M.Sc. Pharmacy Administration and Pharmacy Policy specialising in Regulatory Sciences

2014

The Impact an Accredited Third Party Assessor will have on the Regulator's Response Time

University of the Western Cape

in partnership with

Hibernia College, Ireland

Submitted in partial fulfillment of the award of
M.Sc. in Pharmacy Administration and Pharmacy Policy
Specialising in Regulatory Sciences

April 2012 Cohort

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MRESC007

The Impact
an Accredited Third Party Assessor
will have on the
Regulator's Response Time

Abstract

Background:

Globally Regulators have been under scrutiny for delays in Market Application (MA) approvals. The main issue that surfaces in studies related to these delays is a shortage in competent reviewers. The concept of a Third Party Assessor (TPA) who performs pre-market approvals is introduced, one who will be providing assistance to the National Medicine Regulatory Authority (NMRA), therefore functioning on the principle of Public Private Partnerships (PPPs). The aim of this professional body would be to decrease dossier review time, increasing the availability to medicine, medicine-related products and medical devices that comply with quality, safety and efficacy standards to treatment programs in a shorter time.

Methods:

The study was designed around a mixed-method approach using quantitative and qualitative research methods to evaluate the concept of a TPA providing a support function to the NMRA. The qualitative arm comprised of two sections namely assessing key factors, advantages and disadvantages of international health models (n=7) and PPPs (n=12). The quantitative arm analysed a regulatory professional-targeted survey (n=26) which assessed the susceptibility of the TPA concept, while evaluating critical factors such as what the main reasons (considered by participants) are for the backlog, if SAHPRA will be able to provide permanent relief to the backlog, what the expected time for reviewing an application is, etc.

Results:

The study confirmed that a lack in regulator resources is the main reason for delayed MA reviews and that an improved strategy is needed. The viability of the TPA-concept was supported by 75% of the respondents, and all respondents confirmed that implementing a TPA will reduce the review time. The optimal review time confirmed by frequency tables for New Chemical Entities (NCEs) and generic product applications were 12 - 24

months and 12 months respectively. The years-experience variable was compared using Chi-Square test and symmetrical values, and no significant correlation was found ($p>0.05$).

Triangulation with international health models and PPPs showed consistency in the advantage of reduced time, and the requirement and benefit of skilled resources. The findings were inconsistent for constant communication and its effect on bias and transparency, and if such a partnership should ensue as a phased approach.

Conclusion:

The study concludes that optimal review times will exist if NMRAs make use of a skilled TPA. The study also found that the benefits are not restricted to better timelines and an increased capacity, but that efficiency, performance, skills, innovation, and superior outcomes may possibly be increased as a result of a PPP. Further research would be needed to validate this concept and overcome this study's limitations which included a small sample size.

Declaration

I declare that this thesis that I now submit for assessment on the programme of study leading to the award of Master of Science Pharmacy Administration and Pharmacy Policy Specialising in Regulatory Sciences in has not been submitted as an exercise for a degree at this or any other college. It is entirely my own work and has not been taken from the work of others, save the extent that such work has been cited and acknowledged within the text of my work.

I agree to deposit this thesis in Hibernia College's institutional repository or allow the library to do so on my behalf, subject to Irish Copyright Legislation and Hibernia College Library conditions of use and acknowledgement.

Signed..... Dated..26.04.2014.....

Acknowledgements

I would like to thank my Research Project Supervisor, Miriam O'Donoghue, for her support and guidance during my thesis. I would also like to thank my loving, patient husband for his endless support and my mother for her prayers throughout these past two study-years. Furthermore I would like to thank two exceptional individuals I consider as life-tutors, Melani Botes and Martin Wessels, for their time, advice and critique during this time.

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List of Abbreviations

1. AdvaMed: Advanced Medical Technology Association
2. AIDS: Acquired Immunodeficiency Syndrome
3. AM: Administrations Manager
4. ANDA: Abbreviated New Drug Application
5. ARV: Anti-Retroviral
6. BEMA: Benchmarking of European Medicines Agencies
7. CAMs: Complementary and Alternative Medicines
8. CEO: Chief Executive Officer
9. CFO: Chief Financial Officer
10. COO: Chief Operational Officer
11. CTD: Common Technical Document
12. DNDi: Drugs for Neglected Diseases initiative
13. EC: European Commission
14. eCTD: Electronic Common Technical Document
15. EMA: European Medicines Agency
16. EU: European Union
17. FDA: Food and Drug Administration
18. FDC: Fixed-dose combination medicinal product
19. GDA: Generic Drug Application
20. GRMP: Good Review Management Principles
21. HMA: Heads of Medicines Agencies
22. HR: Human Resources

