Additional regulatory review pathways can facilitate faster dossier approvals in South Africa

by

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Abstract

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Objective

The objective of the study was to perform a comparative review of pathways, timelines and improvements of countries with markets that the South African Health Products Authority (SAHPRA) benchmark themselves against. Furthermore, this study intends to identify the factors that improved and accelerated submissions and approval process in investigated countries and potential introduction of these strategies into the South African market.

Methods

The research is a literature-based retrospective analysis, with the aim to provide a qualitative analysis using information gathered from different regions with which SAHPRA benchmark themselves against. Data was collected from these identified markets' pathways and review routes, from when an application was received, until the date that it was approved or authorised. Data was collected from 1995 through to 2018 to illustrate the effect of accelerated review procedures and set target times. Median approval times were provided when standard and accelerated assessments by the different authorities, were compared.

Results

The results highlight key differences between agency practices, but the median approval time decreased over time, while key barriers were targeted. The introduction of additional and accelerated pathways facilitated the review process. In 2018, the percentage of expedited reviews compared to standard approvals was highest for the United States' Food and Drug Agency (FDA) at 73%, followed by Health Canada at 35% and Japan's Pharmaceutical and Medical Devices Agency (PMDA) at 28%. For both the European Medicines Agency (EMA) and Australia's Therapeutic Goods Administration (TGA) the percentage of expedited reviews compared to standard approvals was 10%. The impact of the expedited review systems enabled the reduction of review times and contributed to faster approvals, as was demonstrated in all countries. The use of target review and response times ensured faster approvals.

Conclusion

The use of dedicated pathways to review different applications, along with set review timelines can extensively benefit the South African review process. Through the evaluation of different systems, comparable investigations can be conducted by SAHPRA and this will allow the authority to gain information regarding the use of promising medicine. The impact of the expedited review systems can enable the reduction of review times and further contribute to faster approvals.

30 October 2019

Declaration ×

I declare that *Additional regulatory review pathways can facilitate faster dossier approvals in South Africa* is my original work. This work for the degree of Master of Science in Pharmacy Administration and Policy Regulation has not been presented or submitted for examination in any other university, and all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full name..ILONA MATTHEW..... Date..30.10.2019.....

Signed.....

Acknowledgements

To my research project supervisor, Professor Jacques Joubert, thank you for your support and guidance. To my family, Daniel, Alex and Nic Matthew, thank you for your patience, endless support and prayers.

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List of Abbreviations

ANDA	Abbreviated New Drug Application
AR	Assessment Report
API	Active Pharmaceutical Ingredient
BsUFA	Biosimilar User Fee Act
CADTH	Canadian Agency for Drugs and Technologies in Health
CDER	Center for Drug Evaluation and Research
CIRS	Centre for Innovation in Regulatory Sciences
CMS	Concerned Member States
CORs	Comparable Overseas Regulators
CTD	Common Technical Document
CHMP	The Committee for Medicinal Products for Human Use
DCP	Decentralised Procedure
EC	European Commission
EDL	Essential Drug List
EMA	European Medicines Agency
EPAR	European Public Assessments Reports
EU	European Union
FDA	(United States) Federal Drug Agency
FPP	Finished Pharmaceutical Product
GDUFA	Generic Drug User Fee Act
GRevPs	Good Review Practices
ICH	International Conference on Harmonization of Technical Requirements
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MCC	Medicines Control Council

MS	Member States
MRP	Mutually Recognised Procedure
MMDR	Australia's Review of Medicines and Medical Devices Regulation
NASs	New Active Substances
NCEs	New Chemical Entities
NDA	New Drug Application
NME	New molecular entities
NP	National Procedure
NOC/c	Notice of Compliance with conditions
NRA	National Regulatory Authority
OECD	Organisation for Economic Co-operation and Development
PDUFA	The Prescription Drug User Fee Act
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PMDA	(Japan's) Pharmaceutical and Medical Devices Agency
PRIME	Priority Medicines
RMS	Reference Member State
SAHPRA	South African Health Products Regulatory Authority
TGA	(Australia's) Therapeutic Goods Administration
USA	Unites States of America
WHO	World Health Organization

Chapter 1: Introduction

Access to affordable medicine has always been a contentious issue and a major challenge in emerging markets. Health systems are under tremendous pressure to improve access and simultaneously be adequately staffed and equipped to meet the demands and requirements of any population (Gray, 2004). Taking into consideration all the improvements in medical research and development on a global scale, certain regions of the world still wait to benefit from timely access to new medicine.

South Africa has a two-tiered healthcare system. The Organisation for Economic Co-operation and Development (OECD) estimates that the private sector looks after the needs of approximately 16% of the population (i.e. 10 million people) while the public sector looks after the needs of 84% of the population (i.e. 48 million people) who cannot afford medical insurance (OECD, 2018). The population has increased gradually since 1960 and with a current estimated population of 58 million people in 2019, there is a great demand for pharmaceutical products in the country (The World Bank, 2019).

With the presence of pharmaceutical companies operating in specialised markets, the country has clinical trial capabilities and the ability to manufacture both active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs). However, high investment costs are required to gain a competitive position within the market, therefore pharmaceutical companies have limited entry into the South African market. This barrier creates a noteworthy reliance on imported APIs and FPPs (Soomaroo, 2017).

The South African pharmaceutical market receives medicines from approximately 130 manufacturers and importers (OECD, 2018) and with a struggling economy, the South African Rand (ZAR) is always exposed, due to fluctuations in the exchange rate. Moreover, the national regulatory process is complicated with a considerably long registration process for both new medicine and generic applications, of which the background will be discussed.

A pharmaceutical product is assessed by the national regulatory authority (NRA) based on the efficacy, safety and quality profile, before it can be sold to the public. The regulator has to balance access to medicine, with a thorough benefit-risk assessment. However, due to poor infrastructure and limited resources, the entire review process in South Africa is delayed, which in turn delays the country's access to medicine. Compounding the delay, are the large number of applications that are received on a daily basis. As approval times are a key indicator to assess the performance of a regulatory agency (Bujar, Patel and McAuslane, 2015), a dramatic improvement in strategy is required to drastically improve the current review processes.

1.1 Medicines Control Council (MCC)

For more than 20 years, the MCC of South Africa faced numerous complaints from pharmaceutical industries and clinical research organisations, that the delays in the registration of medicines were preventing access to affordable medicines. Leng, Sanders and Pollock (2015) found that the increase in applications being submitted were predominantly linked to a large influx of generic applications. Further analysis indicated that this was due to an implementation of an expedited review policy to boost the accessibility of generics in the country. This policy was meant to stimulate a pricing competition in the market. However, it revealed that the regulatory activities, the infrastructure and available resources of the MCC were not able to handle the volume of

applications that started to flood the regulatory authority. Figure 1 refers to the (previous) MCC structure and its expert committees.

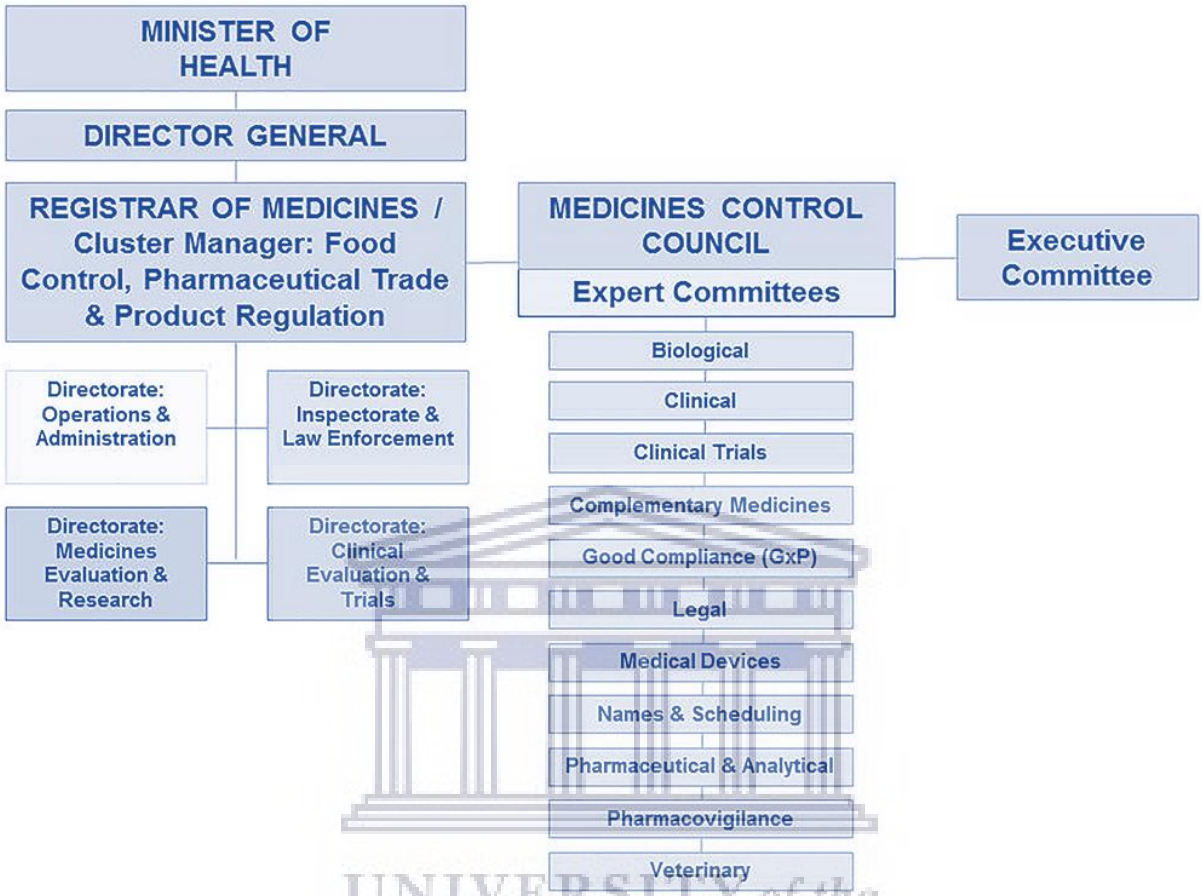


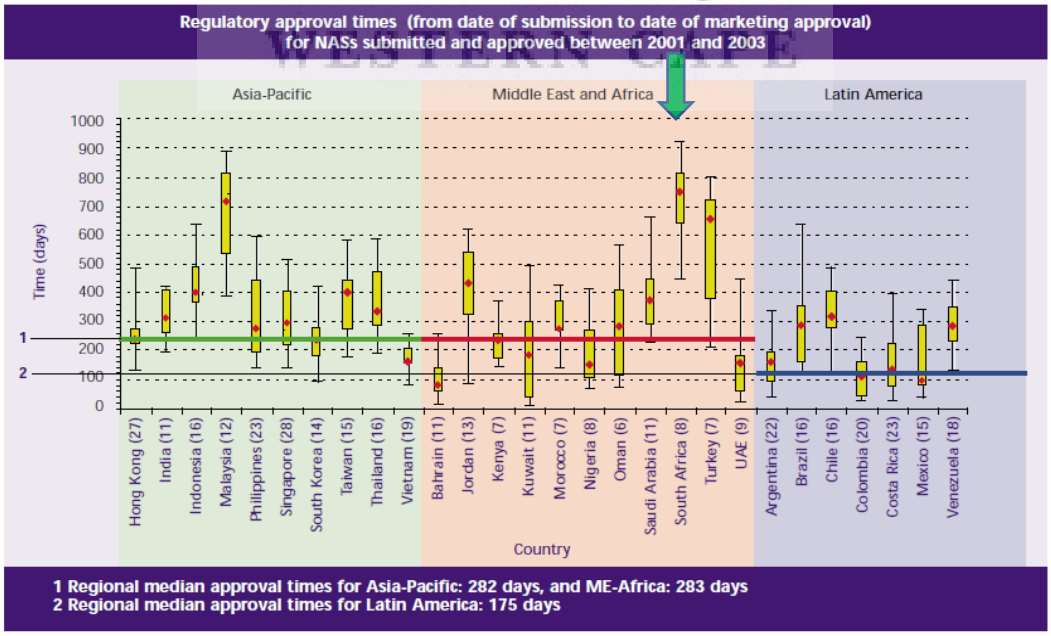
Figure 1. Medicines Control Council Structure. Source: Keyter (2018)

When the Medicines Control Council embraced the Common Technical Document (CTD) format in 2011, it slowly opened its doors to harmonisation. Their aim was to facilitate the submission of information, save industry resources, provide efficient assessment and faster availability of medicine (Taute, 2013). Through harmonisation, the plan was to strengthen the allocation of resources in the country, whilst it established collaborations with other regulatory authorities and effectively combined the regulatory efforts. Collaborating with other countries was meant to reduce regulatory barriers such as unnecessary duplication and ultimately expand on pharmaceutical trade. Nevertheless, efforts of improvement were unsuccessful, and the backlog remained unresolved.

Leng *et al* (2015) stated that the reasons for the continuing NRA backlog was due to:

- Lack of skilled staff, the MCC was dependent on external reviewers from academia and research institutions;
- Absence of an effective document management system, therefore an inability to locate or monitor applications throughout the review process;
- Lack of finances, therefore an inability to improve the existing infrastructure and to attract competent staff.

During the time period 2001-2003, South Africa had a median approval time of approximately 750 days (McAuslane, 2006) compared to approximately 1300 days in 2015 (Liberti, 2017). To place the timelines in context with other emerging markets, Figure 2 and Figure 3 indicates the median approval timelines of South Africa for New Active Substances (NASs), during different time periods. With a current full assessment that can take up to 5 years, it is clear that there are opportunities for an enhanced regulatory review process.



Data are shown for NASs that were submitted and approved between 1 January 2001 and 31 December 2003. (n)= number of NAS. Box: 25th and 75th percentiles. Whiskers 5th and 95th percentiles. Diamond = median

Figure 2. NAS median approval times 2001-2003. Source: McAuslane et al (2006)

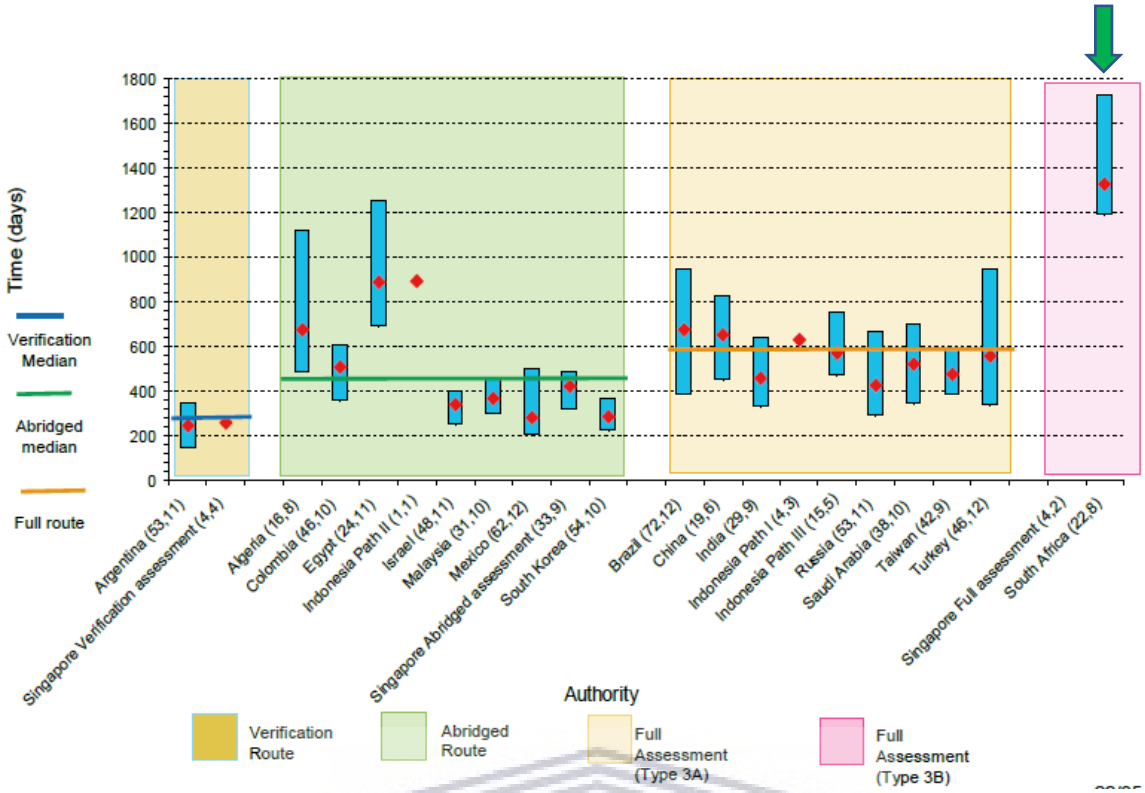


Figure 3. NAS median approval times 2015. Source: CIRS (Liberti, 2017)

1.2 The South African Health Products Regulatory Authority (SAHPRA)

The right to healthcare is enshrined in the South African constitution and the government has taken promising steps toward launching an improved regulatory body, with the intent to review and approve medicine and devices in an efficient manner. SAHPRA is currently responsible for the regulatory review of dossiers, leading to its approval. SAHPRA replaced the MCC in 2018 and is authorised by the Medicines and Related Substance Act (101 of 1965) to control the health products and its respective uses in South Africa. Figure 4 refers to the SAHPRA organisational structure and its functions.

SAHPRA also inherited the historical backlog of 16 000 medicine applications, consisting of both pre-registration and post-registration applications (Low, 2018). They assessed the regulatory procedure in South Africa and recognised the need for change. SAHPRA has therefore made the commitment to diminish this backlog within an ambitious two years and aim to be adequately resourced, with the inclusion of in-house evaluators. Their intention

is to be more system-driven, as opposed to the paper-driven process that caused the delay of approvals over the last two decades.

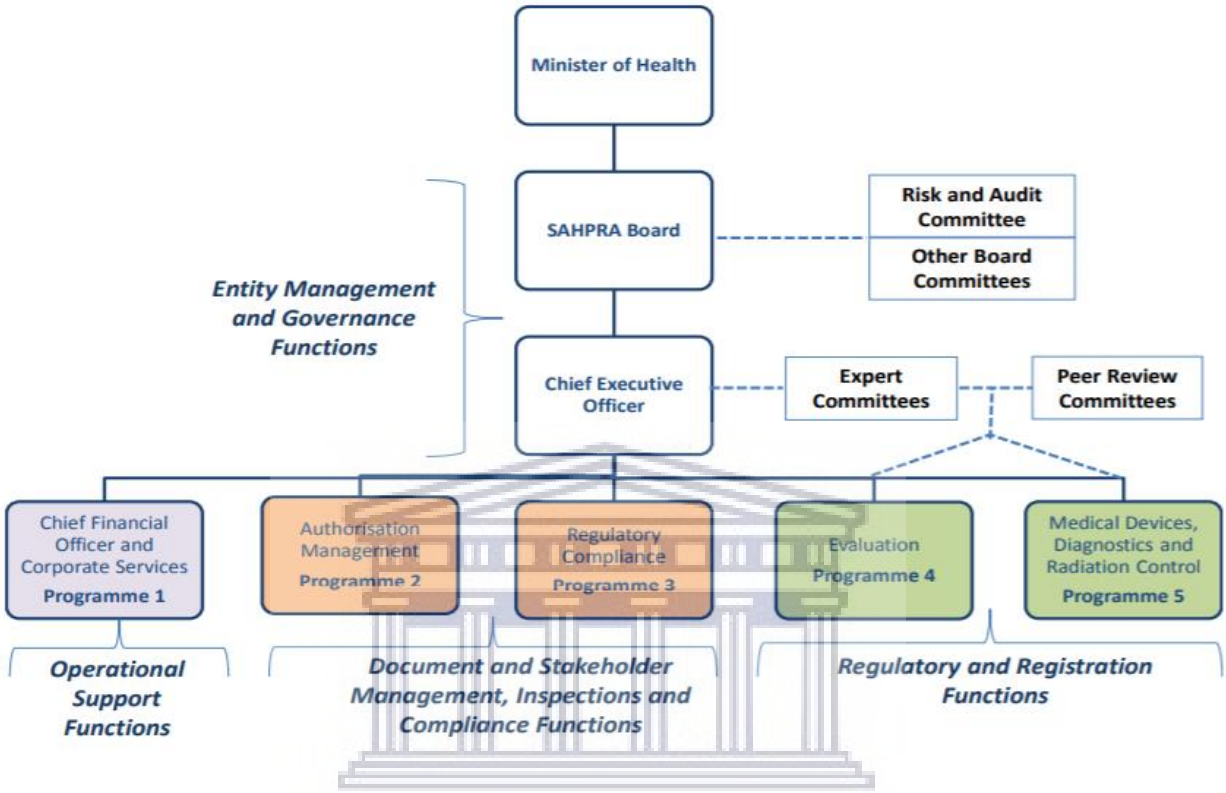


Figure 4. SAHPRA Organisational Structure. Source: SAHPRA (2018)

In a 2018 interview, SAHPRA indicated that they will undertake regulatory investigations of other jurisdictions. They mentioned Australia, Canada, the European Union, Japan and the United States of America (SAHPRA, 2019). Using this information, the purpose of this research was to perform a comparative review of the current South African framework for the submission of applications and compare this to existing review pathways in the abovementioned countries.

