearance programme was initiated, the business-as-usual (BAU) section was provided with the opportunity to start on a clean slate while the backlog clearance programme dealt with all the ~8,220 applications. In the period 2019 to 2022, SAHPRA amended its processes and put systems in place such as the inclusion of a tracker that allows all units to monitor each other; however, even with that, a backlog formed within the BAU section of SAHPRA. The tracker was aimed at providing transparency and synchronisation within the units; however, this did not correct the misalignment as units could still allocate the same applications at different times and communicate the queries at different times. The solution to this would have been to have one set of queries from the different units communicated at the same time by the PC, as conducted in the 2015 study to ensure alignment within units at all times. This meant some units would finalise applications before others, which would lead to misalignment. It should be noted that the root cause of the backlog was not as a result of one factor such as the misalignment of units only, there are a number of reasons, which are detailed in the study, and which is why the risk-based assessment approach was developed as an end-to-end registration process providing corrective or preventative measures or solutions to prevent the root causes from occurring in future.

4.3 Risk-Based Assessment Process

4.3.1 Registration Process

A reassessment of processes was necessary for the authority for improved efficiencies. An improved registration process was employed as detailed in Fig. 4.

The following were improved in the developed process illustrated in Fig. 4:

- Previously, the units were only allocated an application by the HPA, thereafter communication with the applicants would be made by the separate units. A Portfolio Coordinator (PC) responsible for coordinating and collating outcomes from the units was introduced as one communication to the applicants.
- The introduction of the Inspectorate Unit confirming the Good Manufacturing Practice (GMP) status before allocation to other units was included since previously this would only occur once the scientific assessments had been concluded by the PEM, P&A and clinical evaluations of Pre-Registration Units. The inspections being conducted towards the end of the process would further delay the registration of applications.
- The use of a risk-based approach to conduct scientific assessments to reduce the assessment times by the PEM, P&A Pre-Registration Unit with assessments focused on the critical quality attributes of the product.
- The use of a pre-populated evaluation template to aid in the reduction of evaluation times. This allowed for the

technical person to screen the applications to check if the updated information, such as the updated stability data, is as per the requested shelf-life, the updated Certificate of Suitability (CEP) is included, etc.
- Frequent peer review meetings. For the 2016 pilot study, an evaluation week approach was used where a week was blocked for evaluation, during which towards the end of each day evaluators discussed the reports and query letters sent to the HPA. This promoted scientific knowledge sharing and ensured that queries going out to the applicants were critical aspects to be addressed in the dossier and that the queries were standardised. This was only conducted once, and the rest of the applications awaited the P&A Committee meetings held on a 6-weekly basis. This resulted in some delays.

In the refined process in 2021, weekly peer review meetings were introduced, which allowed for better throughput of query letters to the applicants. The selection of the date for each peer review session was based on the availability of evaluators using the When Available poll. The reports were then compiled into meeting documents and uploaded on Google Docs well in advance to allow evaluators to provide their comments. The living document would then show all comments in real-time, allowing all evaluators to see each other's comments. This assisted in drastically reducing the meeting sessions as only specific points of discussion, highlighted by the peer-review panel, were discussed. Most other aspects were collaboratively deliberated on during the real-time discussions via Google Docs.

- The response time was reduced from 90 calendar days to 30 calendar days and only two response cycles were allowed, which the pharmaceutical companies agreed on for the 2016 study.

In the refined process this was further reduced to 10 working days; however, applicants could request an extension if required. The requests for extension were for 41% of the responses, therefore the response timeline was increased to 15 working days for initial responses and 10 working days for further responses.

Once this robust process had been concluded, the products were classified according to risk.

4.3.2 Risk Classification

Ahead of assessing the aspects of the API and FPP, prior work conducted by other NRAs or Regulatory Institutions should be considered. Recognition of the work previously done is termed as reliance. And, according to the WHO, reliance is defined as the act whereby one regulatory authority in one jurisdiction may consider and give significant weight to totally or partially rely upon scientific assessments or inspection reports performed by another authority or trusted institution in reaching its own decision [20]. The relying authority uses this work according to its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities. Historically, SAHPRA had not implemented this review pathway until 2019 when the backlog clearance programme was initiated [48]. The authorities with which SAHPRA aligns itself and uses the unredacted reports of are the European Medicines Agency (EMA); Health Canada; Medicines and Health Products Regulatory Agency (MHRA) in the United Kingdom; Ministry of Health, Labour and Welfare (MHLW) in Japan; Swiss Agency for Therapeutic Products (Swissmedic); Therapeutic Goods Administration (TGA), Australia; and the FDA [50]. SAHPRA is also currently utilising partial reliance through the use of submissions such as CEPs by the European Directorate for the Quality of Medicines (EDQM) and Certificates of Prequalification (CPQs) of the API by the World Health Organisation Prequalification Team: Medicines (WHO PQTm). The developed template in Table 2 therefore accommodates the reliance aspect as well during risk classification.

The non-reliance critical aspects are also considered during quality and efficacy (bioequivalence) aspects of products submitted for approval, and detailed below to assist in the overall classification of the product.

When it comes to defining the risk pertaining to the API, the following key aspects of the API are assessed:

- Availability of a valid CEP/CPQ (Certificates of Prequalification (CPQs))
- Pharmacopoeial status of the API
- Biopharmaceutics Classification System (BCS) of the API (in particular aqueous solubility)
- Solid state properties (solubility, hygroscopicity, particle size distribution (PSD) and polymorphism)
- The concentration of the API in the FPP.

The key aspects to be considered in the FPP are:

- Pharmacopoeial status of the FPP
- Type of dosage form
- Complexity of the manufacturing process
- Excipients
- Container closure system (CCS).

The key aspects in the bioequivalence study:

- The bioequivalence (BE) with the reference products and comparative dissolution with the reference products.

Based on the identified aspects to consider as stated in Table 2, a product could be classified as low or high risk.

4.3.3 Critical Areas to be Reviewed for Low-Risk Products

A combination of literature reported by Tran et al. [32] and the concept paper by the WHO [19], as well as a wide array of expert advice garnered on the approach, categorically assisted in the determination of the critical attributes of manufacturing and overall risk ranking of the product. With this information, the CTD sections and extent of evaluation thereof could be established. The areas of concern have been included below and will be thoroughly evaluated for low-risk applications. The relevant templates are used for assessment with the critical sections included.

The identified critical sections of the CTD for low-risk applications are as follows:

- Module 1.3 Labelling and packaging (Professional Information (PI), Patient Information Leaflet (PIL) and Label)
  - Quantitative and qualitative composition
  - Storage conditions
  - Container closure system
  - Appearance
- Module 1.7.4.1 Batch Release
  - API and Inactive Pharmaceutical Ingredient (IPI) batch release
  - Release (Final Product Release Control (FPRC)/ Final Product Release Responsibility (FPRR))
- Module 1.10 Foreign regulatory status
  - Marketing authorisation information for reliance
- Module 3.2.S. Active Pharmaceutical Ingredient

  3.2.S.1.3 Physico-chemical properties (depending on dosage form)
  3.2.S.2.2 Method of synthesis (N/A if CEP/CPQ is submitted)
  3.2.S.3.2 Impurities (N/A if CEP/CPQ is submitted)
  3.2.S.4.1/2 Specifications (N/A if CEP/CPQ is submitted, however, assess the API specifications by the FPP manufacturer)
  3.2.S.7 Stability (N/A if retest period is stipulated on CEP/CPQ)
- Module 3.2.P Finished Pharmaceutical Product

  3.2.P.1 Components and composition of the final product
  3.2.P.3.3 Manufacturing process/Batch Manufacturing Record (BMR)
  3.2.P.5.1 Specifications
  3.2.P.7 Container closure system
  3.2.P.8 Stability
- Bioequivalence

The sections proposed for the bioequivalence section are included below and are in line with ICH and EMA requirements [51–53]. In the case where a BCS-based biowaiver is requested (BCS class I and III applications), only two sections would be assessed. These include the details of the test and reference product used in the study and comparative dissolution profiles, thus reducing the assessment review times. This template, used as an evaluation tool, would reduce the current reported evaluation timelines, as it is designed to point out and discuss critical aspects of the biostudy.