23. ICH: International Conference of Harmonisation
24. IVD: In Vitro Diagnostic Medical Device
25. KPI: Key Performance Indicator
26. MA: Market Application
27. MCC: Medicines Control Council
28. MD: Managing Director
29. MDs: Medical Devices
30. MHRA: Medicines and Healthcare Products Regulatory Agency
31. MRA: Medicine Regulatory Authority
32. NBs: Notified Bodies
33. NCE: New Chemical Entity
34. NDA: New Drug Application
35. NMRAs: National Medicine Regulatory Authorities
36. NTDs: Neglected Tropical Diseases
37. OM: Operations Manager
38. PA: Personal Assistant
39. PEPFAR: President's Emergency Plan for AIDS Relief
40. PPP: Public Private Partnership
41. R&D: Research and Development
42. RA: Regulatory Agency
43. SAPRAA: South African Pharmaceutical Regulatory Affairs Association
44. SAHPRA: South African Health Products Regulatory Authority
45. SOP: Standard Operating Procedure

46. TPA: Third Party Assessor

47. TPP: Third Party Program

48. UK: United Kingdom

49. US: United States

50. WHO PQP: World Health Organization Prequalification Programme

51. WHO: World Health Organization

Chapter 1: Introduction

Medicine Regulatory Authorities (MRAs) have the arduous responsibility to ensure that medicine, medicine-related substances and medical devices (MDs) approve of quality, safety and efficacy. To successfully fulfill this role; time, dedication and skill are required from reviewers. Technological advances enable innovative medicinal products (or New Chemical Entities [NCEs]) and medical devices, where patient access to low cost treatment, and pharmaceutical competitiveness encourage more generic Market Applications (MAs) to be submitted for approval. MRAs form part of National Health Departments and compete for funds within the healthcare system. While MRAs play an important role in the healthcare system, funds are often more urgently allocated to more directly pressing needs such as providing medical assistance to facilities treating sick members of the population. The limited MRA-human and financial resources result in an imbalance from the increased submissions and time needed for MA reviews, which causes stakeholder tensions and a delay in optimal treatment.

The concept of a Third Party Assessor (TPA) is introduced in this study to perform pre-market approval of dossiers. The intention is for this professional body to supply a support function to the National Medicine Regulatory Authority (NMRA), functioning on the principle of a Public Private Partnerships (PPP), which is the cooperation between the government and private entities. The aim of this professional body would be to decrease dossier review time, making medicine, medicine-related products and Medical Devices (MDs) that approve of quality, safety and efficacy available to treatment programs, in a shorter time.

The South African Medicines Control Council (MCC) is considered one of the most competent MRAs on the African continent, yet severe delays in MA reviews and approvals have existed for many years (Board on Health Sciences Policy, 2012:44), even after aligning with ICH's regulatory harmonization standards and guidelines, and using CTD and eCTD dossier formats. The current process followed (as seen in Figure 1) makes use of the limited and often temporary MCC staff (see Appendix 2 for the current MCC structure) and committee members (Figure 2).

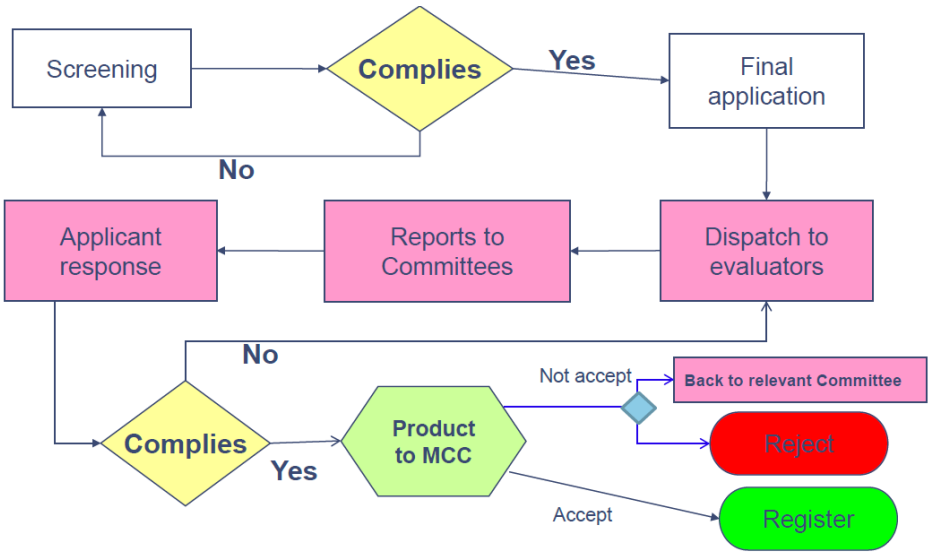

Figure 1: MCC Registration Process (Taute, 2014: 4)