It is assumed that the introduction of accelerated review pathways with predetermined review targets will decrease review times. By adopting or modifying regulatory pathways that have already proven to be successful in different countries, the South African approval

process should become more efficient. The bottlenecks that are hindering the registration process of new applications, generics and eventually variations, can be identified and subsequently streamlined.

1.3 Research question

Will the South African Regulatory Authority's review timelines decrease if additional review pathways with dedicated timelines are introduced?

1.4 The research hypothesis

If the South African Regulatory Authority adopts review and evaluation pathways for product applications similar to existing frameworks in other countries, the review timelines will decrease, and the approval rate will increase.

With the aim of reaching the objectives of this study and to outline the remainder of the thesis, an evaluation of the review framework processes of all identified countries was conducted. This study will provide information on:

- The current review pathway of South Africa and its current timelines or lack thereof;
- Application and review pathways of the countries that SAHPRA intends to investigate;
- Target review times of identified countries;
- Reduction in review times over a period of approximately twenty years due to the introduction of accelerated/expedited pathways in identified countries;
- Additional improvements that was made in mature markets that allowed for the successful implementation of the additional review pathways.

Every delay in approval of medicine is also a measure of access and availability. Taking into consideration all the disparities mentioned, the review pathway should become more efficient in order to provide adequate access to medicine in South Africa.

Chapter 2: Literature review

SAHPRA has shown interest in benchmarking themselves against the mature markets of Australia, Canada, European Union, Japan and the United States, therefore these countries were defined for the review. Coincidentally, these markets used to experience lengthy delays between the 1960s and 2000s and have shown drastic improvements due to a change in their regulatory environment (Wileman and Mishra, 2010). Furthermore, when comparing regulatory agencies, the information that is obtained becomes more valuable if the countries have experienced the same challenges, as stated by Lexchin (2018).

The Centre for Innovation in Regulatory Science (CIRS) compared the median approval times in the abovementioned markets for the periods between 1995 to 1999. For this review, this information was used as a starting point and the individual country's data of standard and accelerated pathways have been collated through multiple studies from 1995 to 2018. The study incorporated the review of new applications only. The current South African review framework will be discussed first and will be followed by the defined markets.

2.1 Medicine Regulatory Review in South Africa

The current medicine review procedure in South Africa was examined, along with its use of review pathways and target timelines.

2.1.1 Review pathways

There are currently three application and review pathways, as seen in Figure 5:

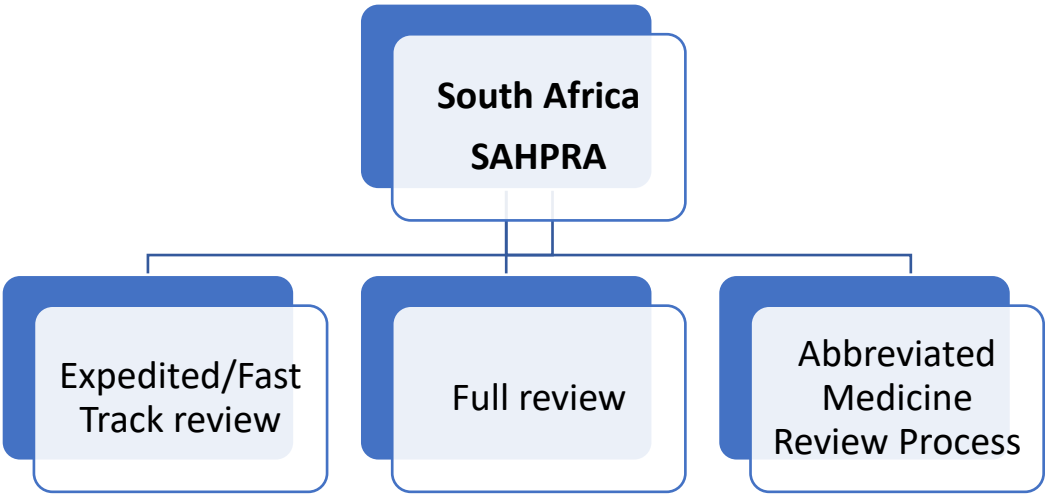


Figure 5: Existing application and review pathways of South Africa. Source: MCC (2012).

2.1.2 Types of review

2.1.2.1 Full Review

This application involves the complete review of clinical and non–clinical studies, with the level of assessment the same, irrespective of the type of application (Keyter *et al*, 2018). This means that New Chemical Entities (NCEs), generics/multisource medicine, biologics, biosimilars, line extensions and call-ups all receive a full review, with a historical review time of approximately 5 years.

2.1.2.2. Expedited Review

Medicine listed in the South African Essential Drug List (EDL) can apply for the expedited review pathway. A pre-application procedure exists only for this pathway. Once submitted, these applications are assigned a priority status in the review system, where fast track applications have a 9 months review target (MCC, 2012). NCEs that are not listed on the EDL can apply for this review, provided they are critical for public health. This is not a realistic target as the MCC and now SAHPRA is yet to achieve this review target.

2.1.2.3 Abbreviated Medicine Review (AMRP)

The AMRP was initiated by the MCC in order to reduce the review time of already approved medicine in countries that the MCC aligns itself with, provided that the application is accompanied with its assessment report (AR). The term 'abbreviated' does not refer to the application process, it is only indicative of the review process (MCC, 2012). The AMRP has no assigned target review time.

2.1.3 Process flow map

The Operations and Administration Unit of the MCC currently receives all applications. From the time of receipt, applications are screened for completeness within fifteen (15) calendar days. Multiple copies of applications are referred to several scientific committees for review, as illustrated in Figure 6.

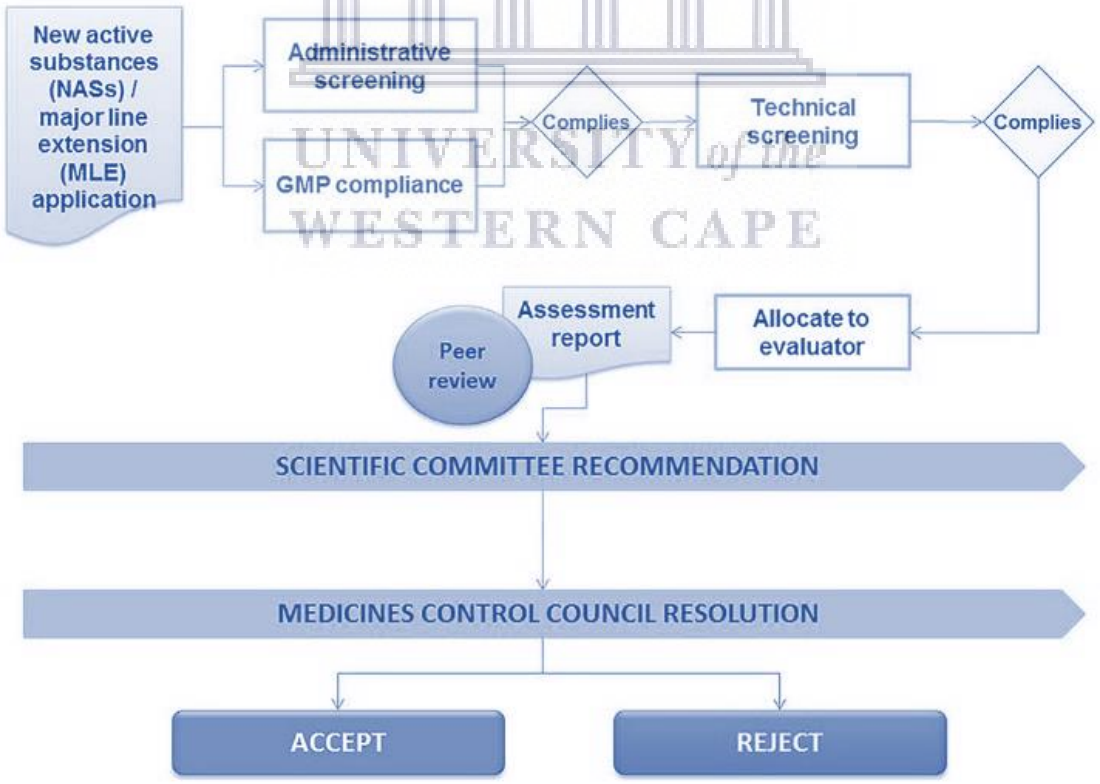


Figure 6. The process flow map of an application. Source: Keyter et al (2018)

Once an application has been assigned to an assessor, the review can be initiated. The scientific data requirements and the extent of dossier assessment are the same for all types of applications. The MCC used both internal as well as external reviewers to evaluate the data. Where internal evaluators had to undergo performance and development reviews, external evaluators did not have any review agreements in place. This arrangement compounded the lengthy delays with a substantial bearing on approval times. The respective scientific committees have no time obligations and there is currently no target time stipulated for the total review period of an application.

All the relevant committees meet every sixty days and an application requires at least four Committee reports in order to proceed to the final meeting that results in final registration. Neither the MCC nor SAHPRA are able to electronically track the dossier or monitor the time spent within each unit, due to the absence of an electronic document management system (Keyter *et al*, 2018).

Targets and milestones allow the monitoring and measuring of all applications to achieve an overall registration or approval time. Figure 7 is a review and registration process map that illustrates the key milestones that has been identified by successful regulatory authorities in other markets, showing the absence of milestone targets as well as the absence of a full review target.

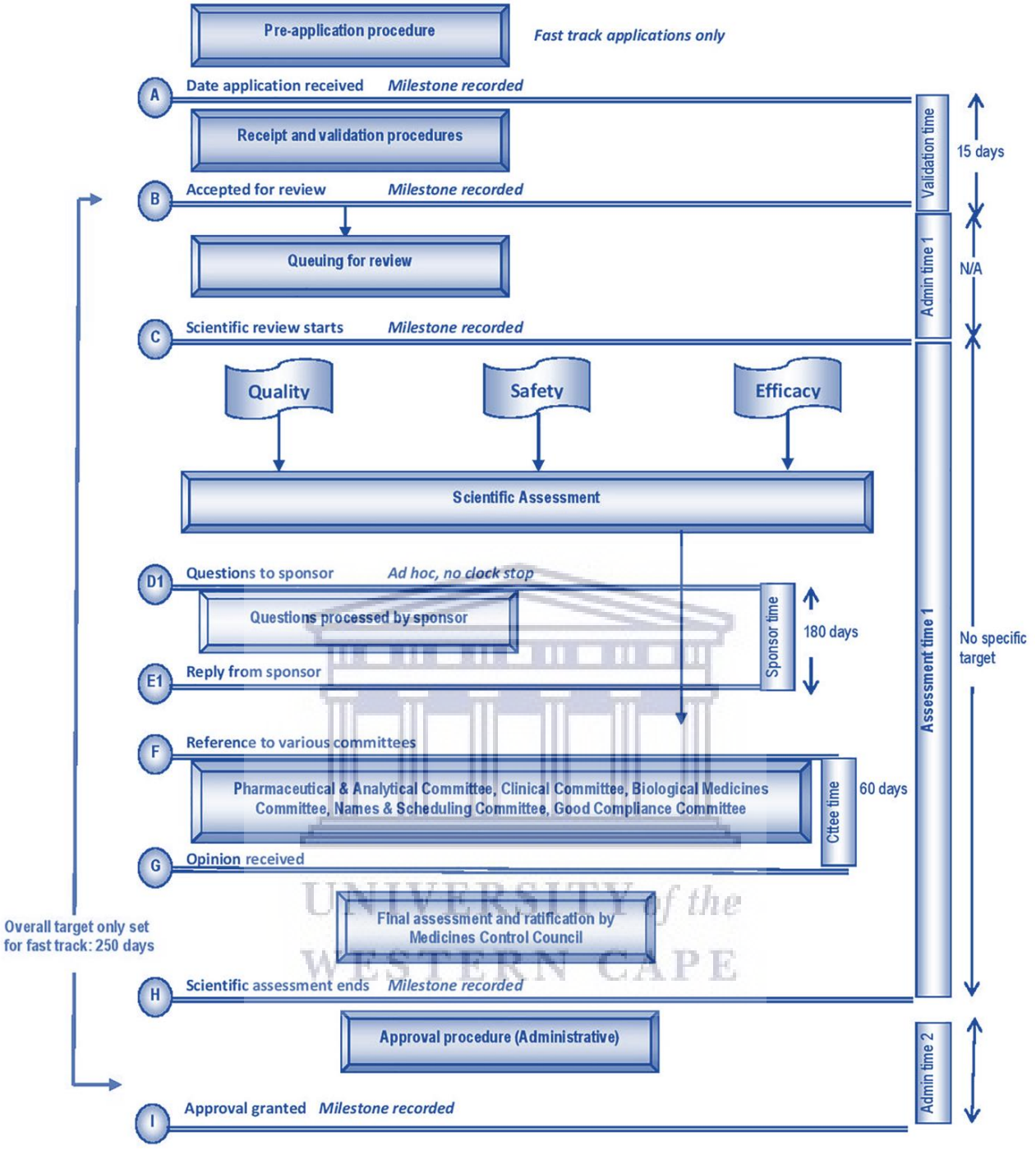


Figure 7: South African registration process map with identified milestones. Source: Keyter et al (2018)

2.1.4 Data analysed

As mentioned earlier in the study, high investment costs are required to gain a competitive position within the market, therefore pharmaceutical companies have limited entry into the South African market, imposing the dependence on imported products. With no monitoring

and tracking system, data was not readily available to adequately quantify the median approval time of both international and local company applications. Still, in a study performed by McAuslane *et al* (2006) and more recently by Keyter *et al* (2018), resultant median approval times were obtained. The studies emphasised the lengthy delays in the review process and how it has escalated over the course of two decades:

2001-2003: Approximately 760 days (Figure 2);

2015 Approximately 1141 calendar days (international) and 1218 days (local) companies (Figure 8);

2016 Approximately 1810 calendar days was the highest (international) and 1086 days (local) companies (Figure 8);

2017 Median approval time approximately 1411 calendar days (international) and 1470 days (local) companies (Figure 8).

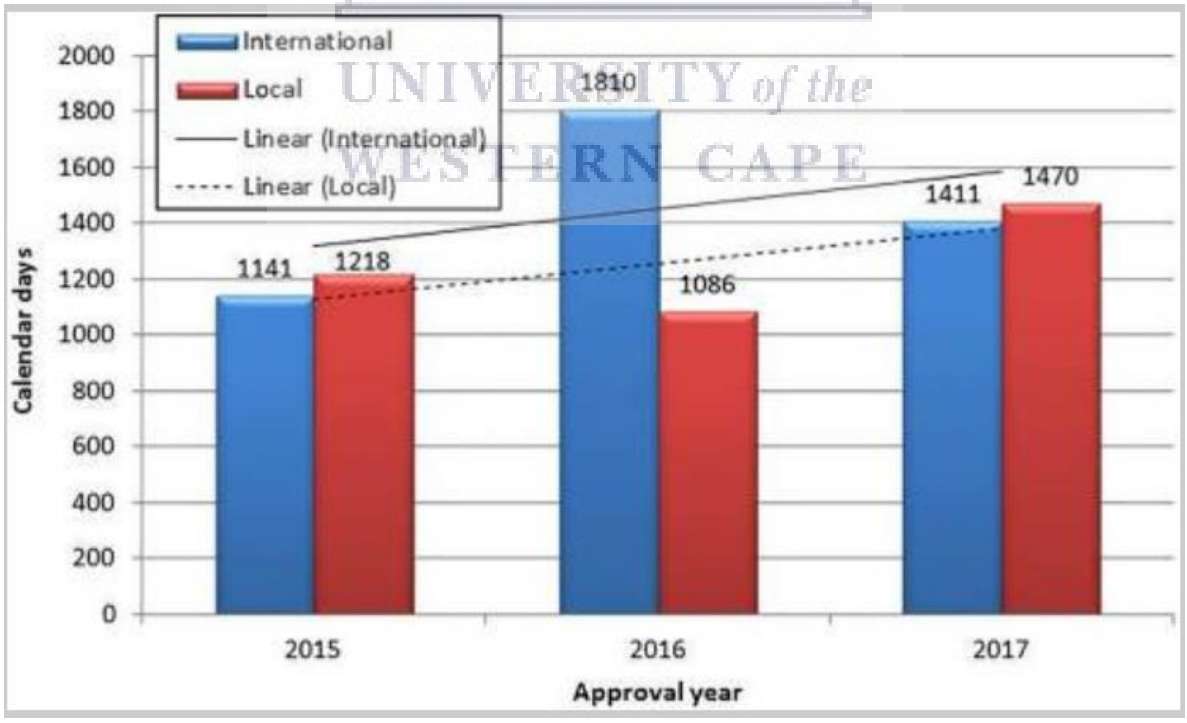


Figure 8: Median approval timelines in South Africa showing results for active substances comparing international and local companies (2015 - 2017). Source: Keyter et al (2018).

2.1.5 Key concepts

Based on the information presented in the South African review process, the following key concepts were identified, and this will form the basis of the study when examining the identified mature markets next:

2.1.5.1 Target Review Times

Realistic performance targets impact the various stages of the review process. Clear expectations and a commitment to defined review and approval times can be highly effective to ultimately achieve the goal. The European Union has extensively reduced their review process due to the agency's clear expectations of specified approval timelines, with a firm commitment to a 210-day approval timeline (https://www.ema.europa.eu/). The US has streamlined its review process for medicinal products to 180 days, with some approvals even faster (https://www.fda.gov/). Table 1 below illustrates review target times of different countries, as extracted from the respective regulatory authorities' websites.

Table 1. Target review times of different countries

Country	**Standard review target**	**Expedited review target**
South Africa	No set target	Provisional target of 250 days
Australia	10.5 months (NAS) 8.5 months (generics)	150 working days
Canada	300 days	180-215 days
European Union	210 days (NAS) 210 days (generics)	150 days
Japan	12 months	9 months / 6 months
United States	10 months	6 months

2.1.5.2 Facilitated and reliance/abbreviated pathways

Kesselheim *et al* (2015) reviewed the trends of expedited approval programmes and concluded that over a period of 20 years, results reveal a statistically significant escalation in medicine that has qualified for the FDA's accelerated programmes. The study is further supported by data from Rodier *et al* (2019) indicating that all five agencies that was reviewed, now offer accelerated programmes tailored to facilitate the review of promising medicine.

From the above, it is clear that the lack of a robust framework has an important impact on the review process in South Africa. As will become evident later, a comprehensive review by SAHPRA of all applications is not very efficient. The introduction of additional review pathways, along with target review timelines, supports the assumption that the review of dossiers will result in faster approvals.

2.2 European Medicines Agency (EMA)

2.2.1 Background

Prior to 1995, medicines in the European Union (EU) were approved for marketing at a national level, a separate application had to be submitted for each country. The lack of a single body created regulatory hurdles and did not allow for a streamlined approval process for the regulators. With financial support received from the pharmaceutical industry, the EU and its member states, EMA was established in 1995. It was formed to unify the practices of the different national bodies within the EU and to minimise yearly costs to pharmaceutical companies. Prior to this, the review of a Marketing Authorisation Application (MAA) was duplicated because companies had to obtain individual medicine approvals in the different member states (Van Norman, 2016).