The identified sections from the bioequivalence template are as follows:

- Details of the test and reference product used in the study (applicable for biowaiver request)
- Comparative dissolution profiles (applicable for biowaiver request)
- Study method and design
- Summaries of statistical and pharmacokinetic data
- Bioanalytical report parameters.

Certain sections are excluded from evaluation for low-risk applications. The rationale for these exclusions, which addresses the risk mitigation for each, are as follows:

- Batch analyses (3.2.S.4.4 and 3.2.P.5.4) are not evaluated for low-risk applications because the stability results (3.2.S.7.3 and 3.2.P.8.3) at the initial time point essentially serve as batch analyses. In addition, the impurities section also includes profiling of the impurities and residual solvents formed, thus these sections mitigate the risk since they are assessed.
- Reference materials sections (3.2.S.5 and 3.2.P.6) are for documentation purposes and do not need to be assessed since the API would have been confirmed already in preceding sections, such as the method of synthesis, impurity section and specifications. In most cases, 3.2.P.6 refers to section 3.2.S.5 of the dossier. The working standard and primary standards are those manufactured by the applicant and synthesis would, therefore, be in line with the proposed methods.
- Pharmaceutical development (3.2.P.2) is not assessed for low-risk applications, because this is research and development conducted by the manufacturer for optimisation of the final manufacturing process for commercial product/s. The final proposed manufacturing process is then assessed in section 3.2.P.3.3 and the information is verified by the batch manufacturing records. In addition, for the oral solid dosage forms that require the submission of a bioequivalence study, certain critical aspects of the pharmaceutical development

section are evaluated. These include in vitro dissolution studies as these are covered in the bioequivalence template for evaluation. For solid oral dosage forms, selection of inactive pharmaceutical ingredients (IPIs) is covered by the bioequivalence assessment where similarity to the reference product is reviewed, and in the case where the excipients are not similar to the reference product, API-excipient compatibility should be confirmed under 3.2.P.2. In the case of liquid dosage forms, excipient similarity to the reference is confirmed under Module 3.2.R.1.4.1 and in the case where the excipients are not similar to the reference product, API-excipient compatibility would be confirmed under 3.2.P.2. The designed templates therefore provide guidance for these.

- Module 3.2.P.3.1 details the full name and address of the final product manufacturer. The name of the final product manufacturer is confirmed in the administrative table at the beginning of the pre-populated template. In addition, the Inspectorate Unit confirms and validates this during inspections.
- Batch formula (3.2.P.3.2) is not assessed since it is confirmed during assessment of the batch manufacturing records, which consist of actual quantities of API/s and IPI/s used for the proposed batch(es).
- Validation of analytical methods (3.2.S.4.3 and 3.2.P.5.3) is not assessed because the product would be pharmacopoeial and only verification is then required. In addition, specification limits provided found to be within ICH requirements will be confirmed since the specification section is assessed for low-risk applications. At most, the evaluator may only confirm the submission of the reports for noting for low-risk applications.

4.3.4 Critical Areas to be Reviewed for High-Risk Products

If a product is classified as high risk, additional sections over and above the ones identified for low risk would also require thorough evaluation and reporting on the respective templates. The additional sections to assess for high-risk products include the following:

- Module 1.3 Labelling and packaging (PI, PIL and Label) – same as low-risk
- Module 1.7 Good Manufacturing Practice – same as low-risk
- Module 1.10 Foreign regulatory status – same as low-risk
- Module 3.2.S Active Pharmaceutical Ingredient

  3.2.S.4.3 Validation of analytical methods for the API – additional section for high-risk applications

- Module 3.2.P Finished Pharmaceutical Product

  3.2.P.2 Pharmaceutical development of the FPP
  3.2.P.3.5 Process evaluation of the FPP validation
  3.2.P.5.3 Validation of analytical methods for the FPP
  3.2.P.7 Container closure system (for sterile applications)

- Bioequivalence

  - Details of the test and reference product used in the study (applicable for biowaiver request)
  - Comparative dissolution profiles (applicable for biowaiver request)
  - Study method and design
  - Summaries of statistical and pharmacokinetic data
  - Bioanalytical report parameters

The justification stated above for the sections that are not to be assessed are also applicable for high-risk applications. Note that risk classification will not be applied to NCEs and biological applications; instead full review will be conducted due to the criticality of the medicines.

4.3.5 Summary of Results on the Risk-Based Approach

In the second phase of the 2015 backlog pilot project for new applications, all 99 master applications were finalised within 9 months, with the median time calculated as 90 calendar days. The outliers were noted as 7, 8 and 9 months as indicated in Fig. 5. These were due to the FPP manufacturers receiving a negative status and therefore inspection had to be arranged by the Inspectorate Unit before evaluation could take place. There were other instances where the applicants requested an extension to submit responses, and this led to the delay in finalisation. For the refinement of the process in 2021, a median finalisation time of 68 calendar days was obtained (Fig. 5). Of the 63 applications, six were withdrawn while in-process in the response phase. However, the initial evaluation was already conducted for these so they were included in the calculations of evaluation times.

From the 63 applications, 21 applications were classified as high risk and 42 classified as low risk as depicted in Table 5. From Table 5, it is observed that all immediate-release tablets and capsules were low risk, which constitute 51% of the applications. From the 90% generic applications that SAHPRA receives, most of these are pharmacopoeial and well-known with readily available extensive research conducted on them; therefore, due to this, classification would be low risk. In addition, the dosage forms were not novel, therefore overall classification was low risk. The same applies for the other dosage forms classified as low risk.

4.3.6 Assessment Timelines

Figure 6 illustrates the reported evaluation times by the evaluators who were part of the two risk-based assessment pilot studies in 2016 and 2021. The graphical depiction shows the calculated median values as 6.3 and 7.0 h in 2016 and 2021, respectively, for low-risk quality assessment timelines. As observed from Table 4, products classified as low risk were immediate-release tablets and capsules, topical gels, mouth wash, throat spray, oral syrups and oral solutions. The median values for high-risk quality assessments were reported as 9.5 and 10 h from the two pilot studies, respectively. Products classified as high risk were sterile intravenous injections and infusions, ophthalmic solutions, delayed-release tablets and sterile lyophilised powders. The bioequivalence study assessment times were 8.4 and 8.0 h using the proposed template and biowaivers reported as 2.3 and 2.6 h with initial response assessment times as 2.6 and 3.4 h. The calculations above were based on a simplified submission that contains one API from one API manufacturer who submitted an Active Pharmaceutical Ingredient Master File (APIMF), with only one FPP manufacturer applied for. In a case where a CEP was submitted, the median evaluation times were 5–6 h for low-risk and 7–8 h for high-risk products; when two APIMFs were submitted, the evaluation times were 11–12 h for low-risk and 13–14 h for high-risk products. This resulted in the deduction that one APIMF assessment takes 4–5 h and one FPP takes 5–6 h to assess for high-risk applications. The reported medians have resulted in a reduction in the assessment times without the compromise to quality as only critical sections that will impact the quality of the product are adequately assessed.

For the Phase 2 pilot study conducted in 2022, the quality assessment timelines for high risk is reported as a median of 14 h and 10 h for low risk. The increased assessment timeline is due to the different quality template used that has been pre-populated by the applicant. The evaluators therefore would spend time validating the information populated by the applicant with the scientific information in the dossier to ensure that accurate information was completed.