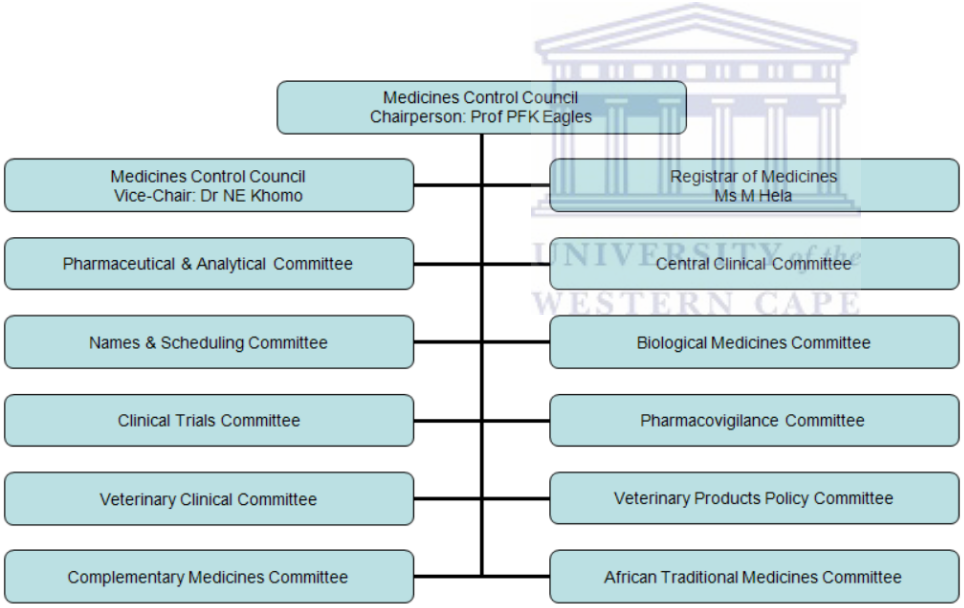

Figure 2: MCC and Expert Committees (MCC, 2003-2013)

The TPA who will act as an extension of the MCC/SAHPRA in terms of responsibility, and independent from the industry to avoid bias, will be a company led by a CEO, driven by performance appraisals (Appendix 3: TPA Organogram). The process as seen in Figure 3 (and outlined in Appendix 4 where the process is described) will ensure that the screening and review is done by the Expert Reviewers (ERs) within a pre-established timeframe.

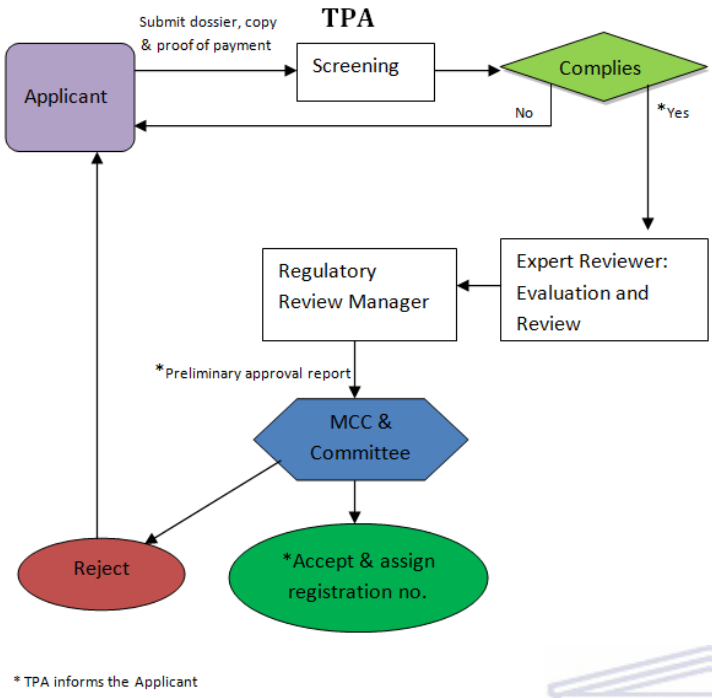

Figure 3: Registration process using the Third Party Assessor

This study confirmed that only one TPA (and not various contracted TPAs) should exist based on exploring benefits and criticism of Notified Bodies (NBs). NBs are private commercial entities licensed by national medical device regulators under the legal framework of Directives 90/385/EEC, 93/42/EEC and 98/79/EC, and are responsible for evaluations and inspections of medical devices in the European Union (EU) to assign Conformance approvals (CE-marking) before it can be marketed. Other international health models that provide assistance to the NMRA structures and operations also explored in this study are:

- Accredited Person Program (APP) / Third Party Program (TPP) for medical devices, part of the FDA's Modernization Act of 1997;
- Generic Drug User Fee Act Program (GDUFA) for generic products jointly proposed by the FDA and industry;
- Prequalification Programme of the WHO focusing on vaccines and medicines for third world-related epidemics such as HIV/AIDS and malaria;

- Article 58 of the European Medicines Agency's (EMA) Regulation (EC) No 726/2004 for WHO targeted diseases;
- FDA's Tentative Approval of generic anti-retrovirals that expedites the availability of generic products; and
- European Benchmarking Agency for setting standards, sharing best practices and identifying areas for improvement.