2.2.2 Marketing Authorisation Pathways

The EMA established four different ways to obtain a marketing authorisation (MA): Central Procedure (CP), National Procedure (NP), Mutual Recognition Procedure (MRP) and Decentralised Procedure (DCP), as illustrated in Figure 9. This allows companies to choose in which member states they would like to market the application.

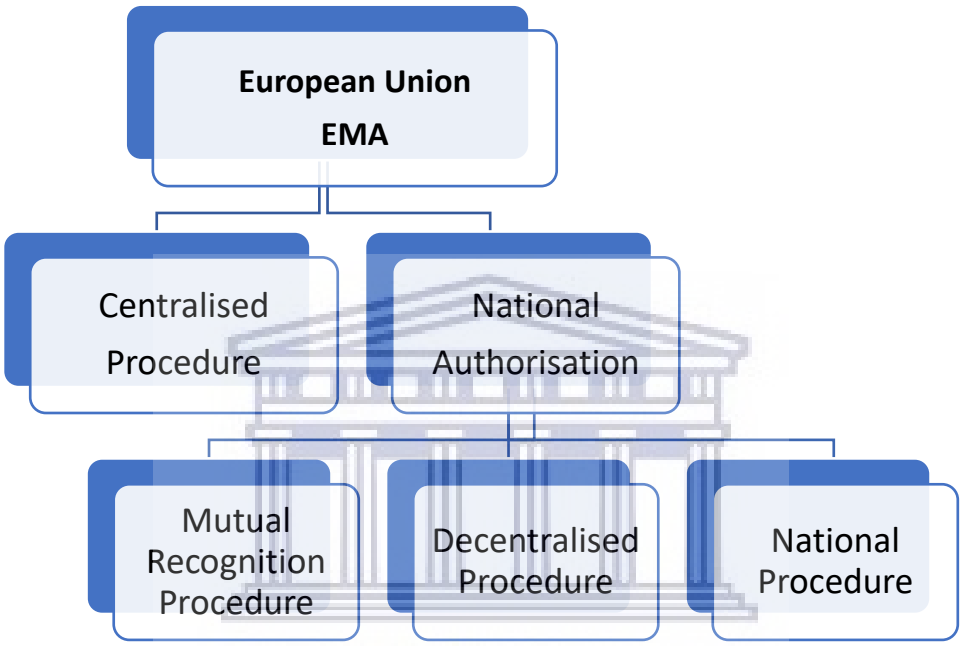


Figure 9. EMA marketing authorisation pathways. Source: EMA (2016)

2.2.2.1 Centralised procedure (CP)

This procedure grants an authorisation that is valid all over the EU. Not counting the clock-stop days when applicant have to provide additional information, this approval is usually issued within 210 days. Table 2 provides the specified timelines for the CP assessment.

The Committee for Medicinal Products for Human Use (CHMP) provides an opinion at Day 210, followed by European Commission (EC) resolution approximately 67 days later. This procedure is open to all innovative products. Upon request from the applicant, the CHMP can reduce the assessment to 150 days. Planning is imperative for innovative products,

hence the EMA recommends that applicants should request a pre-submission meeting, at least seven months prior to submission.

Table 2. Timelines for CP assessment

Article 8(3) Full Application	
Day 1	Start of procedure
Day 1-14	Validation
Day 19	Start of procedure
Day 80	Preliminary Assessment Report
Day 120	List of questions (LOQ)
	Clock-stop for 3 months
Day 121	Submission responses
Day 150	Joint Assessment Report
Day 180	CHMP decision
Day 181	The clock restarts, along with an oral explanation (if necessary)
Day 181-210	Preparation of final product information
Day 210	CHMP opinion
Day 277	EU Commission decision

Source: Van Oers (no date, accessed 2019)

2.2.2.2 National Procedure (NP)

This procedure allows for the approval in individual countries, where the applicant obtains a MA in one member state only, and the marketing authorisation is issued within 210 days.

2.2.2.3 Decentralised procedure (DCP)

This application can be submitted in more than one country, where the applicant can obtain a MA in a Reference Member State (RMS), along with multiple Concerned Member States (CMS). Once all parties have granted their decision, a MA is issued within 210 days. Any member state can be selected as an RMS. Before submitting an application, the applicant

needs to apply for a submission timeslot, as this will allow the RMS to plan ahead of time. This procedure is used mainly for generic applications. Table 3 provides the EMA specified timelines for the DCP.

Table 3. Timelines for the DCP assessment

Article 10 (1) Decentralised /Generic Application	
Day 0	Start of procedure
Day 1-14	Validation
Day 19	Start assessment
Day 70	Preliminary Assessment Report
Day 100	CMS send comments or questions
Day 105	Clock-stop for 3 months
Day 106	Applicants response
Day 120	Consensus – close of procedure No consensus – Assessment Report to applicant
Day 150	RMS + CMS comments to Applicant
Day 160	Applicant Responses
Day 180	Consensus/Close of procedure
Day 195	Break-out session, if required
Day 195-210	Resolution of minor outstanding comments
Day 210	Consensus / Close of procedure

Source: Van Oers (no date, accessed 2019)

2.2.2.4 Mutual Recognition Procedure (MRP)

This procedure allows for an MAA in more than one country. Once a MA is approved in an RMS (issued within 210 days), applicants can submit an application to a CMS (issued within 90 days). The RMS provides a final assessment to CMS based on their investigations, but this may take more than 300 days.

2.2.3 Legal basis of application

The legal basis of an application determines and indicate the content of the dossier. The type of application specifically highlights the importance of different pathways between full applications for review and abridged applications for review, based on the different information found within the dossier (as illustrated in Figure 10).

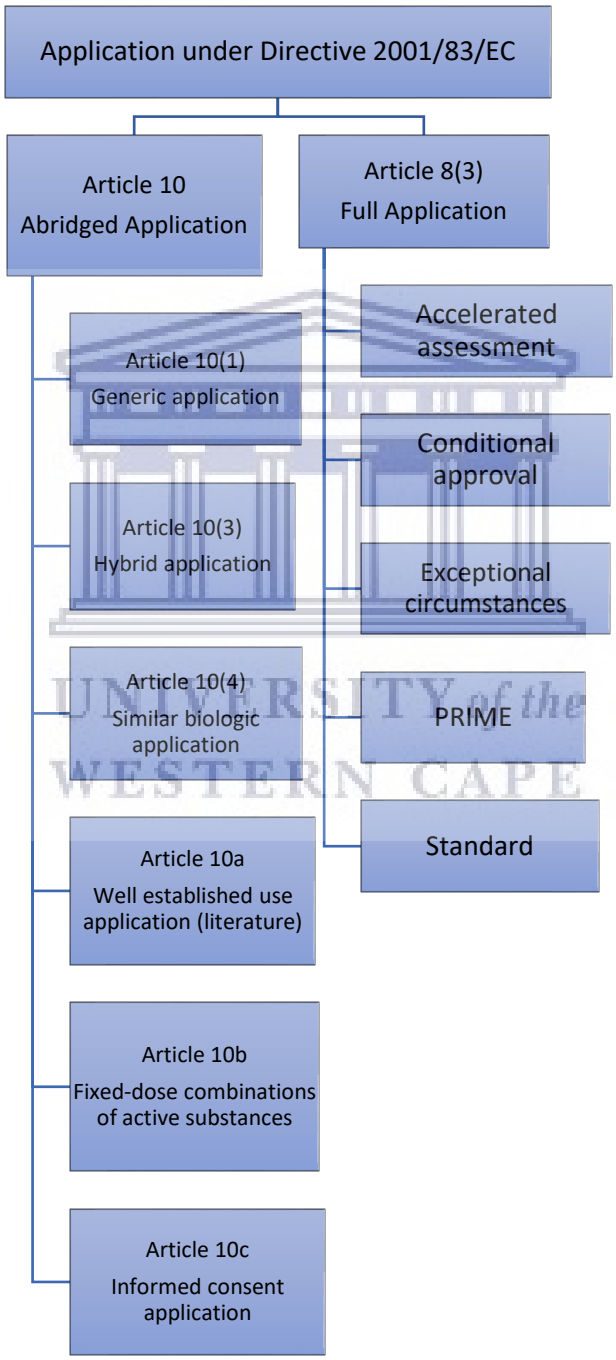


Figure 10. Types of dossier applications. Source: EMA Directive 2001/83/EC (2001)

2.2.4 Milestones for assessment

Four main milestones were identified during the review of a procedure (Hirako *et al*, 2007):

(i) Validation & Start of procedure

The validation stage is a key stage, as it assesses a thorough technical review of the application, that will also allow for an efficient and successful review. This stage includes the submission and the validation stage, whereby the applicant must resolve all validation issues on a national level within a specific timeframe, for the procedure to start. Upon acceptance of the dossier, a procedural timetable with allocated dates is issued by the RMS and shared with CMS and the applicant.

(ii) Assessment of scientific data

Time is allocated to the assessors of both RMS and CMS to review the scientific data and request additional information through a list of questions.

(iii) Response time of applicant

During this time, the clock stops for 3 months, allowing the applicant to timeously respond to all queries and if required, perform additional tests, to satisfy the RMS and CMS comments. Should the applicant require more time, an extension may be granted upon prior arrangement and approval, as the dates for the procedure dates are usually calculated in advance.

(iv) Authorisation stage

In the case of a CP, the CHMP provides an opinion and when consensus is reached, the procedure is closed, and a MA is issued. Figure 11 provides an overview of the a CHMP evaluation for a centralised procedure and its respective timelines.

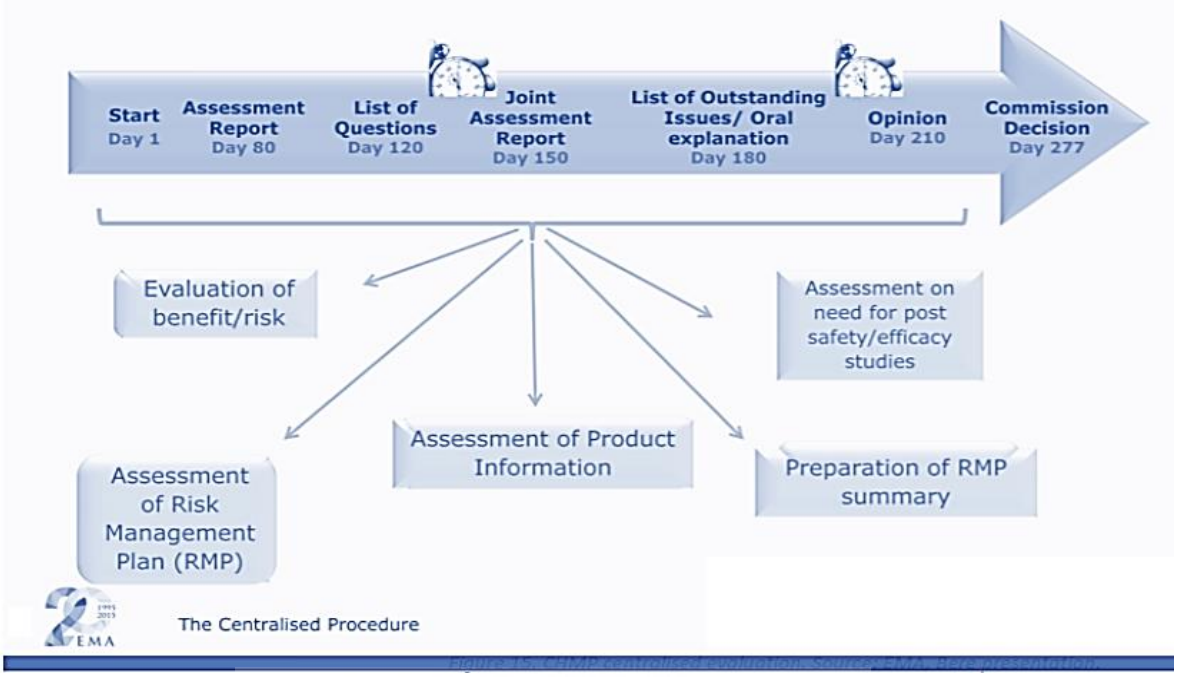


Figure 11. CHMP centralised evaluation. Source: Bere (no date, accessed 2019)

2.2.5 Types of assessment and approvals

Before a medicine is authorised for use in the target population, it undergoes extensive studies to ensure safety, efficacy and the highest quality. However, over the last 25 years, approaches have been adopted to ensure that patients have early access to new medicines. Mechanisms include approval under exceptional circumstances and conditional marketing authorisations (EMA, 2019). Once approval has been granted, EMA publishes a European Public Assessment Report (EPAR) on their website.

(i) Standard assessment

An all-inclusive review of the dossier allows for the assessment of quality, efficacy and safety within a 210 day timeline (excluding clock-stop).

(ii) Accelerated assessment

An all-inclusive review of the dossier allows for the assessment of quality, efficacy and safety within a 150 day timeline (excluding clock-stop).

(iii) Conditional Approval

This approval is granted in the absence of complete clinical data, and chances are slim that it will be provided during the initial review period. However, conditional approval is granted when the benefits outweigh the risks, because it meets the requirements of a specific need. As comprehensive data should be submitted after authorisation, this type of approval should be renewed after one year (Prilla, 2018).

(iv) Exceptional Circumstances

In the event of a rare indication where complete safety and efficacy data of the medicine cannot be provided, this approval may be granted (Bere, no date).

(v) Priority Medicines scheme (PRIME)

PRIME is centred around products that could provide a substantial medicinal benefit over current treatments, or even in the event where no treatment exists. PRIME will be discussed later as part of the implemented improvements that was made to ensure further access.

The regulatory framework of the EU is multifaceted, and it may not be entirely executed in countries with extensive challenges, however their accrued information and processes can provide valuable tools for consideration. The processes may be personalised to minimise clerical intricacies and improve on the regulatory challenges (Škrnjug *et al*, 2019). Questions have been raised regarding accelerated review and how it ultimately affects the safety of medicine. Taking safety into consideration, Arnardottir *et al* (2011) performed a retrospective study to determine if post-marketing safety was affected by 'exceptional circumstances' and 'conditional approval' pathways. It was established that the accelerated reviews were not linked to more safety signals in Europe, but more studies

may be needed. Even with reduced data being submitted, Boon, Moors and Schellekens (2010) concluded that safety concerns were not linked to the 'conditional approval' and 'exceptional circumstances' pathways.

2.3 United States Federal Drug Agency (FDA)

2.3.1 Background

From 1938 until 1962, the FDA had sixty (60) days to reject a new medicine application. Failing to do this, the medicine could be marketed. It was an effective system until the thalidomide tragedy in 1962 and drug laws were amended to add an efficacy requirement to the existing safety rules (Henninger, 2001).

Following the Federal Drug Act in 1962, the FDA was slower in approving new medicine, compared to Germany and Britain. This gave rise to a considerable cross-Atlantic 'drug lag,' whereby new medicine was approved significantly (even years) earlier in Europe than in the US (Vogel, 2001). Furthermore, in a 1974 study by University of Chicago, economist Sam Peltzman calculated that the rate of new drugs was significantly reduced – from an average of forty three (43) per year prior to the law amendment, to an average of sixteen (16) in the decade thereafter (Henninger, 2001).

A further amendment to the Act added more duties and increased the workload, but it did not make allowance for an increase in staff. New molecular entities (NMEs) submitted in 1978 had a review time of 30.8 months, and 30 months in 1983 (Carpenter, 2004). The delay in medicine approvals in the US also deepened with the intensification of the AIDS epidemic and forced the FDA to reconsider their review process by introducing several reforms. The most notable was "*fast track*" approval of the AIDS medicine AZT, which was

approved within two years, after it was revealed to be effective against the HIV virus (Henninger, 2001).

2.3.2 Application Pathways

The framework in the United States (US) shows three major pathways for applications (Figure 12); it allows for the registration of novel compounds, new medicine containing similar ingredients to previously approved products and generics – 505 (b)(1), 505 (b)(2), and 505 (j) (Fisher, 2015).

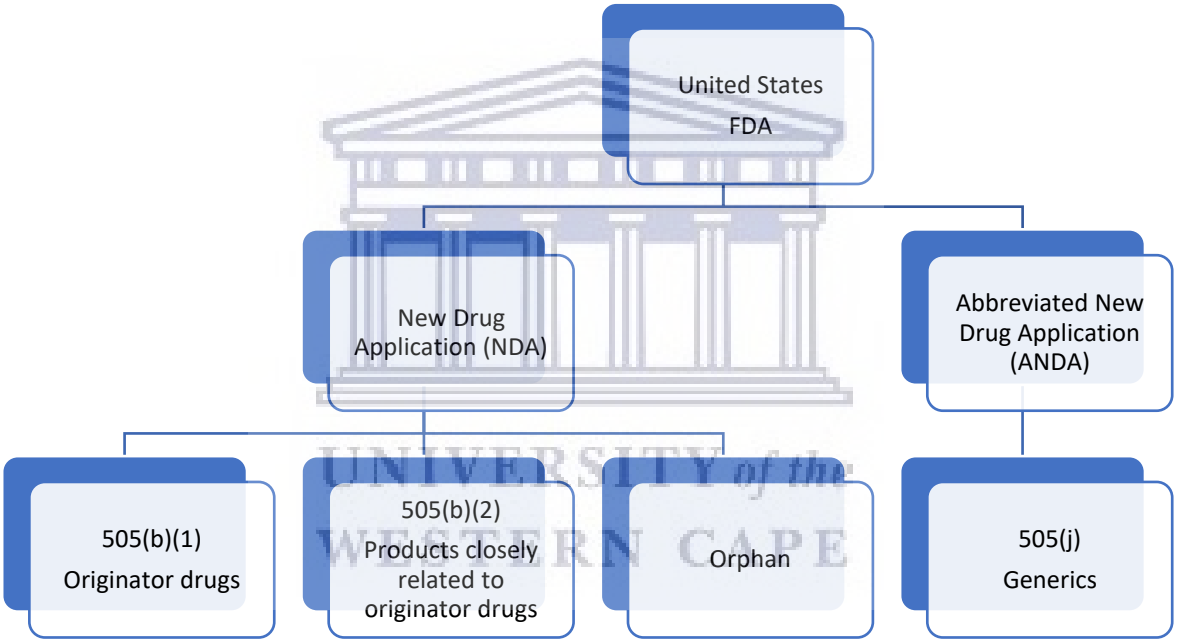


Figure 12. FDA application framework (abbreviated). Source: FDA (2019)

(i) New Drug Application (NDA) pathway

This 505(b)(1) pathway applies to the registration of new medicine only, not previously studied or approved. The application needs comprehensive clinical and non–clinical studies and needs to exhibit efficacy and safety. When an applicant is confident that the new medicine is sufficiently safe and efficacious to meet all the requirements for review

and ultimately to be approved, an application for an NDA can be submitted. The product can be marketed in the US, upon approval.

(ii) New Drug Application (NDA) pathway

This 505(b)(2) pathway applies to the registration of medicine with an active API similar to a product that has been approved previously, preventing the duplication of existing studies during product line extensions (i.e. new dosage forms, new route of administration). These applications involve a fraction of the studies required because you depend on existing reference data, with condensed timelines and at a reduced cost.

(iii) The Abbreviated New Drug Application (ANDA) pathway

The pathway is intended for generic applications of a previously approved innovator product. No preclinical or clinical data is required; however, this pathway requires the demonstration of bioavailability/bioequivalence (BA/BE) studies. The product can be marketed in the US, upon approval (Chahal *et al*, 2017).

The different pathways are significant because it indicates that the FDA provides different options for applications, with twice as many 505(b)(2) approvals, reflecting how organisations are looking to generate new revenue streams and data exclusivity from the relatively short approval timelines (Fisher, 2015).