Once applications that undergo the risk-based assessment pathway are registered, the following post-marketing surveillance or monitoring procedures were proposed and will be conducted:

- The applicant will be requested to provide the Post-Registration reports on a yearly basis to Pharmacovigilance and annual product review report to the Inspectorate Unit. Depending on the information submitted on the reports, the Inspectorate could perform inspections of the non-compliant manufacturer/applicant.
- Ongoing post-marketing surveillance will be conducted on the products by the Inspectorate Unit.
- Re-evaluation of the information (dossiers) after 5 years will be conducted on all applications.

5 Conclusions

The large influx of applications as a result of 'dossier farming' as well as resource constraints experienced by SAHPRA over the years resulted in the formation of a backlog as large as 8220 applications. The organisation needed to implement drastic changes in order to reduce the timelines to promote timely access to medicines. A backlog pilot project was conducted in 2016 to alleviate the existing backlog of applications at the time. The pilot project consisted of 99 master applications and managed to reduce the finalisation timelines to a median value of 90 calendar days. The refined and efficient process was described in detail as well as the knowledge gained from the project. These learnings were used in the refined and optimised risk-based assessment pilot study in 2021. This pilot study was initiated with applications from re-submission window 8 of the Backlog clearance programme project initiated by SAHPRA in 2019. The study was resumed with 63 applications and a median finalisation time of 68 calendar days recorded, which is significantly lower compared to the initial pilot study (90 calendar days) and the current process employed by SAHPRA for the backlog clearance programme initiated in 2019, which resulted in the finalisation time of 501 calendar days. The risk-based approach is discussed in detail as it involves the robust risk classification matrix to employ that allows for the categorisation of a product to the appropriate risk class. The approach also details which sections of the CTD and bioequivalence study are considered critical for comprehensive assessment. The identified sections for the assessment of the two risk classes ensures that quality, safety and efficacy are not compromised while accelerating access to medicine for patients. The risk-based approach therefore essentially aims to reduce the finalisation timelines for quality and bioequivalence assessments for authorities, which will greatly reduce the overall registration timelines. Implementation of this approach by other regulatory authorities will assist in the reduction of the backlog of applications created due to resource constraints and the large influx of applications that are of urgent need for the public.

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Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Data are available upon request to the corresponding author.

Code availability Not applicable.

Author contributions LM: Developed the study design, collected and analysed the data, interpreted the results, and wrote the first draft of the manuscript. ML: Developed the study design, assisted in collecting and analysing the data, provided guidance for the data collection and analysis, interpreted the results, and reviewed and approved the manuscript. JJ: Developed the study design, provided guidance on the data analysis, interpretation and relevance of the results, and reviewed and approved the manuscript.

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RESEARCH

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Regulatory registration timelines of generic medicines in South Africa: Assessment of the performance of SAHPRA between 2011 and 2022

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Abstract

Background Various regulatory authorities are experiencing backlogs of applications which result in delayed access to medicines for patients. The objective of this study is to critically assess the registration process utilised by SAHPRA between 2011 and 2022 and determine the fundamental root causes for the formation of a backlog. The study also aims to detail the remedial actions that were undertaken which resulted in the development of a new review pathway termed the risk-based assessment approach for regulatory authorities experiencing backlogs to implement.

Methods A sample of 325 applications was used to evaluate the end-to-end registration process employed for the Medicine Control Council (MCC) process between 2011 and 2017; 129 applications were used for the backlog clearance project (BCP) between 2019 and 2022; 63 and 156 applications were used for the risk-based assessment (RBA) pilot studies in 2021 and 2022, respectively. The three processes are compared, and the timelines are discussed in detail.

Results The longest median value of 2092 calendar days was obtained for the approval times between 2011 and 2017 using the MCC process. Continuous process optimisation and refinement are crucial to prevent recurring backlogs and hence implementation of the RBA process. Implementation of the RBA process resulted in a shorter median approval time of 511 calendar days. The finalisation timeline by the Pharmaceutical and Analytical (P&A) pre-registration Unit, which conducts the majority of the evaluations, is used as a tool for the direct comparison of the processes. The finalisation timeline for the MCC process was a median value of 1470 calendar days, the BCP was 501 calendar days and the RBA process phases 1 and 2 were 68 and 73 calendar days, respectively. The median values of the various stages of the end-to-end registration processes are also analysed in order to build efficiency within the process.

Conclusions The observations from the study have identified the RBA process which can be implemented to reduce regulatory assessment times while assuring the timeous approval of safe and effective, quality medicines. The continuous monitoring of a process remains one of the critical tools required to ensure the effectiveness of a registration process. The RBA process also becomes a better alternative for generic applications that do not qualify to undergo the reliance approach due to its drawbacks. This robust procedure can therefore be utilised by other regulatory agencies that may have a backlog or want to optimise their registration process.

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Keywords South African Health Products Regulatory Authority (SAHPRA), Registration, Regulatory performance, Generic products, Backlog, Finalisation, Approval time

Background

In the effort to reduce the likelihood of a backlog of medicinal product applications, which has the propensity to build up in medicine regulatory bodies globally, the performance of regulatory review should be measured and tracked [1]. The need for agencies to measure and improve their performance proactively and consistently against stated target times is one of the World Health Organization (WHO) global benchmarking tool parameters [2]. This is especially important for generic products as they increase accessibility and affordability in global healthcare systems. Generic products contain the same quantity of active substances in the same dosage form, meet the same or comparable standards and are intended to be administered by the same route as the innovator products [3]. In most countries, these generic products are marketed only after patent expiration and are normally cheaper than branded innovator medicines [4].

In 2015, China's Food and Drug Administration (CFDA) had more than 21 000 applications in backlog, most of which were generic products [5]. In 2019, the CFDA's 900-day approval period was shortened to 300 days [5]. Their Centre of Evaluation (CDE) employees expanded from 100 in 2015 to approximately 1000 by 2020; this was reported as one of the direct causes of the decline [6]. The increase in human resources, amendments to the 2007 administrative measures and processes for Drug Registration as well as the introduction of additional review pathways were implemented which accelerated access to medicines [6]. The regulatory authority in Brazil, Agência Nacional de Vigilância Sanitária's (ANVISA) also reported that in 2018 there were more than 800 New Chemical Entities (NCE) and generic applications in the backlog with the intent to clear the number by January 2019 with improved registration processes [7]. ANVISA had achieved an approval time of 795 days for generic products in 2013–2016 for 138 products. [1] The United States Federal Drug Administration (USFDA) on the other hand accomplished an approval time of 661 days in 2020 for 737 Abbreviated New Drug Applications (ANDA) approvals and 172 ANDA tentative approvals [8], while the Australian regulatory authority, Therapeutic Goods administration (TGA) accomplished an approval time of 244 calendar days for 85 generic products in 2021 [9]. This shows that the approval times are dependent on the number of applications received in that specific year and the resources available in the authority. The Taiwan Food and Drug Administration stated that they receive an estimated 400 generic applications per annum [10]. The Caribbean Regulatory authority received 11 generic applications in 2018 [11], TGA received 85 applications in 2021 [9] and South African Health products regulatory authority (SAHPRA) received an annual average of 1247 applications in 2019 [12]. It is therefore the duty of the authorities to ensure that the required measures, review tools and developed processes that best suit the situation they are faced with are continuously monitored and efficiencies applied.