The survey that was done as part of this study to explore the susceptibility of the TPA concept investigated if a shortage in reviewers is the main reason for the backlog, if an improved strategy (other than SAHPRA replacing MCC) is needed to eliminate the review backlog, whether TPA is considered a viable option and ultimately if optimal review times will come into effect if a skilled TPA is introduced.

The study also compared what participants considered as imperative roles the TPA should play and illustrates the advantages and disadvantages of the different types of international health models listed above as well as PPPs (not limited to the health sector).

Chapter 2: Literature Review

2.1. Introduction

In an era where technology rapidly advances and an escalating health demand exists, with an increasing life-expectancy of the global population and luring epidemics in developing countries such as malaria and HIV/AIDS, the responsibilities of National Medicine Regulatory Authorities (NMRAs) increase substantially to ensure that safe and efficacious medicines and medical devices that meet quality standards reach the patient in time. MRAs have been under scrutiny for delayed MAs worldwide.

2.2 Optimal Review Times

2.2.1. International Review Times

When considering a country's MRA responsibilities, a starting-point would be to look at the definition of Regulatory Science. The US Food and Drug Administration (FDA) Science Board defined it as the assessment process a public health organisation follows, utilizing scientific staff and resources to expand the evaluation and monitoring capacity, and to modernize and develop new regulatory pathways (FDA Science & Technology Subcommittee, 2007). This report highlighted that the ratio between resource- and demand-increases were disproportionate, similar to the statement made by South Africa's Registrar, reasoning the backlog experienced as a result of evaluators and committee member-amounts being equal to those appointed in 1965 (Thom, 2010).

In the book, Building a National Framework for the Establishment of Regulatory Science for Drug Development (US National Academy of Sciences, 2011), Prof. FitzGerald, Director at the Institute for Translational Medicine and Therapeutics, pertinently excluded methods to accelerate approval from the definition in his guidelines, yet the time it takes for the Regulator to give feedback plays a vital role in the wellbeing of the country's health sector and population. The essence lies in not compromising quality or safety during accelerated reviews, but adhering to predetermined and optimal timeframes. The time-balance required is delicate between proving

safety, making needed treatment accessible to patients and recovering R&D expenditures. Alexander et al. (1991) already discussed the effect on patent life and market entry more than 2 decades ago, with fluctuations in approval times as seen in Figure 4, with the spike observed in the 60's due to the emphasis on safety and efficacy. Delays during this 30-year period were due to a shortage in the Regulator's human resources and the quality of applications to proof safety and efficacy.

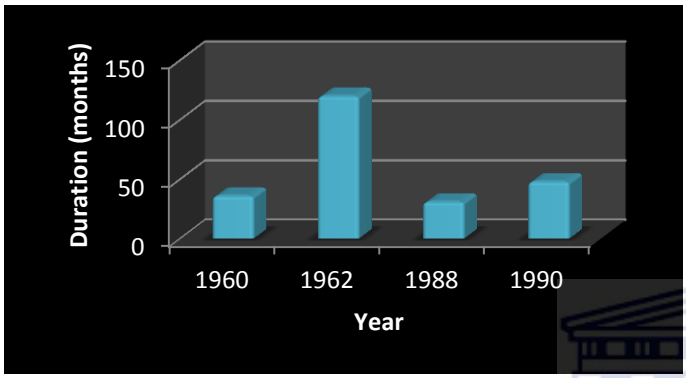

Figure 4: Duration of drug approval process in US between 1960 and 1990 (Alexander, 1991)

A comparison done on the MA approval process time internationally showed that India required the least time, 32-48 days, and the UK's Centralised procedure the most time (of the five countries compared), with 210 days.

Table 1: Comparison of the time required in the drug approval process (Dureja, 2010)

Country	Time for Regulatory Approval of CTA/IND Application	Time for Evaluation of MAA	MAA Fee
Australia	120 day	50 days	$192,400
China	50 days	180 days	DNA
India	16-18 weeks	8-12 weeks	50,000 INR
UK*	35 days	210 days	PS254100
USA	30 days	180 days	$217,787

*By Centralized Procedure; MAA-Marketing Authorization Application, IND-Investigational New Drug, CTA-Clinical Trial Authorization, DNA-Data Not Available.