2.3.3 Types of Review and Timelines

To improve the delays in access (Lipsky and Sharp, 2001), the Prescription Drug User Fee Act of 1992 (PDUFA) specified that standard applications should have a maximum review time of 12 months and priority applications should be reviewed within 6 months. When it

comes to priority review, the FDA has developed distinct and successful methods to making medicine available without delays (as seen in Figure 13):

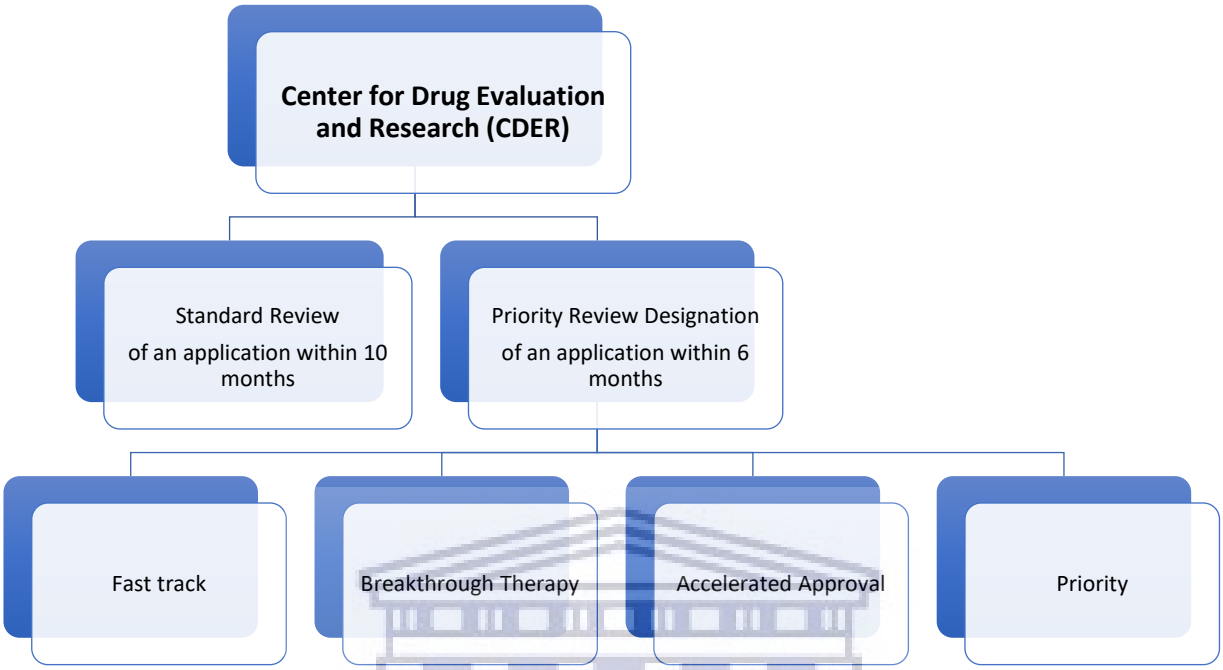


Figure 13. CDER review types with timelines. Source: FDA (2018)

(i) Standard Review

A standard review is applied to medicine where similar products are already marketed, and it offers only a slight enhancement over the current treatments that are being promoted. The 2002 PDUFA amendment subsequently reduced the 12-month standard review period to 10-months.

(ii) Priority Review

These applications offer significant improvements over current treatments, with a review to be completed within 6 months. This designation allows for increased meeting requests to ensure an efficient and quality review.

(iii) Breakthrough therapy

In the event of critical illnesses, this pathway is intended to accelerate the development and assessment of a medicine that is able to prove significant improvements of existing therapies.

(iv) Fast track

For critical illness, this pathway is intended to accelerate the development and assessment of a medicine that is able to provide treatment, where no therapy currently exist.

(v) The Accelerated approval

This pathway is used where the endpoint is thought to reasonably foresee a scientific benefit, like a decrease in the size of a tumour and it will ultimately improve the quality of life. This approval is conditional and subject to post-marketing clinical trials to confirm the expected clinical advantage.

Carpenter *et al* (2008) assessed whether PDUFAs implementation of target review times had any unexpected safety concerns in the US. It was concluded that safety matters were prone to be detected during the clinical phase, rather than after. In addition, Richey *et al* (2009) conducted a study involving oncology medicine and suggested that phase II clinical trials are ideal to detect improvements in clinical results.

Chary (2016) agreed that the fast-track designation is necessary when it comes to life-threatening conditions. However, there have been a number of incidents where fast-tracked molecules have received adverse event alerts. It is advisable that regulatory authorities should be more cautious, as information received from pharmaceutical companies could be misleading or deceptive.

2.4 Japan's Pharmaceutical and Medical Device Agency (PMDA)

2.4.1 Background

The Japanese government have been struggling with delayed medicine approval for decades. In 2000, the Japanese Ministry of Health, Labour and Welfare (MHLW) made a commitment to reduce the time it took to review their applications to 12 months for both regulator and applicant. This commitment placed tremendous pressure on the regulator and 2004 data indicated their application review times at 3.8 years (Tsukamoto, 2011).

The Pharmaceutical and Medical Device Agency (PMDA) came into effect in 2004 and assumed responsibility for reviewing all applications for medicine and medical devices. At inauguration, the agency was completely understaffed to review the amount of applications within the promised timeframe. Reviewers are expected to have wide-ranging expertise pertaining to regulatory affairs and have additional knowledge of the intricacies in assessing medicinal benefits and risks for patients. The PMDA had trouble in finding skilled reviewers and were constantly losing staffing to pharmaceutical companies who offered much more rewarding salary packages (Tsukamoto, 2011).

2.4.2 Review Pathways

Two pathways have been implemented for the new submissions: standard review and priority review. Since 2004, the PMDA has diligently strived to restructure its review process, aiming to provide efficient priority and standard pathways (Figure 14).

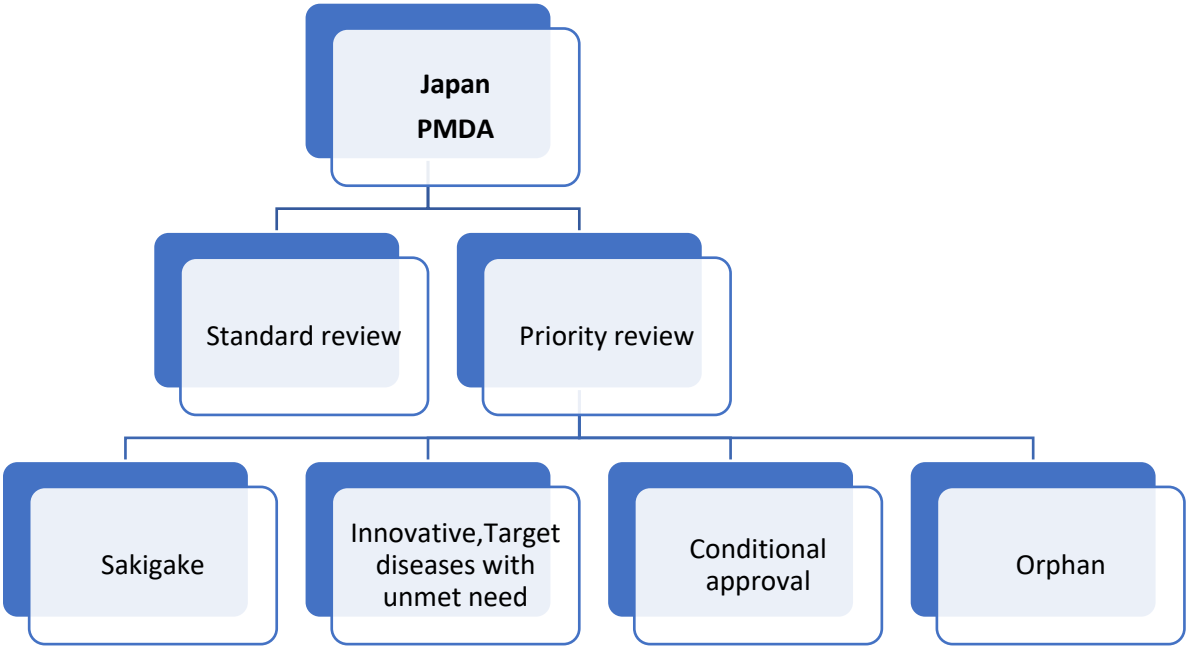


Figure 14. PMDA application and review pathways. Source: PMDA (2019)

The purpose of an expedited pathway is to provide access to pertinent products like orphan applications and specific medicine selected by the PMDA, based on the seriousness of the illnesses and its ultimate use in the medical industry. An automatic priority review is assigned to orphan medicine, specifically for illnesses that affect less than fifty thousand patients in Japan (Feltmate *et al*, 2015). Conditional approval allows for the priority review of off-label medicine, like orphan medicine), for rare conditions. The Sakigake pathway was established recently as part of the improvements made by Japan to facilitate novel medicine and improve access and this will be discussed later.

2.4.3 Registration flowchart

PMDA has made great progress and wants to further predict the review process by setting review targets. New applications must be reviewed within 12 months and priority applications within 9 months. Breakthrough therapy has been given a review target of 6 months. Figure 15 and 16 illustrates the pathway of a standard application by the PMDA.

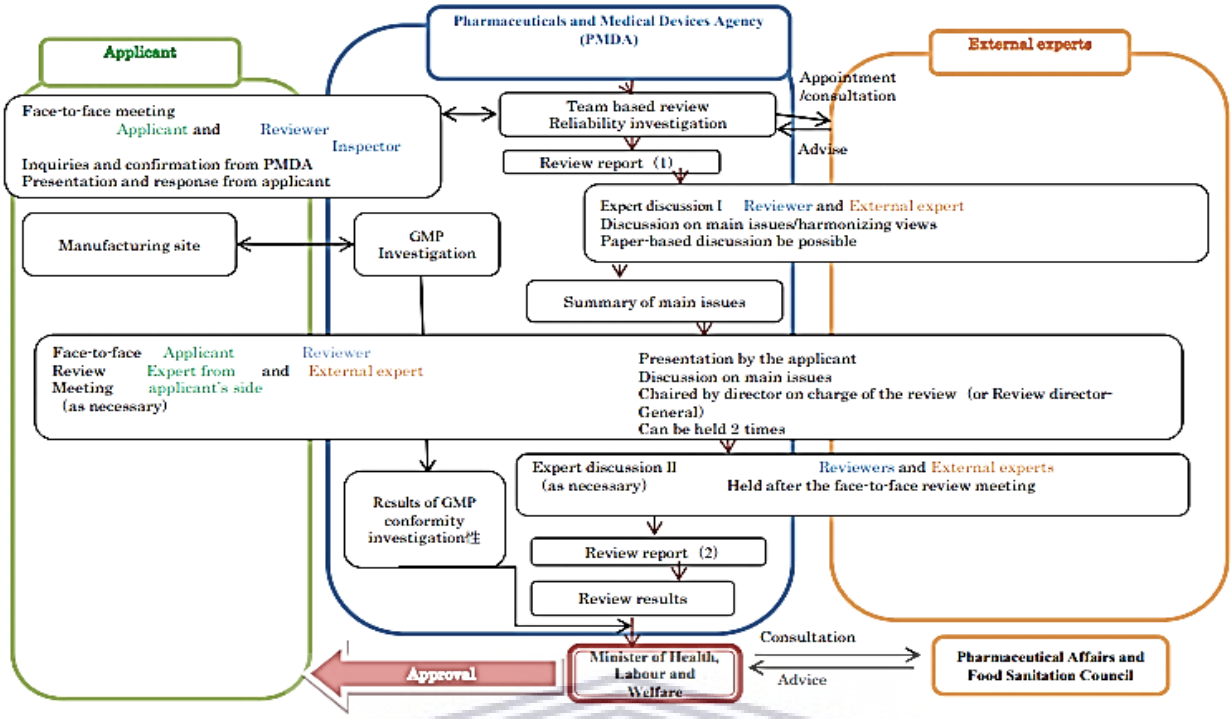


Figure 15. PMDA flowchart. Source: Pacific Bridge Medical (2014).

2.4.4 Standard Timeline for Approval

Figure 16 illustrates the standard timeline (in months) for each stage of the application and approval process of a new medicine application.

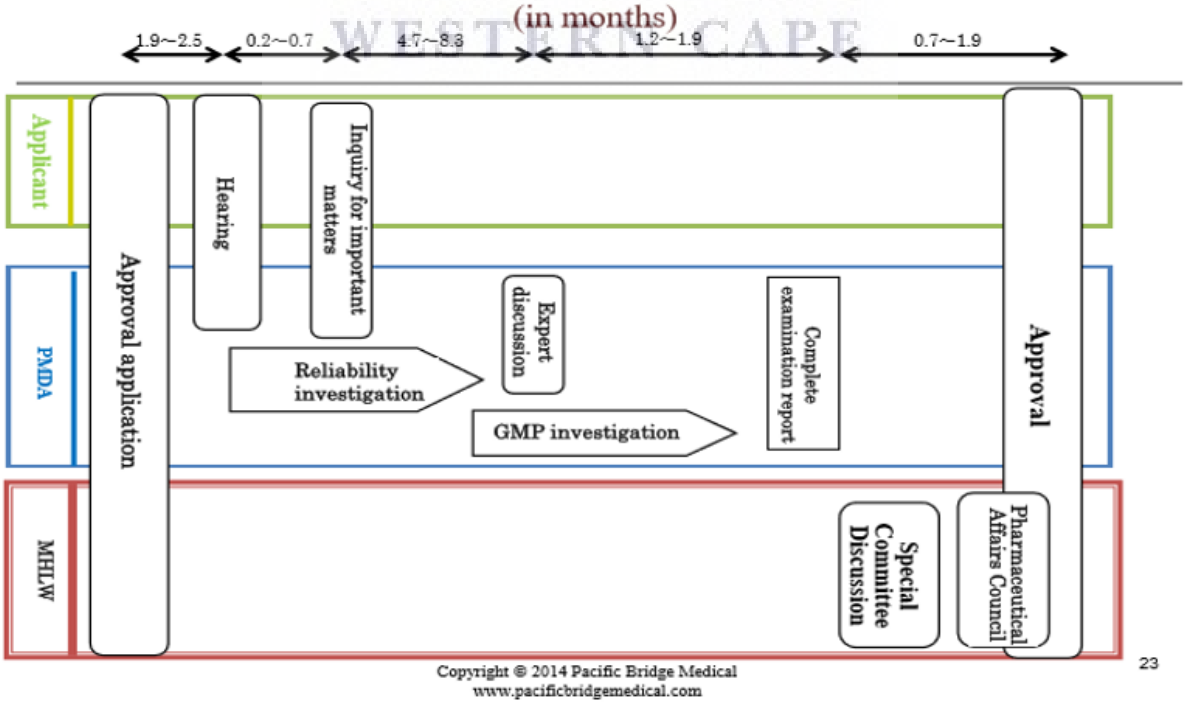


Figure 16. Standard timeline for PMDA approval. Source: Pacific Bridge Medical (2014)

The additional pathways to speed up the review of medicine is important, especially where there is an unmet medical need. Yamaguchi *et al* (2011) evaluated the biologics guidelines of different regulatory authorities, including EU, Canada and Japan and looked at the amount of information that is accrued for follow-up studies related to safety. As processes differ across all regions, it was concluded that the safety information collected post approval, especially pertaining to fast-tracked applications with limited clinical data, should be made available on a global scale.

2.5 Health Canada

2.5.1 Background

In 1996, Health Canada introduced a strategy to allow for expedited review of serious and/or life-threatening conditions. With the implementation of this pathway, target review times of the expedited applications were reduced. As a result of the reduced review times, the regulatory authority was unable to manage the day-to-day performance of the remainder of the applications, causing extensive delays. As a consequence, Health Canada needed to improve the regulatory review of their medicines and devices in order to accommodate a constantly evolving healthcare system (Health Canada, 2009).

2.5.2 Application Pathways

Health Canada's has several expanded pathways, as can be observed in Figure 17.

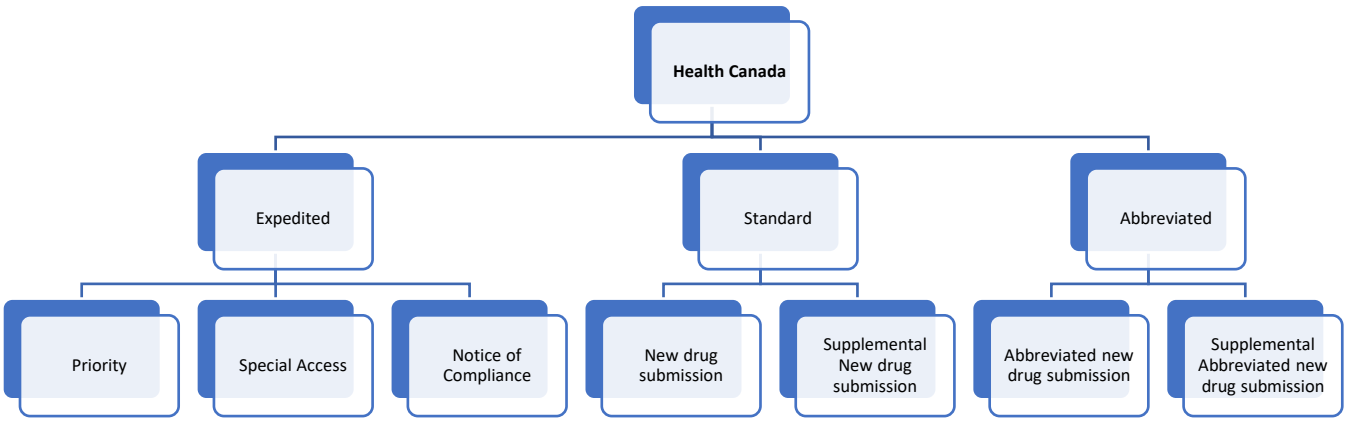


Figure 17. Canadian application pathways (abbreviated). Source: Health Canada (2009)

2.5.3 Review milestones and Timelines

2.5.3.1 Standard review

The performance target timeline for new drug submissions is currently 300 days, as indicated on the registration process map along with recorded milestones (Figure 18).

2.5.3.2 Expedited review types

Once a priority designation has been assigned, the applicant has to submit the application within 60 days. The application will be reviewed within the target review time of 180 days. The expansion of the expedited pathways allowed for the review of the following medicine:

(i) Priority Review process

For new medicine applications that can provide evidence of the required criteria, Health Canada will provide an expedited review.

(ii) Special Access Program (SAP)

The SAP program is for products not authorised for sale in Canada. If a healthcare practitioner requires the need for medical device that has not been approved, access to

the device can be requested, provided that no other devices are available or existing therapy has failed.

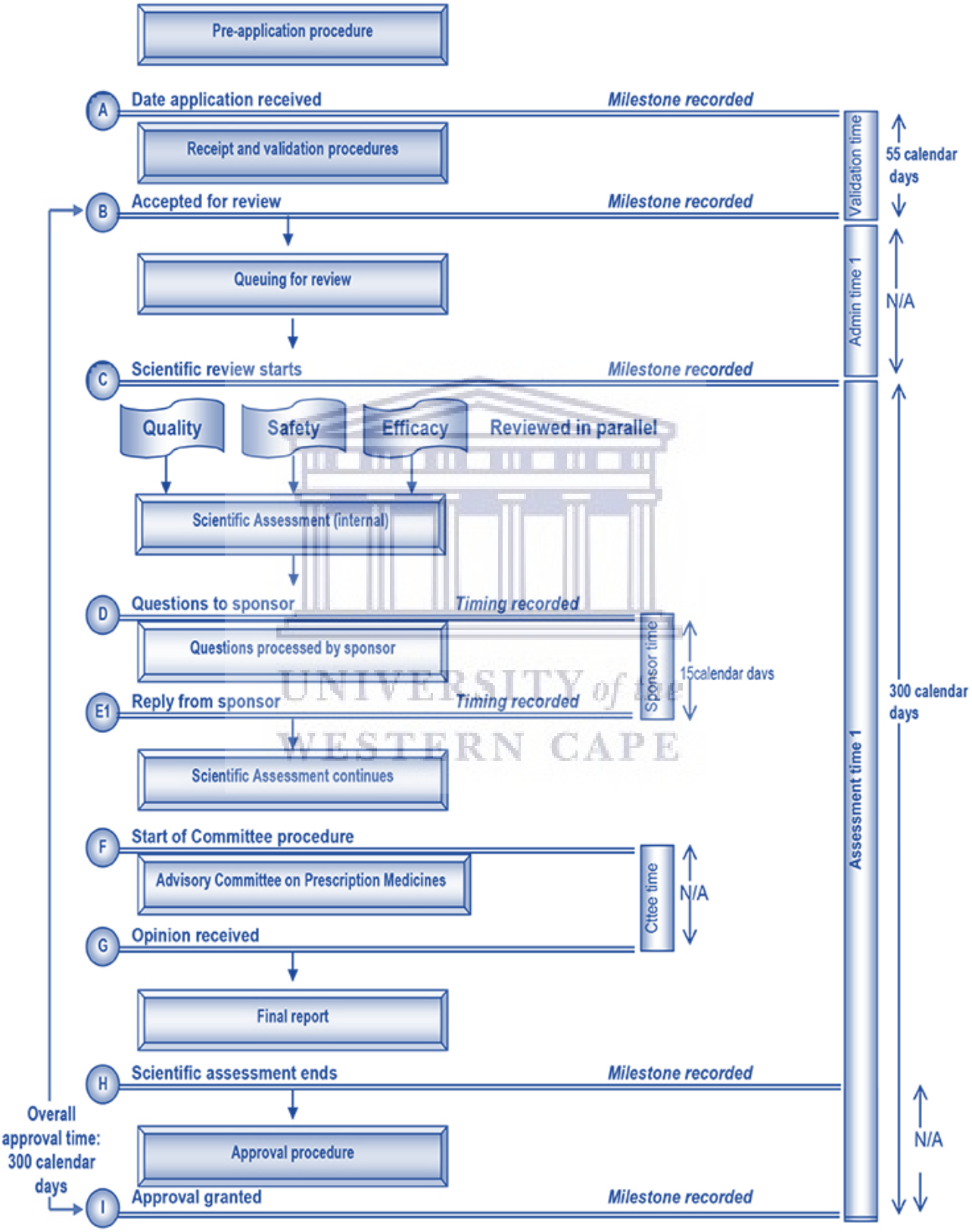


Figure 18. Registration process map for Health Canada. Source: Ceyhan et al (2018)

(iii) Notice of Compliance with Conditions (NOC/c)

NOC/c therapies allow for the prevention, diagnosis and treatment of life threatening and/or debilitating conditions where no therapy is available or where the benefit outweighs the risk and provides significant improvement over current authorised medicines (Health Canada, 2007).