The South African authority, SAHPRA, formerly named the Medicine Control Council (MCC) reported a backlog of approximately 8000 applications in 2016 which highlights the need to review the registration process and apply better efficiencies [13]. The authority had a fast-track process initiated in 2003 which only focused on essential and critical medicines [14]. Due to the backlog that formed, a number of medicines in the essential list were fast-tracked, therefore only these products were allocated and evaluated while other products were allocated only when an evaluator was available. Given that the human resource was at a minimal and a registration process had not been reviewed for more than 20 years, the backlog increased [14]. The operational challenges and resource constraints faced by SAHPRA over the years resulted in the formation of a backlog of approximately 16 000 applications including variations by 2018 [15]. In 2019 when the backlog clearance project (BCP) was initiated, 15 domestic and 48 international evaluators were contracted to assess the quality and bioequivalence assessments while SAHPRA's business-as-usual section operates as normal with the new applications received [16]. This strategy would allow for the authority to function while the backlog is managed as a separate project with the required human resource employed to execute the required end-to-end backlog function. This was aided through the assistance of funding from various entities such as the Bill and Melinda Gate Foundation and the National Treasury of South Africa. This meant that careful monitoring and consistent reporting was required to ensure that the project's goal was executed. With funding acquired and after an in-depth analysis of SAHPRAs backlog by a project managing consulting firm, a target completion time of two years was predicted based on the available resources [16]. This was not executed as planned and it was extended by one year and 4 months [17].

This study, therefore, investigates the end-to-end registration process of generic products employed between 2011 and 2022 for the MCC process and the BCP process in the effort to assess the performance and identify the root causes of the backlog. In addition, the developed robust pathway called the risk-based assessment (RBA) process with remedial steps implemented to mitigate future backlogs is described and compared with the other processes.

Methods

The study assesses three different registration processes used between 2011 and 2022; the MCC process is assessed using a sample of finalised applications between 2011 and 2017; the BCP process is assessed using the applications from three re-submission windows (RW) evaluated in 2020; and the RBA pilot studies assessed in 2021 and 2022 using the sample of applications that were in RW8, 10, 11 and 12. The RBA approach is the robust process that was developed upon further refinement and optimisation of the MCC and BCP process and piloted in 2021 and 2022, titled the RBA pilot study phase 1 and 2.

MCC registration process, 2011–2017

Over the 7-year period, 3148 applications were finalised by the P&A pre-registration Unit within SAHPRA of which 2089 were non-sterile. Thus, due to the large application size at hand, a statistical sampling method became a requirement for this research. The sample selected becomes a true representation of the population and results of the study can be generalised to the population. The method of selection and calculation of the representative sample is comprehensively described by Moeti et al. where a sample size of 325 non-sterile products is obtained and used in the study [13, 18, 19]. By comparing the quality requirements for sterile and non-sterile products it is witnessed that the sterile products require additional assessments in the pharmaceutical development Sect. (3.2.P.2) as well as the process validation and or evaluation Sections (3.2.P.3.5). On the other hand, the non-sterile products would normally require additional assessment in the regional section on bioavailability, therefore, assessment times would be similar for both product types.

Backlog clearance project (BCP) registration process, 2019–2022

In order to eliminate the backlog, in 2019 SAHPRA started a project named the BCP [19]. The project was initiated with ~ 8220 applications in the pre-registration phase [16]. The implemented process allowed for applicants to re-submit the dossiers, as some information may be outdated since they were submitted as back as 2008. Resubmission windows (RW) were then created according to therapeutic categories with those considered essential in the earlier windows.

The applications selected from the BCP were from three RWs, i.e. RW1, RW5 and RW6. RW1 consisted of medicines in the therapeutic category of Human Immunodeficiency Virus (HIV), tuberculosis (TB), vaccines and hepatitis, RW5 was for medicines targeting diabetes, malaria, maternal and new-born health as well as all the priority APIs and RW6 was for medicines targeting respiratory system diseases [20]. An overall of 129 applications from the three windows was employed and only the applications that utilised the full review pathway for quality and bioequivalence scientific assessments were selected. Note that other pathways include the reliance pathway [21] or applications that have previously received preliminary approval from the P&A pre-registration Unit, however, not yet registered and contained minor variations. Since the approval times for these pathways were shorter, this would alter the calculated timeframes, therefore, the applications that undertook the reliance route were not included in the study. The dates at each stage of the BCP registration process for each application were collected from the electronic database/tracker used by the authority.

Risk-based assessment (RBA) pilot study, phase 1 and 2, 2021–2022

The risk-based pilot project was initiated in September 2021 within the realm of the BCP using 63 applications from (RW8) as they were next in line to be allocated for initial full review. RW8 comprised of medicines in the therapeutic category that treats haematological/immunological diseases as well as medicines that are analgesics and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). For further optimisation and reproducibility of the process, the RBA pilot study was up-scaled in April 2022 using 159 applications from RW 10, 11 and 12. The therapeutic categories are; endocrine, nutritional, digestive system and metabolic disease for RW10; skin, subcutaneous tissue, musculoskeletal system and connective tissue for RW11; and eye and ear diseases for RW12 [20]. The implementation was made as an intervention to promote efficiencies within the existing registration process and allow accelerated access to medicines. The dates were collected from the database created during the initiation of the pilot studies wherein all activities and dates were recorded and closely monitored at each stage.

The dates were collected and information was populated in the respective Microsoft Excel®, 365, Worksheets. The differences between each activity were calculated for each product and median values were calculated for each, to obtain the time it takes for each

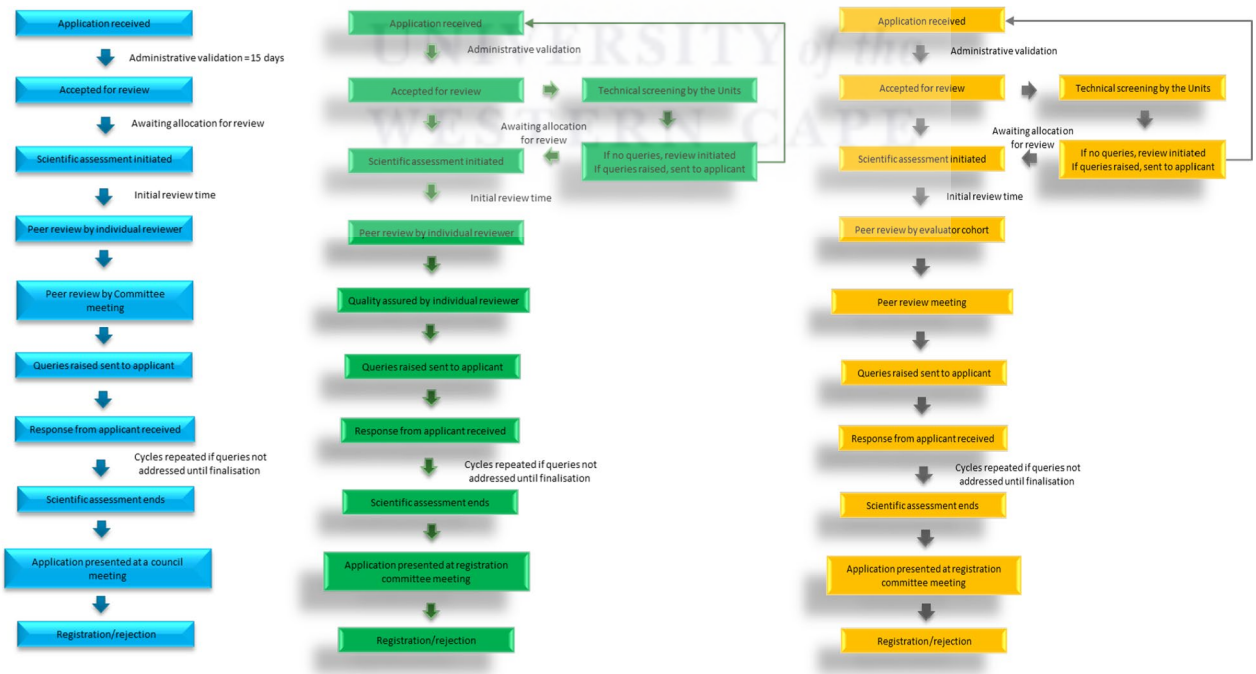
activity within the registration process. Finalisation is the conclusion of an assessment by each respective Unit before registration. It should be noted that the finalisation timeline by the Pharmaceutical and Analytical (P&A) pre-registration Unit, is used as a tool for the direct comparison of the processes as the Unit is assessing the bulk of the information submitted by the applicant.