Melchior's study (2011) on the transparency of Regulatory Agencies (RAs) showed that the FDA was 90% within its performance goal, a drastic reduction from data in Figure 4:

Table 2: Summary of FDA's annual review time and performance goals between 2008 and 2012 (Melchior, 2011: 8)

Original Application Type	Review-Time Goal	Performance Goal FY 2008 – FY 2012 Submissions
Priority	6 months	90% on time
Standard	10 months	

The study also concluded, based on EMA's 2009 Annual report, that 99% of Market Applications (MAs) were assessed within its 210-day review time. The significance seen in this is that although EMA subjected themselves to a more extended time (in Dureja's comparison between the five countries, Table 1), they were the most compliant as seen in this study. New Chemical Entities' (NCE) review times for MRAs which also includes Japan, New Zealand and Canada are summarised in Figure 5.

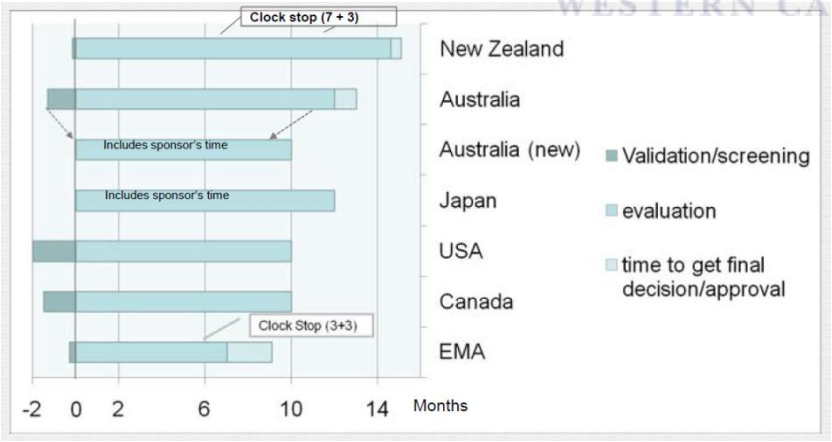

Figure 5: An overview of NCE review timelines for different MRAs (Melchior, 2011: 19)

A recent publication by Davis and Abraham (2013) showed that pharmaceutical companies submitting incomplete and substandard MAs to the FDA were mainly responsible for review-time delays.

In published literature on a workshop summary, FDA Commissioner Margaret Hamburg (2013) expressed the importance of partnerships for a sustainable regulatory infrastructure, rightfully stating that strategies and standards must be harmonized, and that resources will be critical to identify priority areas to ultimately achieve an improved regulatory science.

Dr Bernard Pécoul (2010) stated that a *Drugs for Neglected Diseases initiative* (DNDi) workshop revealed that capacity deficiencies impeded access to much needed treatment. The six main causes identified a lack of:

- Unambiguous legislative framework;
- Financial resources;
- Experienced and qualified workforce;
- Political assistance;
- Stakeholder appreciation; and
- Distribution of regulatory responsibility resulting in neglected areas.

Different regulatory approaches were discussed and rated as seen in Table 3 and a useful action map (Figure 6) which may assist NMRAs determine the urgency, complexity and resource efficiency on a national to global level in terms of capacity.

Table 3: Alternative regulatory approach performance table for NTDs (Moran, 2010: 22)

	Safety, efficacy, quality assessment	Assesses suitability for Africa	Systematic DC input	Expedites access	Resource-efficient	Builds African capacity
Twinned approval	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓
Article 58	✓✓	✓✓	✓	✓		✓
WHO drug and vaccine prequalification	✓✓	✓✓	✓			✓
Parallel approval	✓✓	✓✓	✓		?	✓
Routine and expedited Western approval *(Fast-track, priority review, standard review)*	✓	?				
Orphan approval	✓	?				
First approval by DC regulator	?	✓	✓✓	✓✓	✓	
Accelerated review	?	?		✓		

? *Signifies that the mechanism's delivery against that criterion must be assessed on a case-by-case basis*