Questions have been raised whether Health Canada provides a comprehensive marketing authorisation for medicine that receive 'conditional approvals.' A cohort study was performed, and it was concluded that post marketing studies by Health Canada were actually much more stringent than the US or EMA. However, it has highlighted deficiencies in the studies, more specifically with reference to the quality of the information that is collected by Health Canada. The regulator has optimised their regulations and have decided to be more transparent. In doing so, they will publish the safety and efficacy data of approved products (Lexchin, 2018).

2.6 Australia's Therapeutic Goods Administration (TGA)

2.6.1 Background

The TGA is responsible for regulating therapeutic medicine and it is approached with a risk-based assessment. Australia introduced a streamlined submissions process in 2010-2011, but there was no formalised pathway to expedite the review of medicine. Australia performed a benchmarking exercise and the Review of Medicines and Medical Devices Regulation (MMDR) recommended additional expedited pathways. It was noted that Canada, the US and Europe all have priority review pathways offering faster access to medicine and that Australia was not aligned with their international counterparts (TGA, 2015).

2.6.2 Submission and Review Pathways

The TGA expanded on several of their review pathways (Figure 19):

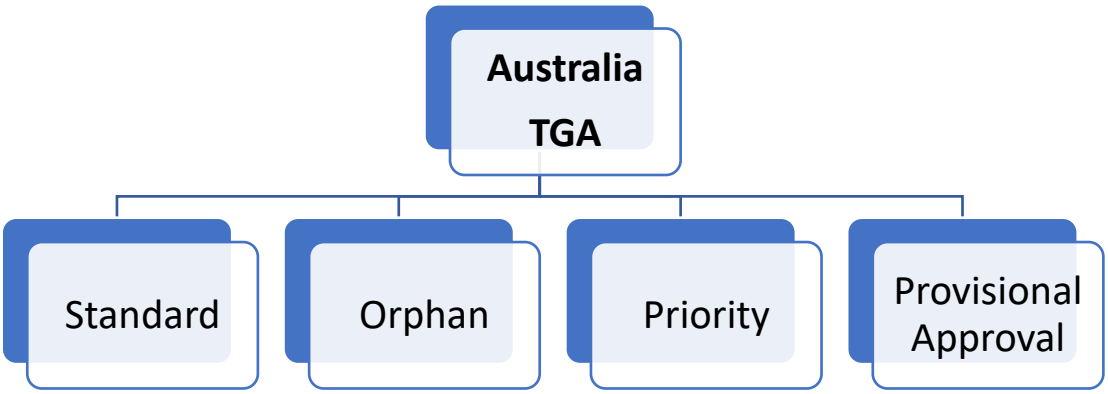


Figure 19. Australian application pathway (abbreviated). Source: TGA (2016)

(i) Standard

For standard review of new medicine applications, the applicant has to provide comprehensive clinical, non-clinical or BABE data, depending on the type of application. A planned evaluation for a standard application is 10.5 months. For generics, the planned evaluation is 8.5 months.

(ii) Priority

With the introduction of the priority review pathway, the TGA now offer an expedited review on medicine for life-threatening conditions, provided that sufficient efficacy and safety information is available to show an advantage over current authorised therapies. Priority reviews must be completed within 150 days, otherwise penalties will be applied.

(iii) Provisional approval

With the introduction of the provisional approval pathway, the TGA now offer provisional

authorisation, provided that early clinical data show promise, with a substantial advantage over current authorised therapies.

2.6.3 Milestones and Timelines

The TGA have an impressive registration framework, consisting of 8 phases which incorporates 8 milestones. Both applicant and regulator are able to plan and track the applications, within specified timeframes (TGA, 2013). Table 4 and Figure 20 in the registration process map represents the phases and milestones.

Table 4. TGA phases and milestones in the regulatory process

Milestones of the various phases in the regulatory process

Phase	Relevant milestone	
1 - Pre-submission	MS1	Outcome of pre-submission planning sent
2 - Submission	MS2	Outcome of application consideration sent
3 - First round assessment	MS3	Outcome of first round assessment and section 31 request for information or documents sent
4 - Consolidated section 31 request response	MS4	End of section 31 request response period
5 - Second round assessment	MS5	Outcome of second round assessments sent
6 - Expert advisory review	MS6	Outcome of expert advisory committee review sent
7 - Decision	MS7	Decision made by delegate
8 - Post-decision	MS8	Administrative and regulatory activities complete

Source: TGA (2019)

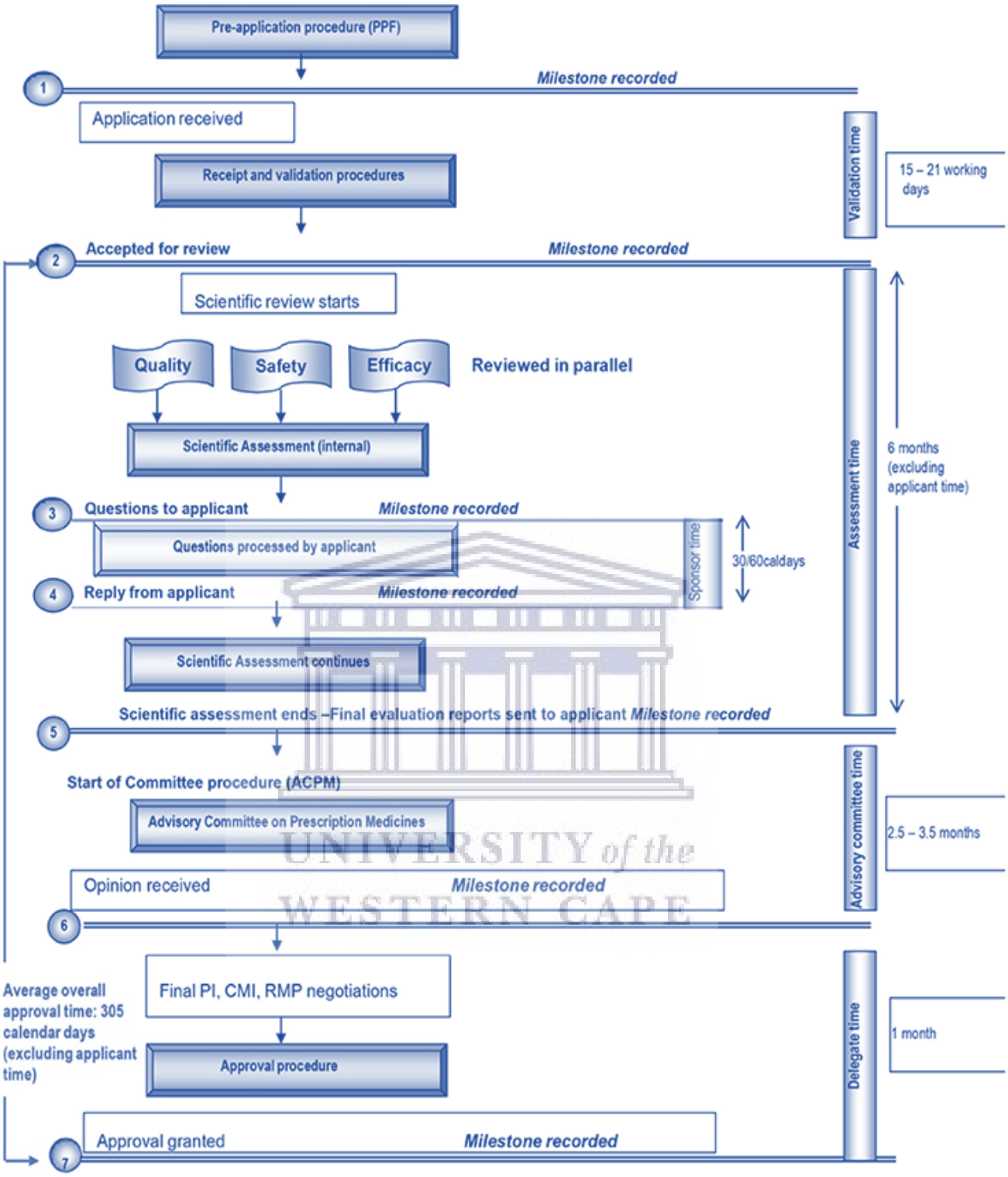


Figure 20. Registration process map for TGA. Source: Ceyhan et al (2018).

The impact of predetermined review times became more evident when statutory timelines were applied, as seen in Europe and Australia. Australia introduced target times for applicants and monetary penalties for the regulator if they did not meet their own target

review time. In Europe, if the clock-stop time (for the applicant) is surpassed by one month, the accelerated assessment lapses to a standard application for assessment (Hirako *et al*, 2007).

Through the evaluation of these additional pathways and understanding what ultimately led to the improved productivity of the pathways in successful markets, South Africa can use the operational tools available to improve the review process effectively.

Chapter 3: Research design and Methodology

3.1 Objective

The objective of the study was to perform a comparative review of pathways, timelines and improvements of countries with markets that SAHPRA benchmark themselves against. Furthermore, this study intends to identify the factors that improved and accelerated submissions and approval process in investigated countries and possible introduction of these strategies into the South African market.

3.2 Rationale for the study

For the purpose of clearing the backlog and reducing review timelines, exploratory data will focus on the different review routes and timelines of existing markets, especially those who previously struggled with a backlog.

3.3 Method

The research is a literature-based retrospective analysis, with the aim to provide a qualitative analysis using information gathered through the years.

3.4 Data collection

The country selection was intentional, specifically countries that SAHPRA has expressed interest in, including the International Conference on Harmonization of Technical Requirements (ICH) territories (namely European, United States and Japan). Data was collected from these mature markets' pathways and review routes, from when an application was received until the date that it was approved or authorised. Data was collected from 1995 through to 2018. To illustrate the effect of accelerated review

pathways and set target times, median approval times were used to compare standard and accelerated assessments. The terms ‘accelerated’, ‘expedited’ and ‘priority’ were used interchangeably during the duration of the study. Review times refer to time taken by the regulator for the review of the application. Approval times refers to time taken by both regulator and applicant to review and respond to an application. In the case of the CP in Europe, the EU Commission time refers to the time taken by the commission, after the CHMP has delivered a decision.

3.5 Ethics

The research was conducted by the author, it is literature-based and therefore no ethical approval was required.

3.6 Limitations

The data was retrieved predominantly from the CIRS, South Africa and Canada was based on information pertaining to new active substances only, as more information was available for these types of applications. As South Africa has no document management system to track information, limited data was available to track the information through the years. Not all review pathways were investigated. To minimise error, CIRS specified their data as an average of 75% approvals. The data in the reports are blinded with respect to the identity of products and only evaluated with respect to evaluation of median timelines of new applications, timelines and subsequent improvements that were made in each country, not the quality of the review. Data was not always available or easy to extract from different regulatory authorities, but the theoretical fundamentals that were collected for the analysis can still be used to propose a structure for accumulating and investigating information in order to design, develop and build a new framework for South Africa.

Chapter 4: Findings and Analysis

This chapter looks at how the median review and approval times have reduced over the past two decades, specifically due to the introduction of different pathways. Evaluating the trends across the ICH regions, namely the EU, United States of America (USA) and Japan, and the impact of accelerated/expedited assessments, the following review data of standard and expedited reviews were collected through the years 1995 - 2018: The same information will follow for non-ICH regions (Australia and Canada).

4.1 European Medicines Agency (EMA)

4.1.1 Data analysis

Standard review

1997: The Central Procedure has been steady since 1997 reflecting an approximate 15 month approval times (Figure 21, CIRS, 2001). The time includes applicant/company response times, as well as EU commission time.

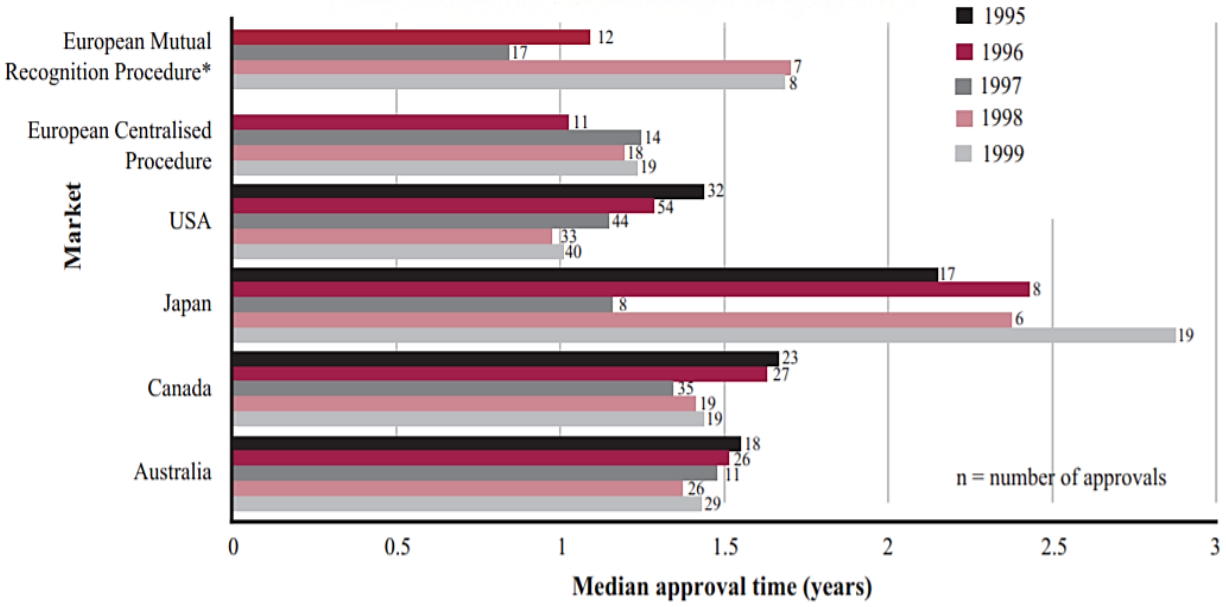


Figure 21. Median approval times 1995-1999. Source CIRS (2001)

2004-2013: Review time for EMA during this decade remained consistent, as can be seen in (Figure 22 and Figure 23, Bujar and McAuslane 2014).

This was possibly due to the dedicated review times allocated to the different pathways.

The median review time was 250 days from 2004-2008 and 251 days for 2009-2013.

Review time excludes applicant/company response times, as well as EU commission time.

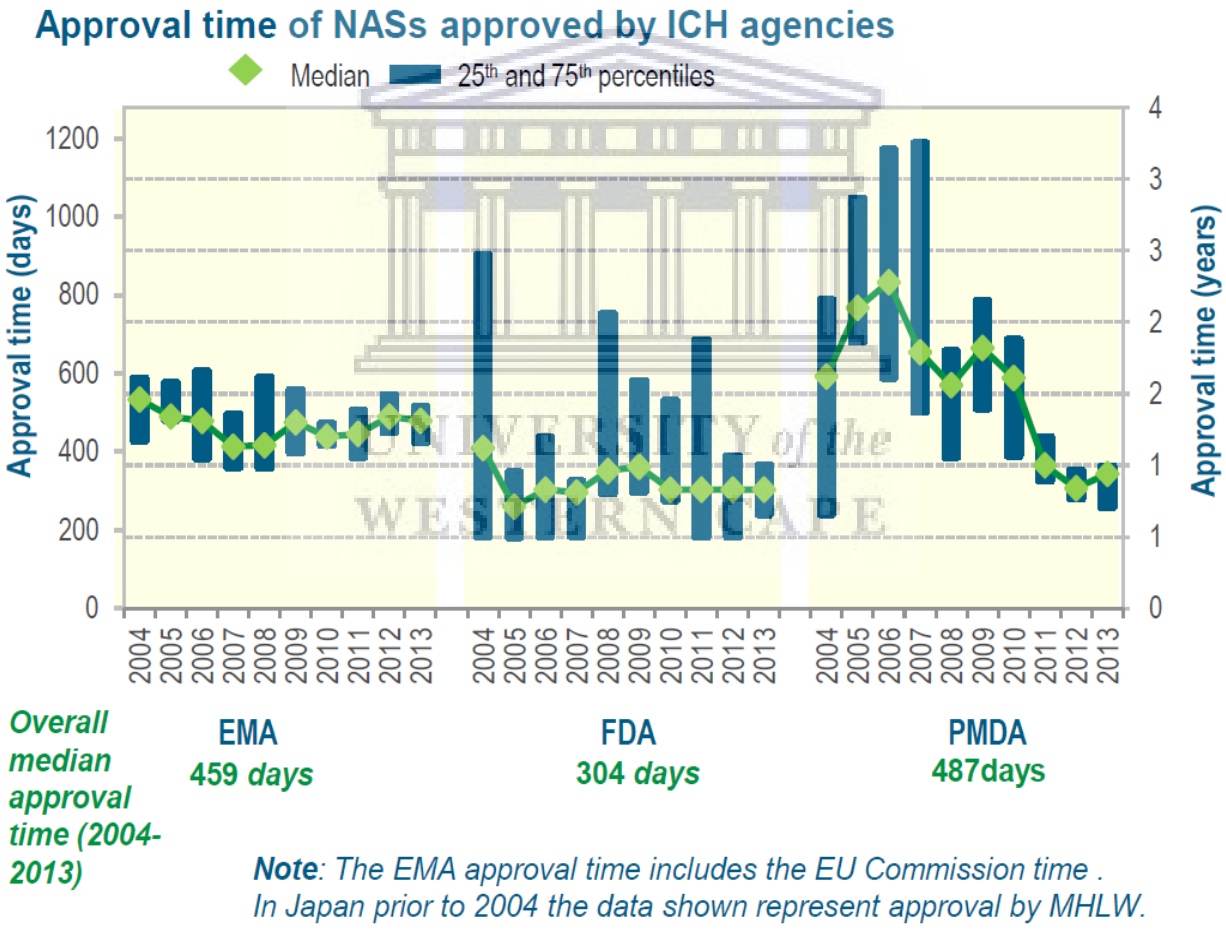


Figure 22. Approval time of NAS approved by ICH agencies. Source: CIRS (Bujar & McAuslane, 2014)

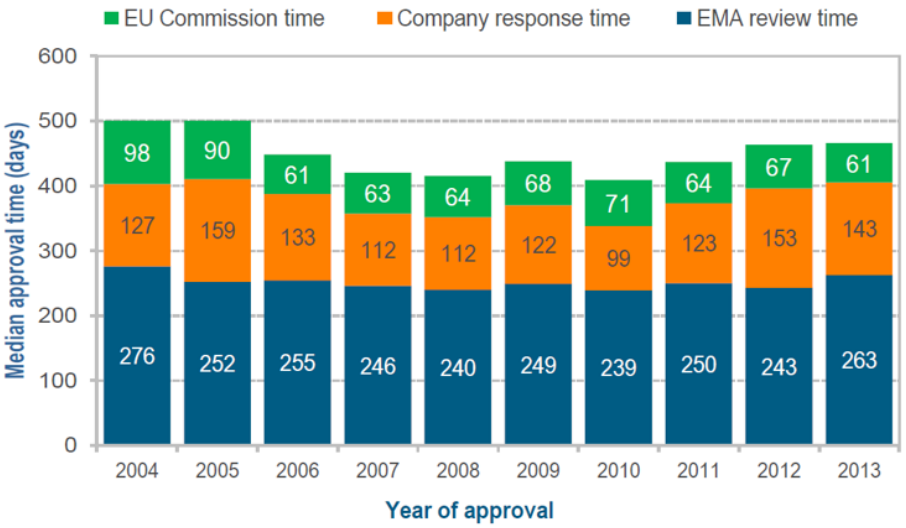


Figure 23. Median review time for NAS approved by EMA 2004-2013. Source CIRS (Bujar & McAuslane, 2014)

2014-2017: Responses from the applicant decreased between 2014 to 2017, resulting in a decreased approval time (Figure 24 on the next page, Rodier *et al*, 2019). The stability observed was mainly because EMA has dedicated timelines that both regulator and applicant must comply with in order for the application to continue to the next step, as set out in Table 2 and 3 (in Section 2.2.2) for new and generic applications.