Results

Brief description of the MCC, BCP and RBA processes

The registration processes remain largely similar with deviations observed in certain steps as highlighted in Fig. 1. Upon receipt of the application, administrative screening was performed within 15 calendar days from the time of receipt for the MCC process. Applications were then routed to the relevant Units, where they are allocated to an evaluator to start the review process for the MCC process while for the other two processes technical screening was performed as illustrated in Fig. 1. Queries raised from the technical screening were sent to the applicant and a response was requested within 10 working days. When all queries were addressed or the application is compliant the allocations for scientific assessments were initiated based on evaluator availability. Due to the limited number of evaluators, the application would wait in queue for an available evaluator before allocation. Once allocated in the P&A pre-registration Unit, the initial scientific assessments were conducted. The peer review stage differed in the three processes as shown in Fig. 1 in that detailed assessment reports prepared by the evaluators were peer-reviewed by the Chair or deputy Chair of the Committee in the MCC process. Thereafter, these were made part of the agenda and shared with the Scientific Committee members for discussion during the meetings held every 6 weeks. In the BCP process, reports were peer-reviewed by an individual peer reviewer and thereafter quality assured by another assigned evaluator based on individual evaluator availability. In the RBA process, once the detailed assessment reports were received from the evaluators, the When Available poll [23] was used to determine the most suitable time for each weekly peer review session. The reports were compiled into meeting documents and uploaded on Google Docs [24] well in advance (5–7 days) to allow evaluators to provide their comments during peer review [22]. The peer review meeting sessions were then held and only specific points of discussion, highlighted by the peer review panel, were discussed.

In the P&A pre-registration Unit, recommendations pertaining to quality and bioequivalence data were sent to the applicant and a response was expected within 90 calendar days for MCC process, 20 working days for BCP process and 15 working days for initial queries and 10 working days for response queries for the RBA



MCC = Blue, BCP = Green, RBA = Yellow.

Fig. 1 Depiction of the MCC, BCP and RBA processes utilised by SAHPRA between 2011 – 2022. MCC = blue, BCP = green, RBA = yellow

process. The response would be reviewed by an evaluator and undertake the peer review process as described for each process. There were no limits to the number of response cycles between the applicant and the authority in the MCC process while this was restricted to only 2 response cycles for the BCP and RBA processes. Once the application is finalised by the P&A pre-registration Committee, the Clinical Committee, Good Manufacturing Practices (GMP) Committee and the Names and Scheduling Committee or their Units thereof, the medicine is considered for registration/approval by the authority at a Council meeting held every 60 calendar days in the MCC process or registration Committee meeting held weekly for the BCP and RBA processes.

Reported timelines for the three processes

The median values at each stage in the P&A pre-registration process were calculated and are depicted in Table 1 for all the different end-to-end registration processes. Figure 2 illustrates the overall median finalisation time for the MCC, BCP and RBA processes as 1470, 501 and 68 calendar days. The second phase of the RBA pilot study was conducted in 2022 and the reported median finalisation time was 73 calendar days which is relatively similar to Phase 1. The results for RBA pilot study phase 1 and 2 as depicted in Table 1 confirm similarity for each timeframe.

In the MCC process, the first row of Table 1 represents cycle 1, where column 2 reflects the median time for the number of calendar days from the date the application

Table 1 The identified activities within the three end-to-end registration processes employed by SAHPRA between 2011 and 2022 and the median timelines of the activities

	Allocation timeframe	Preparation of assessment reports	Peer review process	Quality assurance	List of queries to the applicant	Applicant time
Cycle	Median time in calendar days for registration activities for the MCC process (2011–2017)					
1	682	201	–	-	74 (0 finalised)	347
2	186		62	–	72 (168 finalised)	76
3	56		76	–	74 (116 finalised)	76
4	31		47	–	32 (35 finalised)	56
5	16		16	–	20 (6 finalised)	-
	Median finalisation timeline			1470		
	Median registration timeline			2092		
Cycle	Median time in calendar days for registration activities for the BCP (2019–2022)					
1	278	63	29	35	30 (0 finalised)	84
2	22	35	15	30	15 (30 finalised)	33
3	10	30	10	20	15 (58 finalised)	22
4	7	7	5	10	10 (25 finalised)	20
5	2	11	5	15	5 (13 finalised)	–
	Median finalisation timeline			501		
	Median registration timeline			591		
Cycle	Median time in calendar days for registration activities for the RBA phase 1 pilot study (2021–2022)					
1	431	5	8	–	2 (3 finalised & 2 withdrawn)	25
2	2	2	6	–	1 (44 finalised)	18
3	1	1	7	–	1 (6 finalised & 2 withdrawn)	10
4	1	1	7	–	1 (4 finalised)	–
	Median finalisation timeline			68		
	Median registration timeline			511		
Cycle	Median time in calendar days for registration activities for the RBA phase 2 pilot study (2022)					
1	~2 years	5	8	–	1 (6 finalised)	28
2	2	2	7	–	1 (102 finalised & 1 withdrawn)	15
3	1	1	7	–	1 (44 finalised & 2 withdrawn)	12
4	1	1	5	–	1 (7 finalised)	–
	Median finalisation timeline			73		
	Median registration timeline			–		

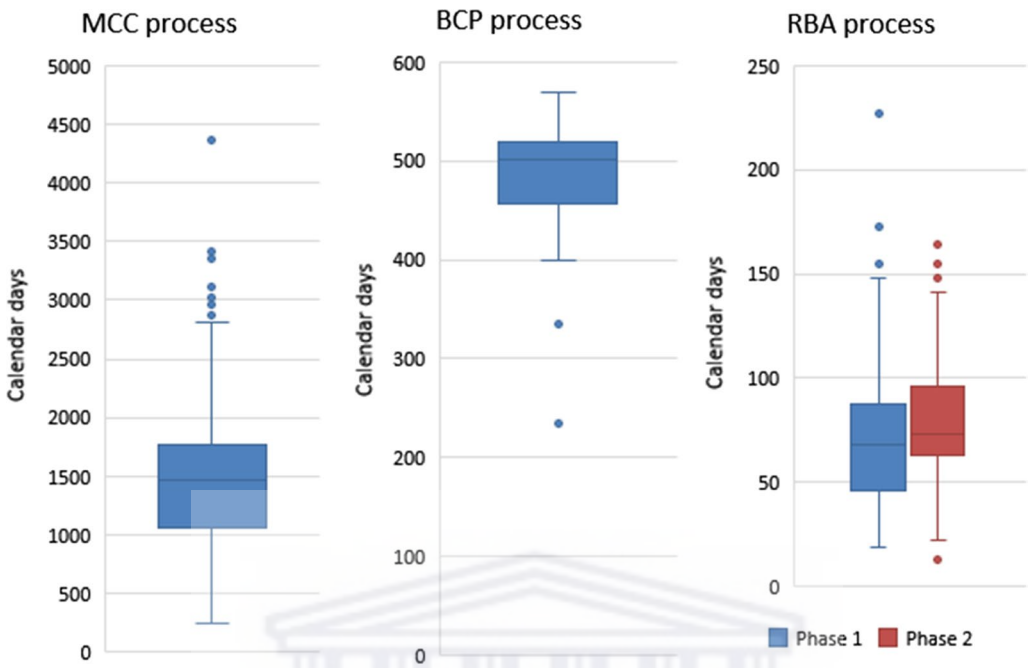


Fig. 2 The graphical representation of finalisation timelines for the MCC, BCP and RBA processes with reported median values of 1470, 501 and 68 calendar days, respectively. *n*; MCC = 325, BCP = 129, RBA Phase 1 = 59 (4 applications were withdrawn before finalisation), RBA Phase 2 = 156 (3 applications were withdrawn before finalisation)