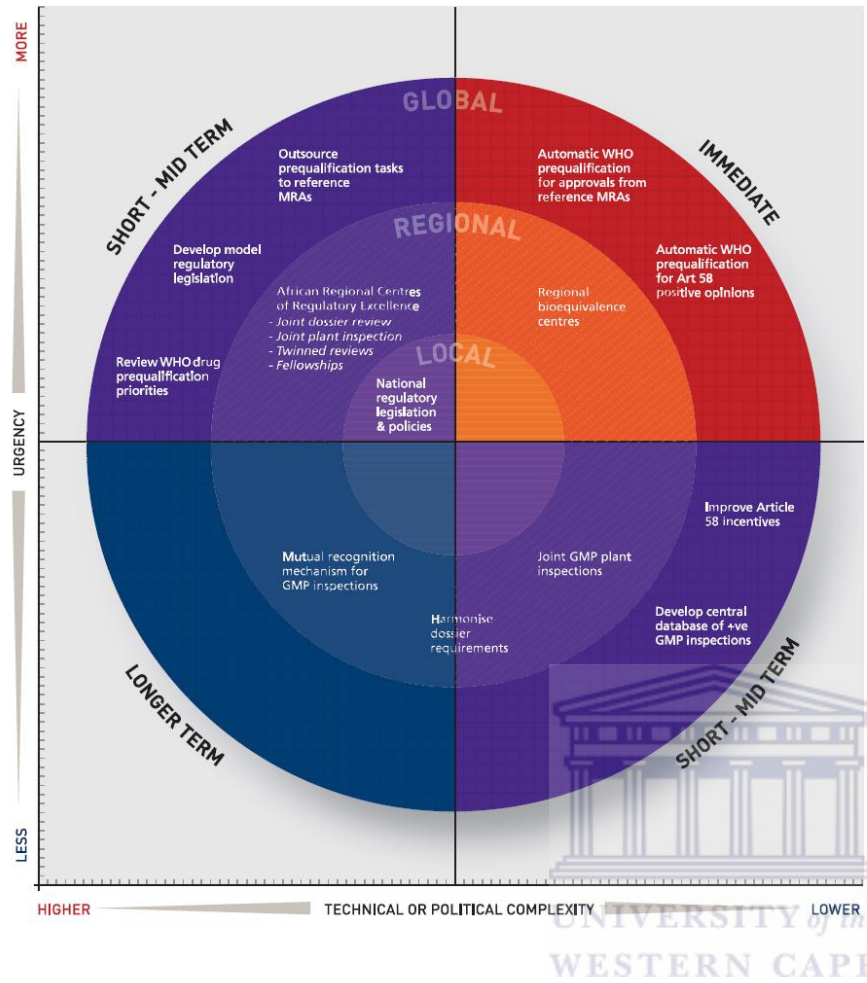

Figure 6: DNDi action map of regulatory capacity-building investments and activities (Moran, 2010: 25)

Limitations to the value of the data in this study lies in the fact that it focused on NTDs (Neglected Tropical Diseases) and on the African continent as a whole. The alternative approaches discussed remained options, are used preferentially by developers, and may require repeated or duplicate reviews (by either WHO or Western MRAs), not making it optimal. The study acknowledges that the medicine discussed may only be required by a small percentage of the Western population, and made proposals from a stakeholder perspective to manage limited regulatory resources and reinforce MRAs as seen in Figure 6.

Dureja's comparison of the drug approval process (as discussed above) concluded that the steps taken by the ICH towards harmonised guidelines, requirements, interpretations and applications of it will reduce duplication of work.

2.2.2 National review times: South Africa

On national level, suboptimal review-timelines were said to be due to both Medicines Control Council (MCC) inefficiencies and substandard applications from pharmaceutical companies. The backlog grew year on year as seen in Figure 7.

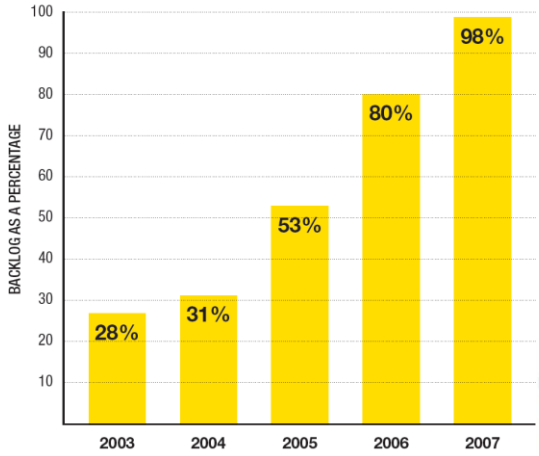

Figure 7: MCC registration backlog 2003-2007 (Thom, 2010)

In 2008 the 'Backlog Project' reduced the 4500 application-backlog (with submissions from 2001) to 1500 (by June 2010), however the support of the Department for International Development (DFID) (SARRAH, 2010). In 2013, 26 evaluators were contracted to accelerate generic registration during the first quarter (SARRAH, 2013). This lead to the problem of using a reactive approach by involving external reviewers, increasing costs, causing inconsistent reviews and uncertain review timeframes, which is not a sustainable long-term solution – a proactive approach is required.