2018: A slight increase in company response time (130 days) was observed in 2018 (Figure 24, Rodier *et al* 2019).

Figure 24. Median time of review process for NASs approved by EMA from 2014 - 2018 Source: CIRS (Rodier et al, 2019)

Expedited review

2005–2012 In terms of Accelerated Assessments for EMA, there was limited use of the expedited review during this period (Figure 25, Bujar *et al* 2015).

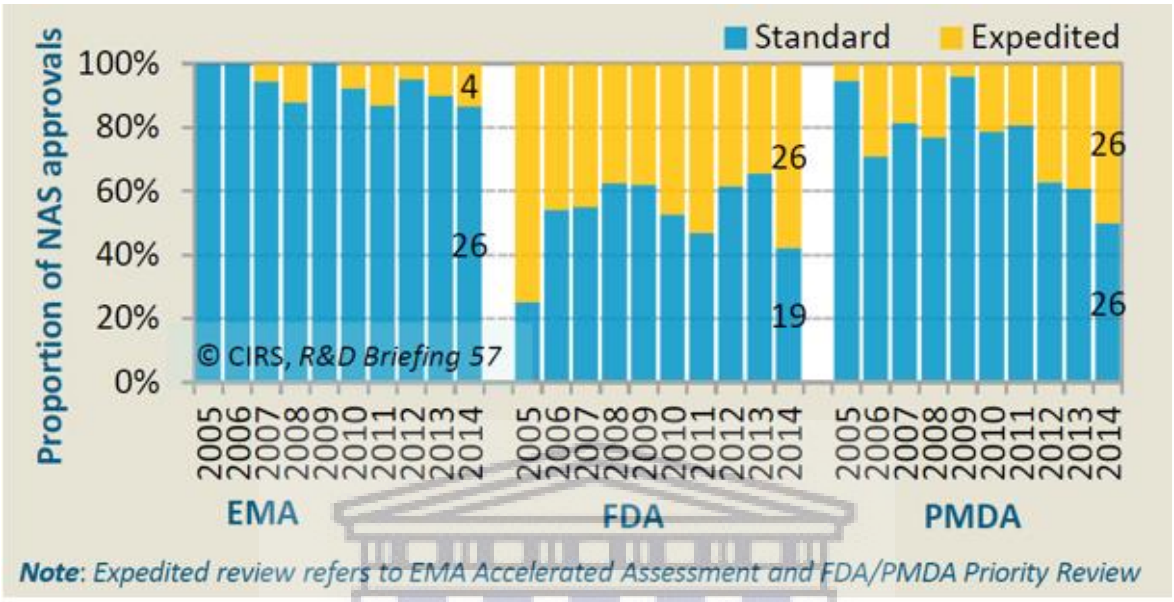


Figure 25. Proportion of NAS approved by review type and approval year 2005-2014. Source: CIRS (Bujar et al 2015)

2013-2017 The revision of EMA's Accelerated Assessment guidelines in 2015 possibly resulted in a considerable amount of approvals and the reduction in approval time was evident (235 days) in 2017 (Figure 26).

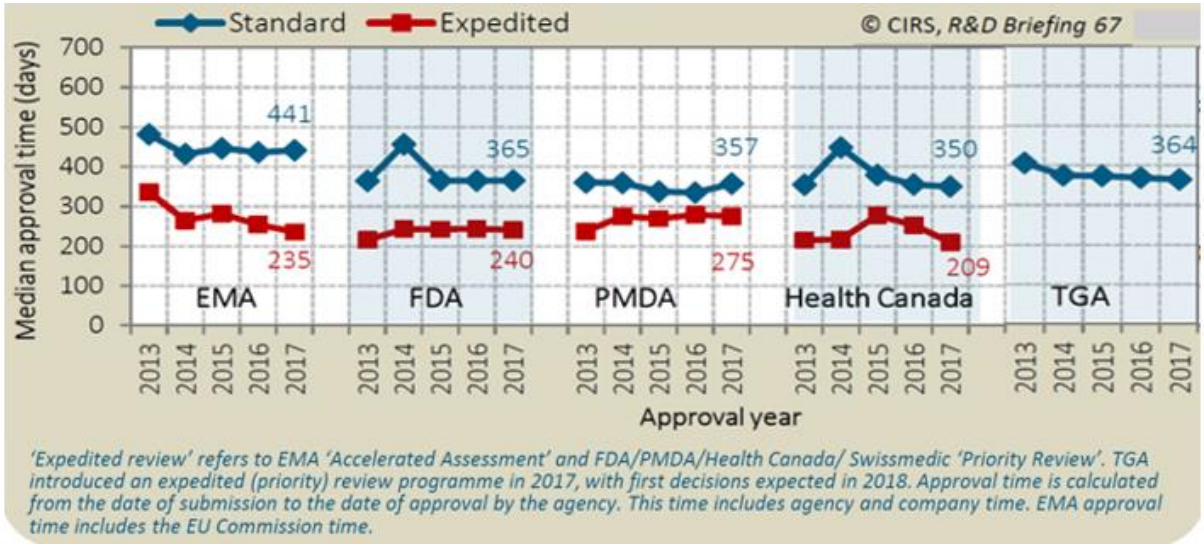


Figure 26. Median approval time by review type (standard and expedited) from 2013-2017. Source: CIRS (Bujar et al, 2018)

2014-2018: For the expedited review of a central procedure, review time was much faster and there was a notable reduction in the commission time of the EU due to the shorter target of 150 days.

Furthermore, the applicant response time was much faster due to the penalties imposed by EMA, whereby an expedited review can be converted back to a standard review, is the applicant does not comply with the clock-stop (Figure 27, Rodier *et al* 2019).

Although there was a massive output of expedited approvals, (7% in 2009-2013 to 15% in 2014-2018), the number of expedited approvals still remained the lowest, which is partially due to the fact the review type can be reverted back to a standard review, if timelines cannot be met by the applicant.

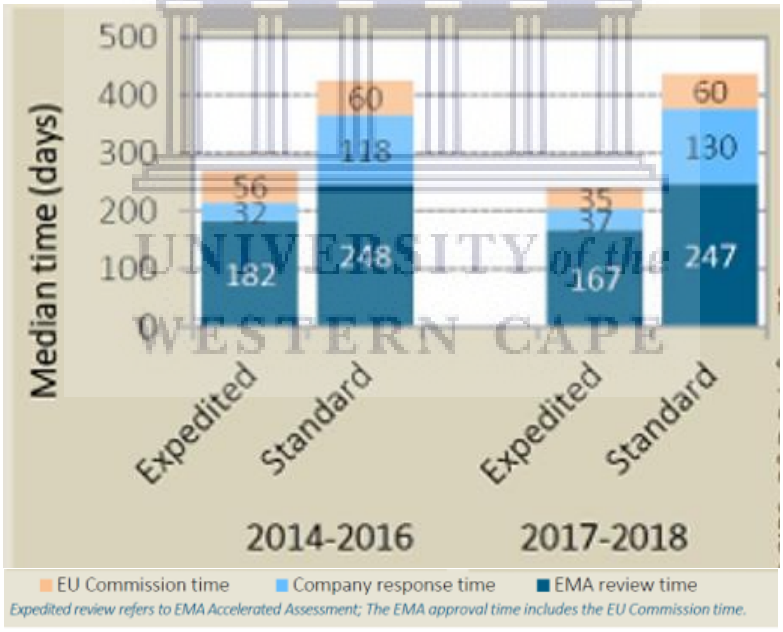


Figure 27. Median time of review process for NASs approved my EMA by review type from 2014-2016 and 2017-2018. Source: CIRS (Rodier et al, 2019)

2018: To emphasize the legislated timelines that should be complied with, three (3) NASs, initially designated by EMA as expedited, were reverted back to a standard review (Rodier *et al* 2019).

2019: Over the last 5 years, 15% of EMAs medicine was approved using the expedited review route and time.

4.1.2 Improvements

EMA is responsible for the scientific evaluation and since 1995, it has made positive improvements over the past two decades. A huge contribution to their successful implementation of pathways can also be accredited to the following:

(i) Planning prior to submission

Before the submission of an application, a request must be submitted by the applicant in order to establish if it is eligible to be reviewed as part of the central procedure. If approved, the applicant should also contact the agency indicating their intended submission, at least 6 months beforehand. This will enable the appointment of rapporteurs to lead the assessment and conduct pre-submission meetings with the applicant, providing them with the best opportunity to obtain procedural and regulatory advice – prior to submission. This also speeds up the validation process. Applicants are also requested to re-confirm the submission date about 3 months before the actual submission, or inform the agency of any delays or cancellations, based on the feedback of the pre-submission meetings.

(ii) Method of assessment

Timetables are categorised according to the type of procedure, with dedicated response times from both the agency and applicant. The timetable allows for traceability to all member states involved, ensuring prompt feedback – without unnecessary delay. For new applications, a list of questions is issued at day-120 for new applications (and day-105 for generics) when the clock is stopped (refer to Table 2 and 3). Rarely can new information be requested after this. This ensures a thorough assessment, without the application going

back-and-forth, and avoiding unnecessary delays. The timetable shows a dedicated commitment of both the regulatory agency and the applicant. Clear expectations and a commitment to defined review and approval times has proven to be highly effective in ultimately achieving their goal.

(iii) Expedited pathways

To provide additional support to conditions where no treatments are available, EMA launched PRIME in 2016. Expedited review for orphan applications encompass the following: adaptive licensing, accelerated assessment and compassionate use programmes (Feltmate, 2015). With dedicated pathways to review different applications, review times from SAHPRA and response times from the applicant, can eventually lead to a dedicated commitment by both parties, allowing for an efficient and streamlined regulatory process.

(iv) Harmonisation and work-sharing

In the EU region, harmonisation was achieved when all member states started working in unison, incorporating communal standards. The work-sharing was achieved whereby one competent authority (RMS) reviews an application in the best interest of another member state (CMS), subsequently preventing duplication of resources (Škrnjug *et al*, 2019).

(v) Sunset clause

To avoid outdated duplicate applications cluttering the pre- and post-authorisation unit, an applicant had to launch an authorised product within 3 years of approval, otherwise the medicine authorisation will no longer be valid.

4.2 Federal Drug Agency (FDA)

4.2.1 Data analysis

Standard and expedited approvals

The split between standard approvals and expedited approvals was not always possible as in certain cases, NAS approvals were designated by the FDA as Breakthrough and as Fast Track.

1995-1999 With a median approval time averaging slightly more than one year and preserving a large amount of approved medicine, the USA data during these years was exceptional (Figure 21). The USA had the quickest review and approval.

1998–1999 During this time, the FDA permitted more approvals for applications than any other country, upholding its efficient framework. The increased approvals were possibly due to the PDUFA implementation that started its operation in 1993, resulting in certain applications intended for serious conditions, to be reviewed within the specified 6 month target time. (Figure 21, CIRS, 2001).

2004-2008 The FDAs median approval time was approximately 303 days (Figure 22, Bujar & McAuslane 2014).

2009-2013 The next 5 years had a median approval time of approximately 304 days (Figure 22).

2013-2017: When comparing the percentage of expedited reviews to standard reviews for the FDA, it was high during this period, with approximately 62% expedited approvals in 2016 (Figure 28, Bujar *et al* 2018).

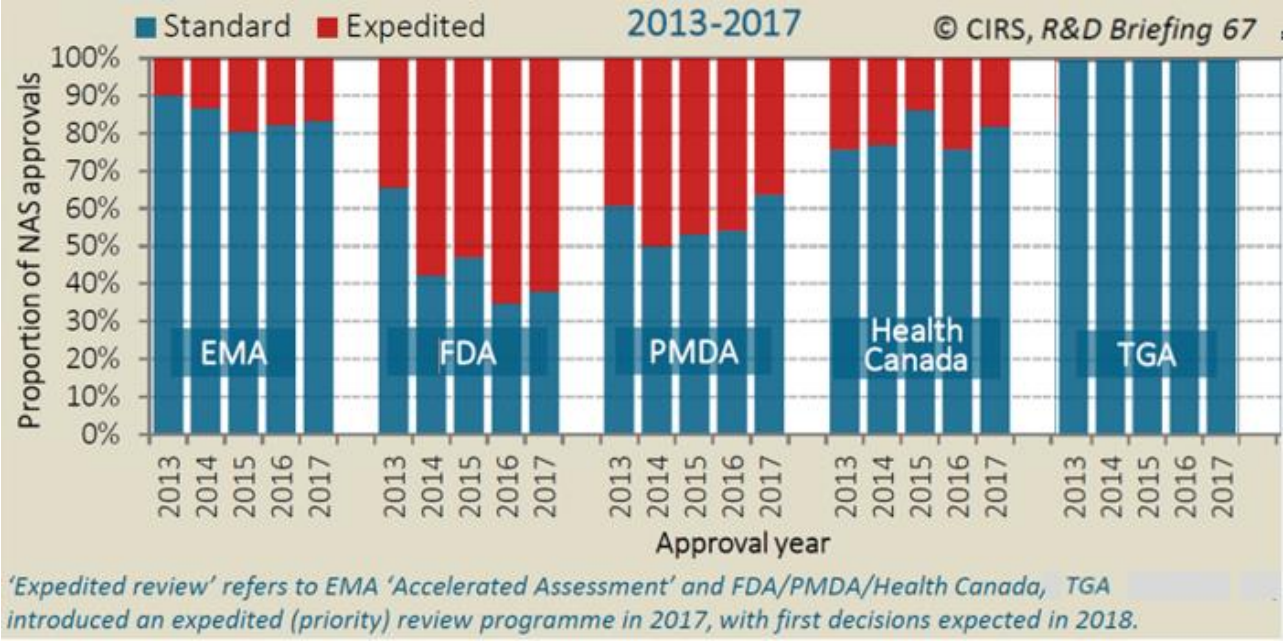


Figure 28. Number of NAS approvals by review type. Source: CIRS, Bujar et al, 2018

2017: The FDA had a fast approval time for expedited applications, it took 240 days (Fig. 26, Bujar *et al*, 2018).

2018: Illustrating a median approval time of 242 days, the FDA again demonstrated the fastest review time by CDER; where 25% of the approved medicine was reviewed as Breakthrough Therapy and 42% as Fast Track (Figure 29, Rodier *et al* 2019).

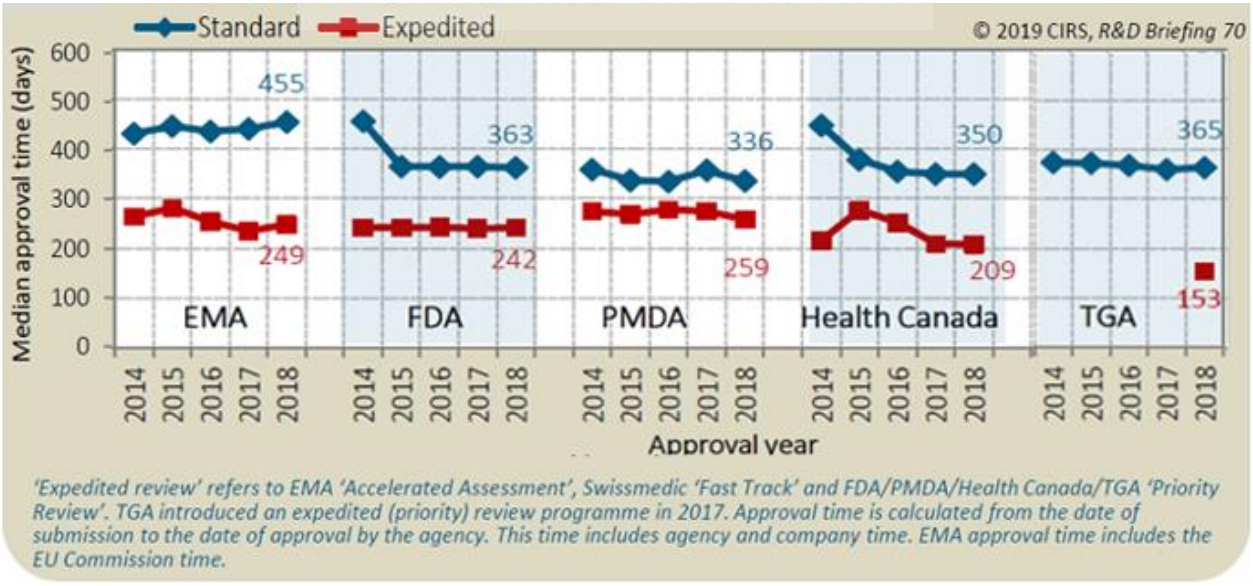


Figure 29. NAS median approval time (days) by review type. Source: CIRS. (Rodier et al, 2019)

2014-2018 The proportion of the CDER's NAS's approved after one cycle increased between 2009-2013 and 2014-2018 from 74% to 86% (Figure 30, Rodier *et al* 2019).

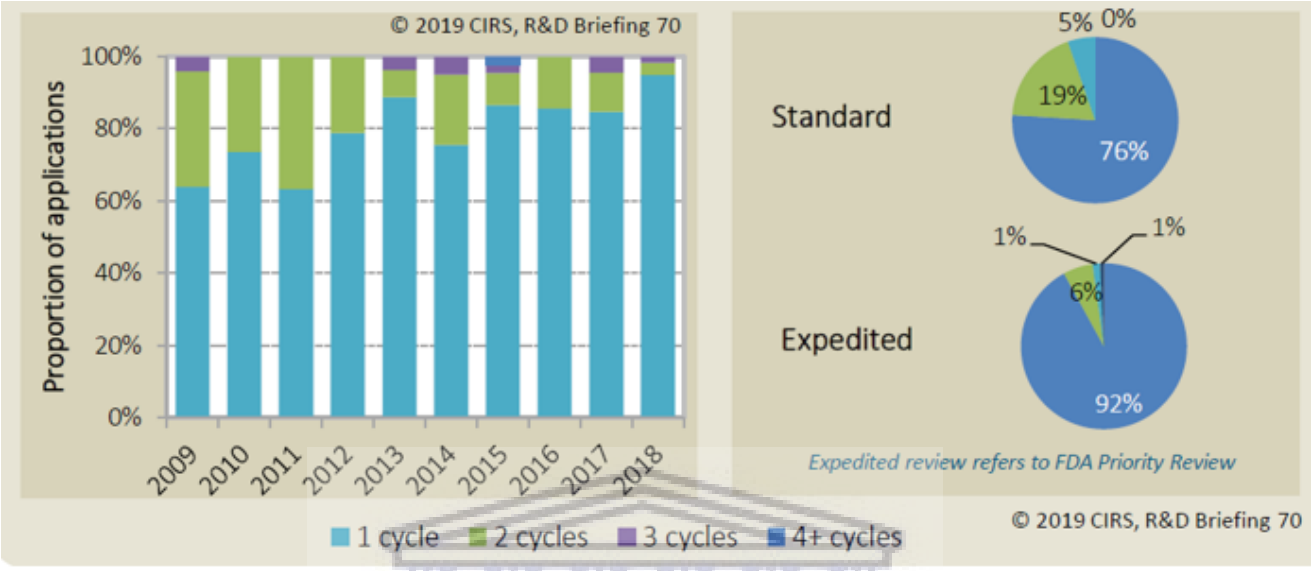


Figure 30. Proportion of NAS approved by FDA CDER by number of review cycles, by approval year and review type. Source: CIRS. (Rodier et al, 2019)

The percentage expedited approvals to standard reviews have been consistently high for FDA and increasing when comparing 2009-2013 (results not shown) to 2014-2018, whereby 42% NASs were designated as expedited by FDA in the first part of the decade, compared with a massive 63% that was approved in the last 5 years.