was received to the time it was allocated for assessment as 682 calendar days. The time taken from the allocation of the application to the evaluator to the time the initial report was submitted is 201 days as indicated in column 3, the time taken from when the report was submitted to the initial peer-review meeting is 171 days, and from peer-review meeting to the time the query letter was sent to the applicant is 74 days. The last column indicates that it took the applicants 347 calendar days to respond to the initial queries, despite being granted only 90 calendar days to respond. This demonstrates how the applicants were also responsible for the delays. It emerged that some applicants would ask for extensions to provide the necessary data, which were granted, while others would exceed the response limit without asking for an extension. Due to the difficulty in obtaining the allocation dates of the responses for cycles 2 through 5 as depicted in Table 1, the time when responses were received to when report was submitted are merged. This is because the dates on which the responses were allocated to the evaluators were not recorded. The MCC process took up to five cycles before a product was finalised for the selected representative sample.

To assess the BCP process, the first row under the BCP median times in Table 1 represents cycle 1, which reflects the median time from the date of receipt to allocation for assessment as 278 calendar days. The time taken from allocation to submission of initial report is 63 days, the time taken from submission of report to the initial peer-review is 29 days, and from peer-review to quality assurance (QA), is another 35 days. The time taken from QA to sending the query letter is 30 days with the applicant taking 84 days to respond to the queries.

For the RBA process, the first row under the RBA median times in Table 1 represents cycle 1, which reflects the median time from the date of receipt to allocation for assessment as 431 calendar days while phase 2 denotes 523 days. The time taken from allocation to submission of initial report is 5 days, the time taken from submission of report to the initial peer-review meeting is 8 days for both studies, and lastly, from peer-review meeting to communicating the query letter to the applicant is 1–2 days. Table 1 also outlines the number of applications finalised or withdrawn in each cycle in column 6. For example, in cycle 1 of the RBA process phase 1, three (3) applications were finalised and two (2) were withdrawn while 6 were finalised in RBA phase 2. Cycles were repeated four times depending on the queries and whether the response from the applicant was compliant or not.

Discussion

Alternative regulatory review models

Authorities use different regulatory review models to expedite access to medicines. These review models include the use of reliance strategy, whereby a regulatory authority in one country may consider and give significant weight to scientific assessments or inspection reports performed by another authority or trusted institution. Verification, abridged, and mutual recognition models are the reliance approaches that are used. Abridged review model is a selective assessment of market authorisation data, provided the product is registered by a reference national regulatory authority (NRA) [25]. This sort of study focuses on country-specific product quality requirements and clinical data for benefit–risk analysis. Verification model allows NRAs to rely on another NRA's regulatory decision by only comparing the submitted data which speeds up regulatory review [25]. SAHPRA implemented reliance models in 2019 and it was anticipated that using the verification and abridged review methods for most generic applications would reduce the backlog, however, this was not the case. SAHPRA considers the following countries as reference NRAs: USFDA, the European Medicines Agency (EMA), individual EU member states, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Swissmedic, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom, and the Australian Therapeutic Goods Administration (TGA) [16]. From this pool of authorities, full unredacted assessment reports are required to confirm the review. The limitations of this model include:

- In some circumstances primarily when European countries are NRAs, applicants have the reports and would share these with the authority, however, in most cases, these would not be available. The applicant must subsequently submit a letter confirming similarity to the reference country's application. The process of obtaining the reports from the NRAs takes months as they have other priorities. In other cases, the NRA requires the principal marketing authorisation holder to submit a declaration of access for the applicant in South Africa for authorisation of sharing the reports which would often take months before receipt of the reports. These result in delays in the registration timeframes
- From the reports shared, it is evident that the majority of the submissions had undergone numerous variations without amendments approval letters. The applications will then be subjected to full review and this will constitute more work as the information from the other regulatory authority required validation.
- Generic, well-known, pharmacopoeial applications registered in NRAs without unredacted reports will undergo a full review. Due to the absence of the reports from the NRA, a comprehensive review would be done even though these applications pose a negligible risk based on the aforementioned characteristics. This approach wastes scarce resources for an organisation with significant resource constraints, necessitating the need for an alternative strategy for such applications.

As a result of the abovementioned drawbacks, approximately 20% of the applications were legible for the reliance pathway and the rest had to be subjected to full review. The RBA model is intended to deal with well-known generic applications that do not qualify for reliance review [22]. In-depth discussions are made for each stage of the registration process to identify obstacles and root causes of the backlog and how they were addressed by the RBA strategy to expedite the registration process.

Allocation timeframe

The median value from receipt of dossiers to allocation for assessment is 682 calendar days for the MCC products finalised between 2011 and 2017, this is considerably higher compared to ANVISA with 214 calendar days for applications approved between 2013 and 2016 [1]. Insufficient human resources resulted in time-lapse of approximately two years from receipt to allocation of the dossiers. Regular applications received in 2012 were only being allocated in 2016 [13]. This demonstrates that since the fast-tracked applications received priority for evaluation, the waiting period for the regular applications was 4 years in 2016 [14]. These delays had resulted in a backlog of 7902 applications in 2016. To eliminate the backlog, in 2019 SAHPRA started a project named the BCP as described in the section above [19]. Due to this, the date of receipt for applications in the BCP and RBA pilot study are the re-submitted dates. These are reported as 278 and 431 days, respectively. The difference in these times is attributed to the different times that were allocated for the various re-submission windows. For instance, RW1 was resubmitted between 01 August 2019–30 September 2019 while RW8 was resubmitted between 01 July 2020 to 30 July 2020 which is almost a year later [20] (see Additional file 1). Applications in earlier windows were assessed first while applications in later windows awaited the availability of evaluators. Although the median values of 278 and 431 days are quicker compared to that of the MCC timeline of 682 days, they remained to be higher than those of ANVISA with a timeline of 214 days. Apart

from ANVISA there has been no other reports on timelines for each stage of the registration process by regulatory authorities. Even with the improved process and re-submissions SAHPRA implemented with the BCP, it was unable to reduce this timeline to a minimum which is what the authority would need to work on improving for reduced turnaround registration times.

Preparation of assessment reports

The time difference between the date the application was allocated for review to date when the report was received essentially determines the time it took to conduct the scientific assessments. Once the products were allocated for scientific review, the MCC process took approximately 201 calendar days to evaluate the quality and bioequivalence aspects of the dossier. A number of factors resulted in this time difference. These are highlighted below:

- The sample selected is on non-sterile products which require the evaluation of both the quality and bioequivalence studies. The available evaluators either had expertise in either one of the areas or both, therefore allocation of these would in most cases be to two different evaluators. Due to the different rates and initiation times of evaluation, one evaluator would have completed a quality assessment while another would not have started the bioequivalence assessment, or vice versa, since the allocations were conducted in bulk and were not monitored.
- The authority had a lack of skilled staff to conduct the scientific reviews and largely used external evaluators. The PEM, P&A pre-registration Unit utilised 15–20 quality evaluators and only 8–10 bioequivalence evaluators. This also led to having more quality sections evaluated while the bioequivalence sections were outstanding in some cases, thus delaying the evaluation times further.
- Once applications were given to the evaluators, there was little to no supervision of them; thus, an evaluator would work on an application for a long time without authority oversight. This led to the inability to track applications during the review process due to the lack of an efficient document management system.
- Since the external evaluators had primary work, they could only evaluate limited number of applications in their free time.