Motsoeneng (2012) reported that it takes up to 60 months for a product to reach the market and costing some pharmaceutical companies up to 3 billion Rand of losses per year in South Africa. Dr Seoka (2012) acknowledged that the delay in medicine registration is unacceptable and that caution must be exercised against short-term solutions in trying to increase MRA capacity. She however argued in favour of national independence while building capacity, and stated that some facts in a dossier may have been overlooked by one country's MRA that

is picked up by another. This is in agreement with Dr Pécoul's statement (also discussed above – p22) that different clinical data will be required and assessed for different populations, and that an appropriate risk-benefit assessment with regard to specific populations will be reliant on the local MRA even if more stringent MRAs exist elsewhere (Moran, 2010). Dr Seoka supported cooperation and building partnerships. A possible gap may be the lack of effective communication between MRAs globally, granting each other access to documentation regarding the decision-making process of specific products, on request, while agreeing to public non-disclosure.

In an interview with the Registrar (Thom, 2010) Ms. Hela stated that two of the main setbacks were the number of temporary staff currently employed at the MCC (which will be replaced by permanent staff with the introduction of SAHPRA) and that a "Tsunami of generics" were submitted and very few NCE submissions.

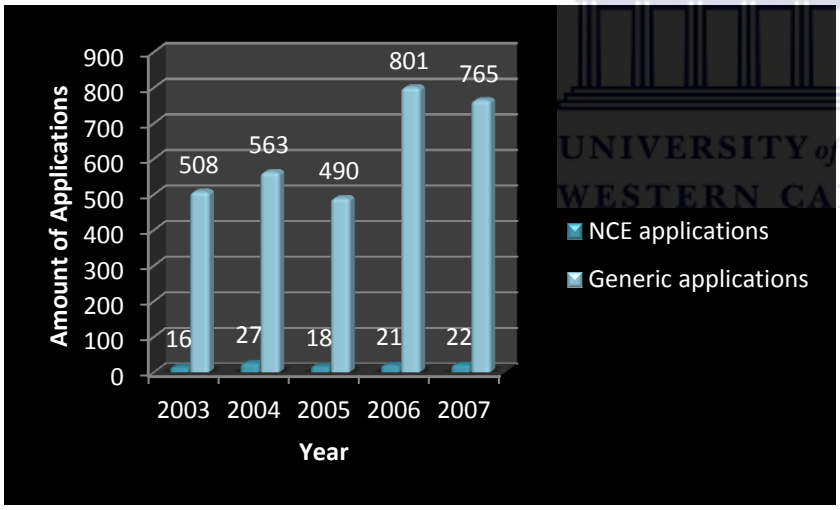

Figure 8: Amount of generic and NCE applications between 2003 and 2007 (Thom, 2010)

Some of the benefits of harmonization and the global use of CTD and eCTD are the increased transparency and reduced time in the review and approval process (Molzon, 2010). In SA the pilot project for eCTD is in the final stages, but teething problems were experienced and more applicant-training is needed. Expectations of a more effective NMRA and a closer working relationship with the local pharmaceutical industry (in terms of

regulations), are channeled towards SAHPRA, who will replace the MCC, and will operate outside of the existing public service, but report to the Minister of Health (Minister of Health, 2014). It was expected to be in place by April 2013, but latest reports indicate that SAHPRA will effectively take over towards end 2014 (Bateman, 2013). SAHPRA will have 400 instead of 150 members (Reuters, 2012), and the submission costs will increase, but the newly published CAMS regulations (requiring a similar process as medicine approval) (MCC, 2013), and its local industry worth R8.5 billion (HPA, 2013) will necessitate increased and competent assessors. The CAMS regulations also increase applications towards category A (allopathic medicine), which previously fell outside this category. Furthermore, the medical device and IVD (*In Vitro* Diagnostic Medical Device) licenses in SA relied on the EU's CE certification (Arazy, 2013), but the new draft regulation was published in April 2014 which will necessitate an additional increase in MRA-capacity. According to the Amendment Bill (2014: 4) the Authority (referring to SAHPRA) is responsible for the regulatory oversight of cosmetics, foodstuffs and hazardous substances. Regulations for cosmetics, disinfectants and food products will also be implemented according to plan in the near future, all of which will further increase the regulatory burden. New technologies e.g. stem cells, advances in biological products, etc. will also require regulatory control, so the demand on the limited resources will grow.