All approvals were within the expedited 6 months review time (Rodier *et al*, 2019). In 2018, the FDA had the highest rate of percentage of expedited to standard reviews, a phenomenal 73%. (Figure 31, Rodier *et al*, 2019).

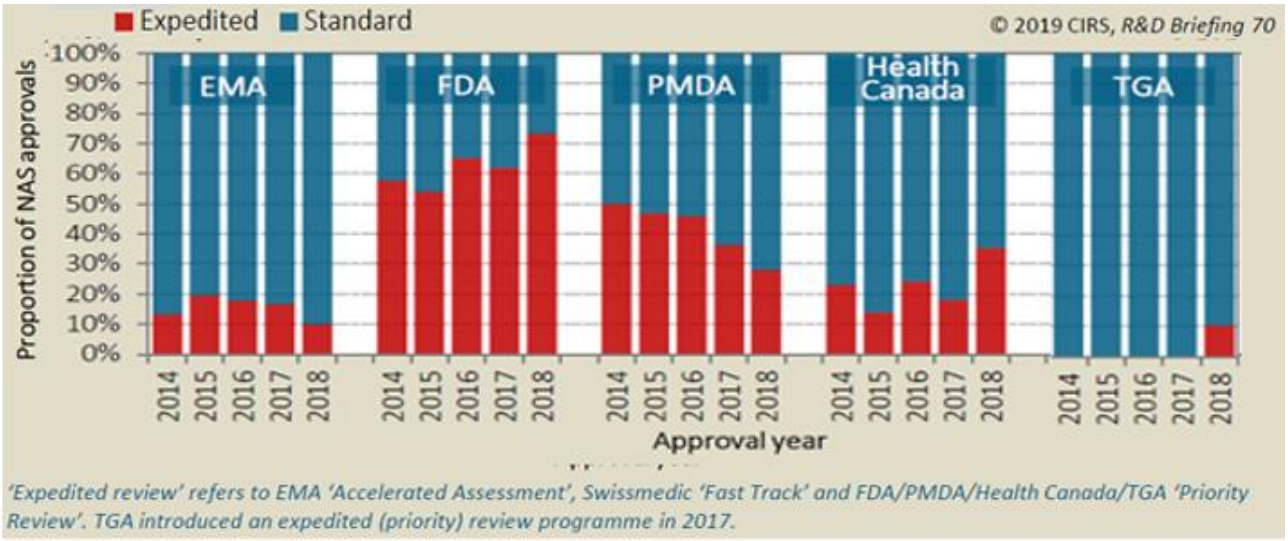


Figure 31. Proportion of NAS approvals by review type. Source: CIRS (Rodier et al, 2019)

It has been more than 25 years since the implementation of user fees which revolutionised the review process in the US. Apart from the application fee, there is an annual program contribution from the applicant/sponsor. The increased revenue allowed the FDA to make many improvements, the FDA could speed up the application review process through necessary staffing, infrastructure, scientific advice and stakeholders' meetings.

4.2.2 Improvements

(i) PDUFA

The PDUFA implementation was strategic in reducing the review and approval time. To strengthen, improve and expedite the regulatory framework, the FDA gathers fees from pharmaceutical companies on an annual basis. Furthermore, it allows for the recruitment of additional reviewers and support staff. Considerable changes and improvements were already noted in the early stages of PDUFA I (1993-1997), whereby backlogs from earlier years were drastically reduced. The increased review staff at CDER allowed the FDA to pledge review target times and the goals were slowly reached. By 1999, they were

performing at optimal levels; 35 drugs were reviewed and approved within one year, increasing access of medicine by means of expedited reviews and approvals (Lipsky & Sharp, 2001). The revenue further allowed for technological improvements, allowing for further enhancements to the proficiency of the application review process.

Further initiatives of the FDA included improved communication between applicant and regulator, during clinical trials, before a submission and during the review of the application, leading to further performance improvements. Owing to the success of the Act's implementation, new programmes were established: Medicare Device User Fee Amendments (MDUFA), the Generic Drug User Fee Amendments (GDUFA), and the Biosimilar User Fee Act (BsUFA) (FDA, 2018).

(ii) Expanding commitment to generics and biologics

The generic industry has always been successful and in 2017, it accounted for 89% of the prescriptions dispensed. Based on the exponential growth, the generic unit within the FDA was understaffed and could not stay abreast of the growth of the generic market. In 2012, Congress in consultation with stakeholders, passed GDUFA. In exchange for the FDAs commitment to performance goals and to maintain their target review times, the pharmaceutical industry agreed to pay user fees. Furthermore, the FDA agreed to expedite the review of a "first generic" ANDAs, as it will stimulate competition within the generic industry.

(iii) BsUFA

BsUFA was passed in 2012. The Act permitted the FDA the necessary funds to develop and improve the use of an abbreviated pathway for biosimilars (Woodcock, 2017).

4.3 Japan's Pharmaceutical and Medical Device Agency (PMDA)

4.3.1 Data analysis

Standard review

1995-1999: Japan had the longest median approval time, of all the countries that was compared in the 2001 study (*Figure 21)*.

2004-2008 Median approval time was approximately 689 days (Bujar & McAuslane, 2014).

2009-2013 Median approval time was approximately 367 days (Bujar & McAuslane, 2014). The review time showed relative consistency.

2004-2013 During this decade, review times for NASs showed a drastic improvement by 2011. The PDMA was aiming to achieve a 12 month review time for new medicine applications and 9 months review time for priority products. The introduction of set review times made a significant difference in the performance of PMDA; however due to the limited pathways, it took them more than a decade to show improvement.

The median approval times for products approved from 2004-2013 were approximately 487 days for PMDA (Figure 22, Bujar & McAuslane 2014).

2017: The PMDA had a review time of approximately 357 days for standard review (Figure 26).

2018: The PMDA had a median approval time at 336 days for standard review, with the smallest difference of 77 days between standard and expedited review (Figure 29).

The percentage of expedited reviews to standard approvals for the PMDA reflected as 28%.

Japan experienced an increase in expedited percentage when comparing 2009-2013 and 2014-2018, from 25% to 43% (Figure 31, Rodier *et al*, 2019).

Expedited review

2009-2013 The PMDA review time showed relative consistency, slowly rising to match and better the FDA review times (Figure 29).

There was considerable decrease in time, priority review times dropped from 478 to 270 days between 2004-2008 and 2009-2013 (Figure 32 Bujar & McAuslane, 2014).

2005-2014 During this decade, the percentage of expedited reviews increased consistently and doubled for the PMDA in 2014 (Figure 25).

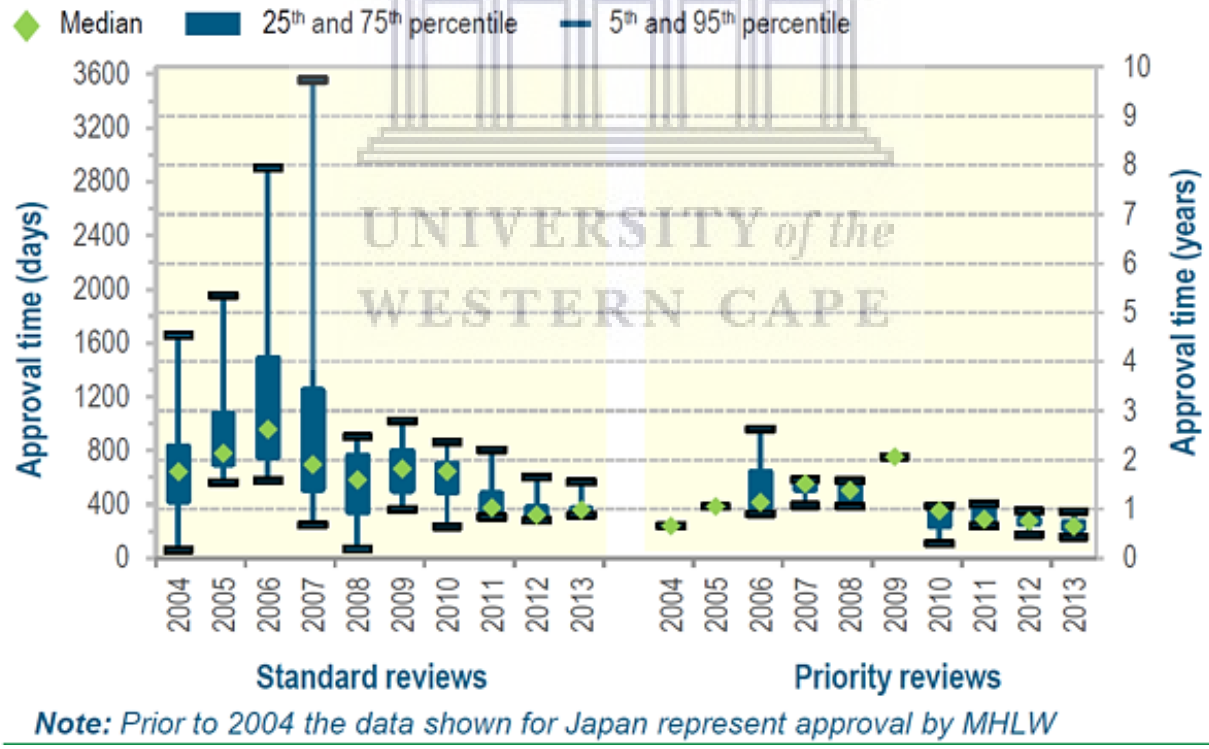


Figure 32. Approval time of NASs approved by PMDA by review type. Source: Bujar & McAuslane, 2014

2013-2017 The approval time for PMDA was approximately 275 days for expedited review (Figure 26).

	The percentage of accelerated approvals has remained high, experiencing an increase when comparing 2008-2012 (results not shown) to 2013-2017 from 22% to 45% (Figure 28, Bujar *et al*, 2018).
2018	The PMDA median approval time for expedited review was approximately 259 days (Figure 29).

The PMDA introduced an additional pathway, set target review times and increased their staff complement to facilitate the review process and accelerate the approval process. It is noted that over the last five years (from 2014-2018), the proportion of expedited approvals by PMDA has decreased year-on-year, whereby 43% of approvals were approved in the expedited review pathway.

4.3.2 Improvements

(i) Japan's Sakigake Approval Pathway

In 2014, Japan's PMDA announced the provision of priority review and accelerated approval to new breakthrough therapies. The Sakigake pathway was launched in 2015, and similar to the FDA's breakthrough designation, Sakigake designation is given to drugs that show "prominent effectiveness" or "radical improvement" over existing therapies based on preclinical or early clinical studies. This was necessary because while reviews were getting faster for standard products, reviews for priority products grew longer (Kanayasu, no date).

The accelerated approval pathway was created to halve review times for breakthrough medicine that could launch in Japan before any other market. The pathway can also be used for new indications or new formulations for previously approved drugs (McCallister, 2017). To facilitate and expedite the application, a dedicated person is assigned to

manage the flow of the application. Meetings between the applicant and regulator are approved to make the Sakigake application and review process more efficient, all while aiming to review within the 6 month target. As of March 2019, seven Sakigake products have been reviewed and approved (PDMA, 2019).

(ii) Resources

In order to achieve their performance goals, PMDA has drastically increased its reviewers, as can be seen in Table 5. To date, staffing resources has increased fourfold (PMDA, 2019). Over the years, the government worked hard to make the regulatory processes as efficient as possible. Due to the increased resources, review times are at its lowest. With a massive improvement in the processes, it is helping patients in both Japan and its neighboring countries.

Table 5. PMDA increase in employees

Full-time employees	**April 1, 2015**	**April 1, 2016**	**April 1, 2017**	**April 1, 2018**	**April 1, 2019**
Total (including executives)	820	873	906	915	936
Review department	532	560	578	575	561
Safety department	165	185	190	198	224
Relief department	36	37	39	39	39

Source: PDMA (2019).

Looking at the trends across the non-ICH regions of countries that align themselves with ICH regions and the impact of accelerated/expedited assessments, the following review data was collected from Canada and Australia through the years 1995 – 2018.

4.4 Health Canada

4.4.1 Data analysis

Standard review

1995-1999: Canada's approval times for during 1995-1999 was approximately 1.5 years (540 days) (Figure 21).

2017: Median approval time was 350 days (third fastest, after FDA and PMDA) (Figure 26).

2018: Median approval time was 350 days (third highest after FDA and PMDA) (Figure 29).

Since 2014, there has been a continued improvement in the approval review times, with a reduction of 99 days (Figure 29).

Expedited review

1995-2016 In a cross-sectional study, Lexchin (2018) observed the usage of therapeutic innovation and priority review of the period between 1995 to 2016. Of all the products approved during that period of 1995 - 2016, the standard pathway approved 70.3% of products and the priority pathway approved 29.7% of products. During this period, Health Canada's priority review process remained stable. This indicates that almost 30% of Canada's approvals between the time period of 1995 – 2016 were approved within the expedited review time frame (Figure 33).

Key: Percentage of medicine approved through different pathways in Canada.
Grey—percentage with Notice of Compliance with conditions
Orange—percentage with priority review
Blue—percentage with standard review

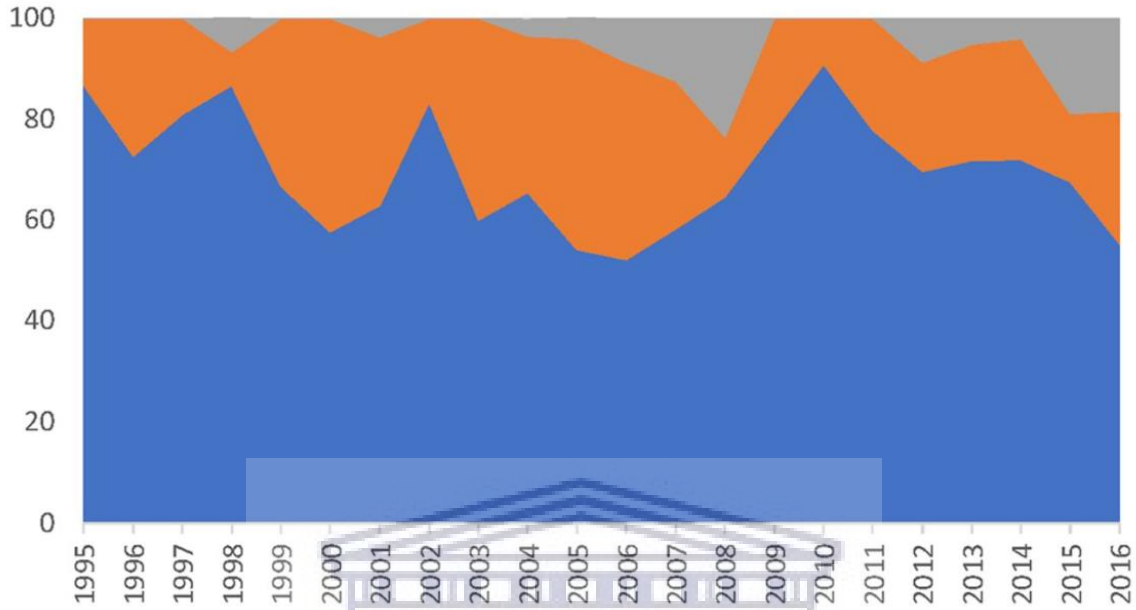


Figure 33. Percentage approvals of Health Canada through different pathways. Source: Lexchin (2018)

2018: The difference between standard and review was 141 days for Health Canada (Figure 29). The ratio of expedited approvals to standard review continued to grow and reached a high of 35% (second only to the FDA) (Figure 31).

4.4.2 Improvements

Health Canada has put together several projects over the past 2 decades to ensure that all medicine is safe, effective and of good quality.

(i) Stakeholder engagement

Working together with all stakeholders, they have developed a Consultation and Stakeholder Information Management System (CSIMS). Through this engagement

system, stakeholders partake and stay informed of current projects through meetings, webinars, publications, consultations and policy documents. Their long-term plan is to continuously improve their regulatory system, improve communication and to ensure access to medicine.

(ii) Expansion of regulatory review

Further emphasis is placed on the improvement of the regulatory framework, expanding expedited review pathways, ensuring access to generics and biosimilars, and revising outdated regulations to better manage biosimilars. A further strategy to improve the access and review process, is to make use of foreign reviews and recommendations. Seeing as many submissions are happening on a global scale, it is sensible for Health Canada to use foreign reviews to shorten the timeline for approval. The agency is also working collaboratively with Australia, Singapore, and Switzerland to share ideas and consider some common assessments. The agency is also striving to deliver better access to digital health technologies, which is an important and rapidly growing field in medical devices (Gori, 2018).

(iii) Collaboration and Work-share

By expanding collaboration with other health partners, it ensures better alignment with regulatory review. The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends the reimbursement for a drug and this process happens after the review for approval of the product. This means that there is a longer wait for patients to get the medicine they need. By working in parallel and sharing information, the time can be reduced (Gori, 2018). With so many innovations happening so rapidly, Health Canada acknowledged that it must adapt its processes accordingly (Health Canada, 2019).

4.5 Australia's Therapeutic Goods Administration (TGA)

4.5.1 Data analysis

Standard

1995-1999 Australia's approval times for during 1995-1999 was approximately 1.5 years (18 months) (Figure 21).

2008-2017 The decade has seen little variation in the approval times for the standard pathway, with the TGA being consistent in the median approval times.

2017 The median approval time was approximately 364 days (Figure 26).

2018 The median approval time was approximately 365 days (Figure 29)

Expedited

2017 The priority review pathway was launched by the TGA, but no approvals were granted in 2017.

2018 Three expedited approvals were granted (Figure 31). The median review time for the 3 products approved through expedited pathway was approximately 153 days (Figure 29). The difference between standard and expedited review was approximately 212 days for TGA (Figure 29). To place this in context, Figure 29 indicates that the differences with other comparable countries.

With a target review time of 150 days, the priority review began in 2017. In terms of comparable data, it should give rise to parallel prospects of treating serious and life-threatening conditions when using the expedited reviews in Australia, as it did in other markets. In 2018, 10% of Australia's products were approved in the expedited review pathway.

4.5.2 Improvements

(i) Expedited pathways

TGA benchmarked themselves against recognised markets and added two expedited pathways, Priority Review and Provisional Approval. Both pathways allow for meetings prior to submission, provided that applicants comply with the application requirements. The regulator can provide guidance to the applicant, explain application process and make allowance for the necessary resources to be available for the review of the dossier (TGA, 2016).

(ii) *Collaboration and Work-share*

In addition to the two new approval pathways, TGA also opened consultations for enhanced global partnership in medicines regulation. The MMDR analysis proposed that TGA should take more advantage of the reviews that was done by comparable overseas regulators (CORs) in their existing activities, with prospects to work-share with CORs to be utilised more effectively (TGA, 2016).

Chapter 5: Discussion

According to the World Health Organisation (WHO) (2002), medicine approvals have always been a concern of pharmaceutical companies, regulators, patients and healthcare professionals. Although all agencies have the same goal, their processes, practices and timelines differ from country to country.