The time gap from first allocation to the time the report was received was substantially reduced from 201 to 63 calendar days for the BCP timeframes due to careful monitoring to achieve the project's aim of clearing the backlog in two years. This demonstrates how important it is to carefully oversee the registration process from beginning to end, especially in the P&A pre-registration Unit. This was also facilitated by the fact that there were more than thrice as many evaluators (63) employed to carry out the assessments as there were for the MCC process. The BCP also changed the assessment tools used which impacted on the review times. The timeline was further reduced to five (5) calendar days in the RBA phase 1 process utilising only 10 evaluators for the 63 applications and 17 evaluators for 159 applications in RBA phase 2. The five days were sufficient for the evaluators to submit their assessments owing to the strategic bulk allocation process that was used with identified similarities of applications. On average, 2 to 3 applications each week were allocated, and the evaluators would submit all the reports at once. RBA employed meticulous and thorough monitoring of each stage of the process as well as strategies to refine and reduce the review timelines. The implementation of the risk-based approach by SAHPRA is extensively reported on by Moeti and colleagues [22]. The report includes the evaluation timelines which are lower compared to the two processes detailed above.

A trend is observed with response cycles with the timelines becoming shorter as the cycles increase. For cycles 2 through 5, the MCC process had median values of 186, 56, 31 and 16 days from the time the response was received to the completion of the evaluation report, whereas cycles 2–4 for the RBA process saw a reduction with median values of 4, 2 and 2 days. The median evaluation time for the responses was also reduced to about three hours for initial responses. The RBA process evaluated the responses internally to effectively shorten the timelines compared to when external evaluators are assigned. The use of internal staff was, therefore, cost-saving.

Peer review process

The MCC process involved an additional individual peer review to be completed prior to the committee's peer review meeting, which contributed to 171 calendar days to the time taken to peer review the initial reports that were received. EMA reported on their target assessment time of up to 120 working days for initial reports which incorporates the review and peer review process while ANVISA reported 19 days for assessment and peer review [1, 26]. The combined timelines are much shorter compared to that of the MCC process. The reports from the MCC process were peer-reviewed after the evaluations were concluded by the Chair or deputy Chair of the Committee before being discussed at the Committee meeting. This meant that the peer reviewer would need to get the hard copy dossiers to conduct an in-depth

review of all the applications. Upon completion, the meeting documents were compiled and couriered to the Committee members, who also reviewed the documents independently. The P&A Committee met every six weeks, which limited the number of meetings to six or seven per year, each lasting 3.5 days, and during which the product conclusions were made. As a result, there were delays as limited reports could be discussed for one peer-review meeting session.

Since the MCC process produced a median value of 171 calendar days which is over six months, it was necessary to modify it and employ a monitoring mechanism in order to shorten this timeline. The BCP process, therefore, amended the peer review process and included a one-person peer review as well as a one-person quality assurance approach. The Committee meeting setup which promoted collaborative scientific decision-making was removed from the process. The median timeline was reported as 29 days from the period when the report was received to when it was allocated for peer review; 35 days from the period when the report was peer-reviewed to when it was assigned for quality assurance; and 30 days from the period when quality assurance was initiated and concluded. This is an overall median time of 94 calendar days for the peer review process employed in the BCP process. The refined BCP process suffers some drawbacks such as lengthy non-standardised queries to the applicant which resulted in requests of multiple extensions to respond to queries raised by the authority. In addition, significant inconsistencies in the queries were observed; applicants would receive different queries for similar products as different reviewers were used and inappropriate peer review was conducted. This also led to significant delays in registration times.

The peer review meeting approach, which is also employed by the USFDA and EMA was reinstituted in the RBA process [26, 27]. Weekly peer reviews were held, allowing for a quicker flow of query letters to the applicants. The peer review meetings provided evaluator alignment in terms of the review criteria used. These sessions also played an important role in facilitating thorough scientific debate regarding the queries raised by the primary reviewer, based on the risk to the product in question. The approach required the peer reviewers to apply analytical thinking and research skills to determine the relevance of the initial queries based on the data provided and type of application, as well as its risk to the end user. Soliciting multiple experienced reviewers to provide peer reviewer input was effective, as it ensured thorough review of all critical quality attributes, which, in turn, offered assurance that only products of high quality, safety and efficacy were approved. The timeline was significantly decreased to 10 calendar days in the RBA process. Given the expertise of evaluators employed, the meetings acted as a platform for peer review and quality assurance. The When Available poll [23] was used to determine the most suitable time for each peer review session based on the evaluators' availability. The reports were then compiled into meeting documents and uploaded on Google Docs [24] well in advance (5–7 days) to allow evaluators to provide their comments [22]. The living document would then show all comments in real-time, allowing all evaluators to see each other's comments and refer to the electronic version of the dossier on the regulatory agency reviewing software, EURSNext, when required. This assisted in drastically reducing the meeting sessions as only specific points of discussion, highlighted by the peer review panel, were discussed. Most other aspects were collaboratively deliberated on during the real-time discussions via the Google Docs. This approach further minimises the risk as multiple assessors peer-review an application and can comment on the notes made by other peer reviewers which further facilitated review and reduces registration time considerably.

List of queries to the applicant

In the MCC process, a median value of 74 calendar days, which is significantly high, was observed between the time when the peer review is completed to when the query letter is issued. Without detailing the peer review process, ANVISA claimed a time difference of 19 calendar days for this stage [1]. Once the peer review meetings were concluded in the MCC process, query letters were created using the meeting minutes. Lack of oversight and control resulted in the P&A Unit exceeding the targeted 14 calendar days for this step.

Since the peer review meeting approach was not used for the BCP, this timeline is not provided; nonetheless, the determined median value from the date of receipt of the quality assured report communicating the deficiencies observed was 30 calendar days, whereas the median timeline for the RBA process was two (2) days for this timeframe. This step required proper planning and preparation. The internal evaluators who coordinated the peer review meetings ensured that the query letters were prepared well in advance and amended as reviewers made comments in the live Google Docs. After the meeting, the letters are revised based on contentious issues, which takes a few hours before being forwarded to the Portfolio coordinator (PC). The applicant would then receive the query letters from the PC. A delay of one day is observed which can be improved to ensure that the PC shares the query letters immediately upon receipt.

Applicant time

The analysis revealed that the calculated median value was 347 calendar days instead of the 90 days that was requested for response to the query letters in the MCC process. Given that ANVISA claimed a median response time of 120 days [1], this is noticeably excessive. EMA also allocates a response time of 3–6 months to the applicant once the clock-stop is paused [26]. There were numerous extension requests and a lack of response monitoring tool to easily identify when the target time is exceeded. Therefore, in some instances, the applicant would surpass the time without requesting extensions which led to a significantly high median value. This demonstrates the criticality of an effective monitoring tool at each stage of the process. The PCs were, therefore, introduced in the BCP and RBA process, to monitor and identify when the target time is exceeded.

The response timeframe was shortened to the 20 working day target period in the BCP from the 90-day target of the MCC process, however, the median timeline of 84 calendar days was obtained. For the RBA process phase 1, the calculated median value for the initial response from the applicant was 25 calendar days, with a target response time of 15 working days. The difference in RBA response times for cycle 1 (25 days), cycle 2 (18 days), and cycle 3 (10 days) and a similar trend for phase 2 was attributed to the initial queries receiving a 15-working-day response window taking in cognisance, the magnitude of the queries raised, while subsequent queries received a 10-day response window. The applicant's response time largely depended on the type of queries recommended; if significant adjustments are suggested, they requested a longer extension which was granted, and this resulted in a longer approval time.

Response cycles and delaying queries

If the queries raised in the query letters are not addressed, the response cycles would repeat. The authority did not set a limit on the number of response rounds in the MCC process, which slowed down the finalisation timeframe. The average response cycles were five, and the maximum period for an application to be approved was 4361 calendar days. Lack of monitoring and control allowed some applications to go unattended until the applicant inquired about the status of the application.

The other aspect which led to multiple response cycles is common deficiencies observed in the quality and bioequivalence study evaluations which resulted in back-and-forth communication with the applicant [13, 18, 19]. The deficiencies in the specification sections of the API and FPP were the most prevalent and included requests to tighten the proposed specifications of the product. In such cases, the applicant would provide a justification for retaining the proposed specification, but the authority would either decline or request additional supporting data, resulting in extended cycles. These were particularly common for tightening impurity limits, assay limits, and dissolution limits, when applicable. The applicant would offer the justification listed below for not tightening the proposed specifications:

- Request to gain further experience of the product and obtain data from future batches to be manufactured before tightening the specifications.
- Justifying retaining the limits based on the results observed in the stability data.
- Justifying retaining the assay limits based on the limits stated in the pharmacopoeia when the submitted results show that the percentage label claim of not less than 95.0% can be attained for the lower limit.
- Justification to use specifications that are wider than the bioequivalence batch results.

These were some of the justifications provided that were not accepted by the authority. The specifications are set and proposed based on the submitted data, any specifications wider would not be accepted since batch-to-batch consistency and reproducibility should be maintained throughout all future batches manufactured compared to the initial validation and bioequivalence batches.

The stability sections also had recurring deficiencies such as the request for further stability data to support the proposed retest or shelf life. These fell under the common deficiencies reported by SAHPRA and are discussed extensively in the recent publications [13, 18, 19]. The response cycles would be shortened as all requirements could be met with the approach of informing manufacturers of the common deficiencies identified.

Final adoption for registration

Once the product was finalised in the MCC process, it was sent to the administrative Unit to be collated with outcomes from the other Units before it can be registered. The median value for this stage was calculated as 482 days. This was attributed to the following:

- The initiation of evaluations was conducted at different times therefore finalisation within Units was not synchronised.
- Finalised product history packs were not sent to the administrative Units immediately upon finalisation.
- The inspections were undertaken after the P&A preregistrations and Clinical evaluations Units completed their scientific assessments. Historically, the

assessment process has been lengthy, and sites may not be GMP-compliant at the time of approval; hence, inspectors opted to perform inspections after assessments were complete. If the result was a negative GMP status, an inspection had to be rescheduled, which slowed registration, and in certain cases resulted in a rejection if the manufacturer did not meet the required GMP standards.

The following serve as potential solutions to obtain a reduced median registration time for this step:

- Sending queries simultaneously to applicants can reduce the number of unsynchronised finalisations. Units must therefore constantly discuss which applications to evaluate first. Having Units that are ahead of others in terms of evaluations would not result in registration; rather, additional personnel can be provided to the Units with the most work.
- With the synchronisation between Units executed, the finalisation of an application would be at similar times and properly monitored by the administrative Unit, now called the Health Product Authorisation (HPA) Unit.
- Inspections must be undertaken at the beginning of the process, and the status of the manufacturer must be established before scientific evaluations can be conducted.
- Increased frequency of registration meetings from six-weekly in the MCC process to weekly in the RBA process.

The last two solutions above were utilised in the BCP and RBA procedures, resulting in substantial improvements of the timeframes to 125 and 61 calendar days, respectively. RBA Phase 2 study saw a reduced timeframe of 33 days since most of the applications were already finalised by the other Units.

Finalisation timeframe

Finalisation is the conclusion of an assessment by each respective Unit before registration. The finalisation timeline facilitates a comparison of the three processes utilised by SAHPRA between 2011 and 2022. The timeline was reported as 1470, 501, and 68 calendar days, for the MCC process, BCP process, and RBA phase 1 process, respectively, as depicted in Fig. 2. The median finalisation time of 73 calendar days was observed for the RBA phase 2 pilot study which consisted of a larger sample of 159 applications with a similar process as RBA phase 1. The finalisation time for the RBA process was drastically shortened, which is largely attributed to the strategic refinement, implementation of efficiencies, assessment style and ongoing monitoring of the registration process. The detailed examination of the MCC process enabled the authority to clearly identify the root causes inside the process; once these were discovered, the optimised and efficient RBA procedure was developed and piloted. The results clearly demonstrate that this procedure would reduce the backlog that has accumulated over time. It is crucial that each stage of the RBA process, as depicted in Table 1, has a precise deadline and monitoring mechanism to guarantee that these timelines are adhered to. The upscaling to 159 applications of the RBA procedure confirmed its repeatability and reproducibility with similar median timelines obtained. This robust procedure can therefore be utilised by other agencies who may have a backlog or want to optimise their registration process.

Registration/approval timeframe

It was determined that the median approval/registration time between 2011 and 2017 was 2092 calendar days. Relative to other regulatory authorities, such as TGA with 244 calendar days for 85 applications in 2021 and ANVISA with 795 days between 2013 and 2016, the calculated median time for the MCC process was exceptionally long. [1, 9] This approval time was recorded as 591 calendar days for the BCP but was reduced to 511 calendar days for the RBA process. The median approval time for the RBA is due to the substantial amount of time the application waited in the queue for allocation. These applications had already been resubmitted early to mid-year 2020 and were awaiting allocation until September 2021. Therefore, almost 18 months had lapsed. This was deduced from the observed calculation of the median finalisation timeline of 68 days, thus, the remaining 443 days were attributed to applications waiting in line for allocation.

Conclusion

This study identified the root causes which led to the formation of a backlog in the investigation of the MCC process. The factors were identified as inefficient processes employed, lack of monitoring and control, insufficient skilled staff for conducting the scientific assessments and limited review pathways employed. The most critical root cause was identified as the lack of monitoring and control by the authority in each step of the registration process which inevitably led to lengthy approval times. Comparison with the Brazilian authority also revealed that the claimed timeframes for the period 2011–2017 are much longer and must be substantially reduced to provide South African citizens with expedited access to medicine. The implementation of the BCP in 2019 introduced measures and resources that allowed for careful monitoring of the process.

These contributed to reducing the reported end-to-end registration timelines, but they continued to remain longer than those reported by other authorities, and the targeted timelines were not met. In addition, the authority continued to develop a backlog despite the implementation of the process; consequently, more optimisation and refinement was required to meet the reduced timelines. The RBA approach was then piloted in 2021 and 2022, and its findings were much better than those of the previous two processes. A finalisation timeline of 68 and 73 calendar days was reported for RBA Phase 1 and 2 pilot studies, respectively, which is significantly shorter than the 1470 and 501 days indicated for the MCC and BCP processes. This rigorous RBA approach may also be used by regulatory agencies throughout the world to alleviate a backlog or to improve the efficiency of the existing process.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40545-023-00537-0.

Additional file 1: Table S1. The overview and approval times of the samples used in the Backlog clearance project and Risk-based assessment processes.

Author contributions

LM: developed the study design, collected and analysed the data, interpreted the results and wrote the first draft of the manuscript. ML: developed the study design, assisted in collecting and analysing the data, provided guidance for the data collection and analysis, interpreted the results and reviewed the manuscript. JJ: developed the study design, provided guidance on the data analysis, interpretation and relevance of the results and reviewed the manuscript. All authors read and approved the final manuscript.

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Declarations

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Not applicable.

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Competing interests

No conflicts of interest that are directly relevant to the content of this article. The views expressed in this article are the personal views of the authors and may not be used or quoted as being made on behalf of, or reflecting the position of SAHPRA.

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