Decisions regarding products are made daily; more importantly, the processes that agencies utilise must be robust enough to guarantee that a comprehensive dossier review can take place. It should be built on the foundation of a solid decision framework to ensure good quality decision-making. For a regulatory authority to operate at optimum levels it should have resources such as: money, staff and an efficient regulatory review process. However, diversity between countries can represent challenges as they try to learn from one another's strengths and capabilities and more specifically to understand how to make their own processes better. Through performance measurement, realistic goals and objectives can be set. It can also provide information on areas of performance that require resources, further development or improvement (Pichler and Wang, 2011).

While certain countries partake in autonomous audits, most countries depend on data obtained from other markets. By systematically mapping the process of agencies and defining the milestones and indicators for comparison, common milestones can be identified through shared information of multiple sources and stakeholders.

Over the last two decades, various approaches have been introduced to streamline their application and review processes and to efficiently use available resources. Based on the results obtained with the benchmarking exercise, the following improvements should contribute to successful transformation.

5.1 Additional pathways for submission and review

According to the WHO (2015), the objective of Good Review Practices (GRevPs) is to help accomplish timeliness, expectedness, reliability, transparency, clarity, proficiency and high quality in both the content and management of reviews (WHO, 2015).

The introduction of additional pathways, as was successfully implemented by the various regulatory authorities, should provide flexible options to applicants/sponsors to facilitate the speed of a regulatory review process. They have also recognised that content-specific pathways are easier to evaluate when the assessors are familiar with the specific type of application.

Similarly, specific review types improve speed, quality and enhance the efficiency of the review. Different categories of products, for example NCE/NAS and generics, both currently fully assessed by SAHPRA, should be reviewed based on the type of application, as the size and intricacy of each application differ greatly. Non-specific pathways result in longer review times. The recognition of dedicated pathways to review different applications by SAHPRA, should allow for an efficient and streamlined regulatory process.

Expedited review systems have also been introduced to further accelerate the review process in established markets. Liberti *et al* (2016) termed the accelerated pathways as 'facilitated regulatory pathways' (FRPs). These pathways are specifically developed for faster review and approval of medicine, where the benefit outweigh the risks. All five agencies that were reviewed, provide priority review pathways, specifically to increase the review time of innovative medicine applications. Figure 34 provides a snapshot of all the facilitated pathways across the different agencies.

© 2019 CIRS, *R&D Briefing 70*	New active substance (NAS) approval type		2018 NAS approvals, number	2018 NASs, %	Expedited, % of 2018 approvals	2018 median approval time, days
EMA	**Overall approvals**		**40**			**436**
	FRP	Accelerated Assessment (referred in Briefing as Expedited)	4	10		249
		Conditional Approval	2	5	0	507
		Exceptional Circumstances	3	8	0	570
		PRIME	2	5	0	342
	Orphan		17	43	18	463
FDA	**Overall approvals**		**60**			**244**
	FRP	Priority (referred in Briefing as Expedited)	44	73		242
		Accelerated Approval	5	8	80	245
		Breakthrough Designation	15	25	93	243
		Fast Track	25	42	100	242
	Orphan		35	58	86	243
PMDA	**Overall approvals**		**32**			**323**
	FRP	Priority (referred in this Briefing as Expedited)	9	28		259
		Sakigake	2	6	100	152
		Conditional Early Approval	1	3	0	234
	Orphan		8	25	100	263
Health Canada	**Overall approvals**		34			**348**
	FRP	Priority (referred in Briefing as Expedited)	12	35		209
		Conditional (Notice of Compliance with conditions)	2	6	0	370
TGA	**Overall approvals**		29			**363**
	FRP	Priority (referred in Briefing as Expedited)	3	10		153
		Provisional Approval	0	N/A	N/A	N/A
	Orphan		10	34	20	335

TGA introduced an expedited (priority) review and provisional approval programme in 2017, with first decisions in 2018/2019. Health Canada does not currently have an orphan policy. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.

Figure 34. Facilitated regulatory pathways (FRP) and orphan status timelines. Source: CIRS (Rodier et al, 2019)

In 2018, the percentage of expedited reviews compared to standard approvals was highest for FDA (73%), followed by Health Canada (35%), PMDA (28%), EMA and TGA (10%) (Figure 28) (Rodier *et al*, 2019). The impact of the expedited review systems enabled the reduction of review times and contributed to faster approvals, as was demonstrated in all countries.

Having demonstrated the results of the above countries, it should be kept in mind that the implementation of different pathways will have limitations in South Africa, due to the current resource constraints highlighted below. However, the different aspects of these

discoveries and successes should serve as a guide to establish the best approach that needs to be taken by SAHPRA.

5.2 Setting target review and response times

The time taken by a regulator to review an application is directly linked to the measurement on the regulator's performance and efficiency. To further attain a more predictable process, agencies have introduced specific target times and deadlines for both the regulator and the applicant. This provides a dedicated commitment by both applicant and the regulatory authority, to finish the reviews in an expected time frame, and in some cases with the inclusion of penalties if target times are not met. This target approach can also provide transparency around the different pathways, enabling efficient outcomes. In 2018, the difference between standard and expedited reviews were 212 days for the TGA, 206 days for EMA, 141 for Health Canada and 121 days for FDA (Figure 29) (Rodier *et al*, 2019).

The review of an application is a vastly multifaceted evaluation process in order to guarantee that the application meet the comprehensive regulatory evidence required for quality, efficacy and safety. SAHPRA's level to which they may accomplish the swiftness of the review within a predetermined target time, as well reliability, quality, precision and proficiency, can have a tremendous effect on access of essential medicines to patients (WHO, 2015).

As part of the non-ICH region, SAHPRA can identify with Canada's history. By assigning an expedited review policy to a selected group of submissions i.e. generics in the early 2000's, it impacted on both Canada's and South Africa's ability to meet performance targets for all their submissions. This allowed for delays in the review process, which

compounded over many years in South Africa. Furthermore, learning from their experience, Australia took the initiative to benchmark themselves against markets like the FDA & EMA and revealed that they are not aligned with the regulatory framework of their counterparts. SAHPRA can do the same and can learn from TGA's implementation of new drug approval pathways, in order to expedite the review of medicines.

5.3 Stakeholder engagement

The main aim behind the pre-submission meetings is to establish communication, and to provide interaction and subsequently positive results to both the applicant and the regulator. Fostering early discussions will ensure that clinical trial participants provide only the data required for the application, avoiding unnecessary tests and procedures, especially when funding and/or staffing is problematic. It also allows the regulator to provide essential advice prior to and during the review process. By providing pre-submission advice for companies to discuss the different submissions before and during the review process, applicants can obtain scientific advice early in development stage of a medicine and at major conversion points and stay within compliance with the advice recommended by the regulator. A good example of this is Canada. When Health Canada expanded their regulatory review process, it became more successful through stakeholder engagement.

More importantly, the regulatory authorities have demonstrated that meetings prior to submission and their availability during the review process, has contributed to less delays and ultimately resulted in faster review and approvals. Early engagement is the key to a streamlined application and the South African market can benefit from this arrangement. It will demonstrate SAHPRA's support, highlight their commitment to transparency and show dedication to ensure an efficient process.

5.4 Resources

The efficiency of a medicine application review is reliant on a satisfactory number of competent reviewers following sound and ethical practices and resources. Reviewers should have up-to-date scientific expertise as they need to critically appraise scientific information and provide assessments that are repeatable and are easily grasped by others. The FDA and Japan have recognised the need for review and administrative personnel and have actively worked towards increasing their staff complement in order to improve efficiency.

In 2018, SAHPRA stated that they employed an equal number of internal employees and external reviewers, both providing the service of ensuring that the day-to-day operations are taking place. Staffing is one of the biggest limitations and SAHPRA has identified the need for increasing staffing resources. They have advertised a variety of vacancies for enthusiastic, self-motivated people with a wide range of professional qualifications and skills. With an increase in staff, it should be emphasized that the training of the reviewers should also be adequate and focussed. In doing so, they would like to bring the skill and expertise of reviewers in-house and to provide a more efficient regulatory service. By 2023, they envision a staff complement of 450 permanent employees.

5.5 Harmonisation and workshare

Global Harmonisation should ideally be done in two steps, described by Juillet (2007) as *Harmonisation of content* (referring to mutual recognition of studies and data) and *Harmonisation of format* (referring to exchange of information and recognition of assessment); both a necessity to a successful marketing authorisation.

International work-sharing can be an important contributor to regulatory alignment and to creating access to larger markets. The EMA is a perfect example of how work-sharing can be leveraged to create efficiencies.

As there is a shift towards global harmonisation in the pharmaceutical industry, the idea of parallel applications all over the world should become a reality. Mutual recognition of assessments (as can be seen in the EU) can become a framework to increase the access of medicine. ZaZiBoNa's goals are to harmonise regulatory functions throughout Africa. It was initiated amongst the regulatory bodies in Zambia, Zimbabwe, Botswana, and Namibia. Currently the MCC/SAHPRA partakes in this venture (Keyter *et al*, 2018). This is a move in the right direction, but it should be explored further (to include other continents) to recognise processes and reports (like EPAR) that would allow for a more efficient regulatory review process.

Chapter 6: Recommendation and Conclusion

When evaluating the data of all countries, key differences between agency practices do exist, but in general:

- The median approval time decreased over time, while key barriers were targeted;
- The introduction of additional and/or accelerated pathways facilitated the review process;
- A commitment to target review and response times ensured faster approvals.

This data supports the hypothesis of this mini-thesis in that the use of dedicated pathways to review different applications, along with set review timelines, can extensively benefit the South African review process. Through the evaluation of different systems, comparable investigations can be conducted by SAHPRA to gain information regarding the use of promising medicine and the impact of the expedited review systems can enable the reduction of review times and contribute to faster approvals.

SAHPRA should define the distinct phases in the regulatory process first, in order to provide transparency and accountability for both the regulator and applicant. Through constructive stakeholder engagement, further commitments are required by both the regulator and applicant in order to achieve target timelines.

The MCC and SAHPRA have never had review and response targets, but going forward, SAHPRA has benchmarked ambitious review times; they have specified that 275 days will be allocated for NCEs and 180 days for generics (Low, 2018). These timelines are not realistic as SAHPRA has not achieved the staff complement needed to perform at optimal levels. Phasing in staff over five years means that target review times can only be achieved

post this period and not in the two years that was mentioned. While recruiting, SAHPRA should also re-evaluate their service level agreements (SLAs) with outside assessors and/or consultants. Agreements should be tightened to ensure that deadlines are respected, especially pertaining to applications with specific time restrictions.

SAHPRA receives a portion of its funds from the national fiscus through the National Department of Health budget and the balance of SAHPRA's funding is raised through charges for services supplied in the conduct of its mandates. They may also receive donations in accordance with the National Treasury Regulations. It is expected that SAHPRA will receive most of its funds from fees. Their objective is to deliver better, faster services and therefore justify increased tariffs. Several functions (like radiation control), are currently provided without charge and this will change in future (SAHPRA, 2019). From a financial aspect, this does not seem enough for SAHPRA to achieve their ambitious goals to improve regulatory performance. In order to achieve financial sustainability, they will need to revise their fee structure.

The use of technology systems should be implemented by SAHPRA to further maximise efficiency. The application of management systems for tracking and monitoring of applications will result in the monitoring of timelines and workflow, without compromising the standards of approvals.

Furthermore, as part of the reduction in backlog, SAHPRA has requested applicants to cancel many duplicate applications currently adding to the volume of applications that are exacerbating the backlog. Going forward, the possibility of a sunset clause can benefit the agency, especially where the lifecycle of duplicate dossiers is not always maintained.

SAHPRA has embraced the harmonisation process through the Pharmaceutical Inspection Co-operation Scheme (PIC/s), ICH and WHO, and identifies that collaborations and harmonisation should stimulate endless opportunities for growth and development. Building from this experience, a regulatory reliance pathway should allow SAHPRA to accept the approval of other recognised regulatory authorities in order to grant a South African approval, with minimal review. Harmonisation should also be further explored and/or strengthened, whereby assessments completed by other regulatory bodies, can be recognised by SAHPRA. This is an essential measurement to improvement and elevate patient access to quality health products on a global scale. With an aim to using resources efficiently and ultimately to avoid delay, the standards for investigating safety, efficacy and quality that is implemented by SAHPRA, should be universal too. Harmonisation should strengthen the allocation of resources in South Africa, as it establishes collaborations with other regulatory authorities and effectively combine to the regulatory efforts. This reduces regulatory barriers such as unnecessary duplication and improving pharmaceutical trade and ultimately, facilitate access to medicine.

The results presented in this study should incite dialogue, debate and further discussions when considering options for improvement in South Africa. Of the countries that were examined in this study, it was evident that there was a reduction in review times due to the introduction of additional pathways and target review times. By streamlining the review process based on the information that was gathered, the regulatory framework of SAHPRA can become more efficient and access to medicine can improve.

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Proposal Title:

The introduction of additional regulatory review pathways can facilitate faster dossier approvals in South Africa

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This proposal is submitted in support of a mini thesis and in partial fulfilment of the requirements for the degree of Master of Science in Pharmacy Administration and Policy Administration in the School of Pharmacy, Faculty of Natural Sciences, University of Western Cape.

Table of Contents

Title**:**

The introduction of additional regulatory review pathways can facilitate faster dossier approvals in South Africa.

Introduction:

The access to affordable medicine has always been a contentious issue and a major challenge in emerging markets. The countries' health systems are under tremendous pressure to improve access and simultaneously be adequately staffed and equipped to meet the needs and demands of the population (Gray, 2004).

With a view to using resources efficiently and ultimately to avoid delay, scientific standards for investigating quality, safety and efficacy should be universal too. This should ideally be done in two steps. Juillet (2007) brilliantly described it as *Harmonisation of content* (referring to mutual recognition of studies and data) and *harmonisation of format* (referring to exchange of information and recognition of assessment), both a necessity to a successful marketing authorisation.

For more than 20 years, the MCC of South Africa faced numerous complaints from pharmaceutical industries and clinical research organisations, that the delays in the registration of medicines were preventing access to affordable medicines. The South African Health Regulatory Authority (SAHPRA) is now responsible for the regulatory review of dossiers, leading to its approval. SAHPRA replaced the MCC in 2018 and is authorised by the Medicines and Related Substance Act (101 of 1965) to control the health products and its respective uses is South Africa.

Study Problem:

The regulatory review processes of the SAHPRA are delayed due to poor infrastructure and limited resources. Compounding the delay, are the large number of applications that are received on a daily basis (Leng et al, 2015). The regulatory authority has to balance access of medicine, with a thorough benefit-risk assessment. As approval times are also a key indicator to assess the performance of a regulatory agency, a dramatic improvement in strategy is required to further drastically improve the current review processes. Every delay is also a measure of access and availability.

Once an application has been received, there is no time period allocated for the review of the dossier. There is also no specific time allocated to the individual stages of the different committees that review the different sections of each dossier. Furthermore, the document requirements between different application does not differ, whereby NCEs and generic applications follow the same assessment path (Keyter, 2018). This ultimately results in a considerably long review process.

Research Purpose:

A recent study performed by Keyter et al. (2018) assessed the regulatory review process in South Africa and recognised the need for an enhanced process. Their research and findings are significant and relevant, as it highlights the key focus areas needed to transform the organisation at an operational level. One of the identified focus areas were the need for an enhanced regulatory review process.

With a current review process that can easily take up to 5 years, it is clear that there is an urgent need for alternative pathways and opportunities for an enhanced regulatory review process. Using the already identified key milestones and timelines used by other countries, the research purpose is to alleviate the backlog and reducing the review timelines. As part of the restructuring process, SAHPRA should consider different review pathways, specifically those that have proven to be successful in other regulatory regions. In doing so, medicines that can treat serious conditions or can provide substantial improvement over current therapies, can be approved within faster timelines and made available to the public.

The research hypothesis for this study is as follows: "If SAHPRA adopts review and evaluation pathways for product applications similar to existing frameworks in other countries, the review timelines will decrease, and approval rate will increase."

Objective:

The purpose of this research is to perform a comparative review of the current South African framework for the submission of applications and compare this to existing pathways in other countries. In order reach the objectives of this study, an evaluation of the review framework processes of different countries, including the European and United States (US) will be conducted. These mature markets used to experience lengthy delays between the 1960s and 2000s and have shown drastic improvements due to a change in their regulatory environment (Wileman and Mishra, 2010).

By adopting or modifying regulatory pathways that have already proven to be successful in different countries, the approval process should become more efficient. The bottlenecks

that are hindering the registration process of new applications, generics and eventually variations, can be identified and subsequently streamlined. Clear expectations and a commitment to defined review and approval times can be highly effective to ultimately achieve the goal. The European Union has extensively reduced their review process due to its agency's clear expectations of and specified approval timelines, with a firm commitment to a 210-day approval timeline (EMA). The US has streamlined its review process for medicinal products to 180 days, with some approved even faster (FDA).

The ICH's mission is to achieve greater harmonisation on a global scale in order to ensure safe and effective medicine that are of superior quality. In addition, its aim is for medicine to be developed and registered in a well-organised and in its most resource-efficient manner. When the Medicines Control Council (now known as SAHPRA) embraced the Common Technical Document (CTD) format in 2011, it opened the doors to harmonisation. Their aim was to facilitate the submission of information, save industry resources, provide efficient assessment and faster availability of medicine (Taute, 2013). Harmonisation strengthens the allocation of resources in a country, as it establishes collaborations with other regulatory authorities and effectively combine the regulatory efforts. This reduces regulatory barriers such as unnecessary duplication and improved pharmaceutical trade.

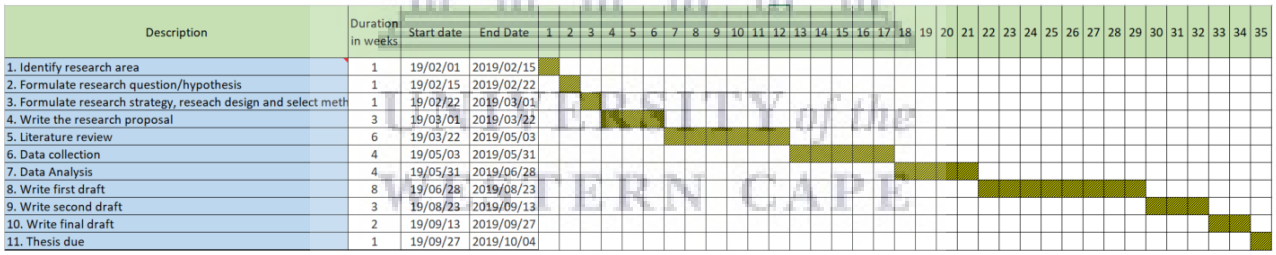
Methodology:

The research is a retrospective literature-based review, with the aim to provide a qualitative analysis using information from existing guidelines and timeframes. The analysis will be useful in providing historical data that is needed for studies (Statsdirect, 2000). The methodology assumes that the review processes in mature markets are made up of different stages with allocated timelines assigned to each stage. The specification defines a uniform structure to each step in the review process.

By identifying the different processes, stages and timelines from different regulatory authorities, the information can be used to benchmark against current South African processes. Through the evaluation of successful existing pathways and understanding what ultimately led to the improved productivity of emerging markets, South Africa can use the operational tools available to improve the review process effectively.

The analysis will also combine sources of information from guidance documents and data that is collected from published information by regulatory authorities, books, online journals and articles. This literature research methodology indirectly provides access to information (Lin, 2009). The research documents will be retrieved from the databases and the websites of relevant international organisations, research institutions and other organisations.

Milestone and Time plan:



Description	Duration in weeks	Start date	End Date
1. Identify research area	1	19/02/01	2019/02/15
2. Formulate research question/hypothesis	1	19/02/15	2019/02/22
3. Formulate research strategy, reseach design and select meth	1	19/02/22	2019/03/01
4. Write the research proposal	3	19/03/01	2019/03/22
5. Literature review	6	19/03/22	2019/05/03
6. Data collection	4	19/05/03	2019/05/31
7. Data Analysis	4	19/05/31	2019/06/28
8. Write first draft	8	19/06/28	2019/08/23
9. Write second draft	3	19/08/23	2019/09/13
10. Write final draft	2	19/09/13	2019/09/27
11. Thesis due	1	19/09/27	2019/10/04

Ethical Considerations:

The research aims to maintain good ethical standards, with no conflict of interest. As this is a literature-based review, ethical approval from the University of Western Cape Ethics Committee is not required as no research subjects or confidential information will be used.

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