The concern remains if the new MRA will be able to accommodate all dossiers and ensure timely reviews. In the UK the Medicines and Healthcare Products Regulatory Agency (MHRA) makes use of Notified Bodies (NBs) for medical device audits and MA reviews (MHRA, 2013), the FDA of Third Party Programs (TPP) for medical devices by Accredited Persons (FDA CDRH, 2001) and Tentative Approval for generic ARVs (FDA, 2013). The WHO's Prequalification Programme focuses on vaccines and medicines for third world-related epidemics such as HIV/AIDS and malaria (WHO, 2011) and the European Benchmarking Agency for setting standards, sharing best practices and identifying areas for improvement.

The Amendment Bill makes allowance for SAHPRA to liaise with any other regulatory authority or institution for matters of common interest and to enter into agreements of cooperation. It also confirms that one of its objectives is to ensure a timeously evaluation and registration process (2014: 4).

2.3 Research Question

Will the MRAs review time for Market Applications decrease if a permanently appointed, competent Third Party Assessor is used, who is trained by an MCC/SAHPRA accredited trainer and program?

2.4 Hypothesis

If MRAs make use of a skilled Third Party Assessor, optimal review times for Market Applications will exist.

Chapter 3: Methodology

The study was designed around a mixed-method approach using quantitative and qualitative research methods to evaluate the concept.

3.1 Qualitative Analysis

The qualitative component of the study followed the methodology of grounded theory leading to categorization of data, namely coding, which is considered as the essential analytical process rather than a segment of qualitative research (Corbin and Strauss, 1990). This iterative approach provided structure to the TPA-concept, in support of proving or disproving the hypothesis. During the initial step, namely open coding, the following categories for this study were constructed, which compared international models using the concept of mediators in the market application review process:

- Market application category;
- Purpose/Primary role;
- Scope of practice;
- Assessed by;
- Criteria for designation/Qualification standards/Requirements;
- Advantages;
- Criticism; and
- Unique, beneficial initiatives.

Public Private Partnerships' (PPPs) advantages and disadvantages were coded and evaluated and during the second step, axial coding, the relationships between the international models in the health sector and PPPs (not limited to the health sector) were assessed, investigating integration and correlations between the categories (Walker, 2006).

The core category of the study, namely establishing if optimal review times will exist if a TPA (or mediator) is employed (proving or disproving the hypothesis), emerged from the final step, namely selective coding, where the other categories were related to the principal categories of review times and permanently appointed, trained and competent staff.

A significant property of grounded theory is theoretical sampling (Charmaz, 2006), where a deeper understanding is obtained of the concepts explored. It is essential in this research as the concept of a TPA is new and has never been explored before, meaning that investigating concepts similar to this is fundamental to establish a foundation for this theorized body. Theoretical sampling is also an important method for triangulation, again supporting this study as independent data was collated and compared to increase comprehension of an unfamiliar and new concept.

3.2 Quantitative Analysis

The quantitative arm of the study was a survey distributed via email to members of the South African Regulatory industry. This was done to assess the susceptibility of the concept of a TPA and to evaluate the factors considered as important by this population (in the light of a TPA), the optimal review time for New Chemical Entities (NCEs) and Generic product applications, the main reasons for the current backlog and most importantly, if a TPA would reduce the review time of dossiers from submission to market approval. In South Africa the Regulatory professionals belong to the South African Pharmaceutical Regulatory Affairs Association (SAPRAA), which has a total of 250 members. The total amount of survey respondents (n=26) formed part of the inclusion criteria and voluntary completed the questionnaire. Individuals from the pharmaceutical sector that formed part of the exclusion criteria were those not directly involved in the regulatory process e.g. retail pharmacists, hospital pharmacist, recruiters etc. Actual respondents consisted of:

- Regulatory Pharmacists;
- Consultants;
- Quality Assurance Pharmacists / Quality Compliance Pharmacists / Quality Assurance Officers;

- Regulatory Pharmacist Assistants / Regulatory Affairs Assistants;
- Directors;
- Legal Advisors; and
- Regulatory Food Scientists.

No NRA-members participated in the survey which reduced unbiased results.

Although probability sampling is considered to be the superior sampling method to keep sampling error to the minimum, to be a true representation of the population, and to decrease bias while increasing generalisation and validity (Brennan, 2013), it was not possible to sample via this route for this research project. The study made use of non-probability sampling for the survey, as the survey was distributed to the population of national regulatory professionals via email, of which the sample is considered those who were willing to complete the questionnaire. For ethical conformity a disclaimer was added to the survey email to ensure that participants were aware that they voluntarily participate in the anonymous survey and were allowed to withdraw at any time (refer to Appendix 5).

The main variable of the questionnaire considered was the years experience in the Regulatory field. Methods included descriptive statistics, Spearman's rank order correlation, Pearson's chi-square to test the relationships, and Phi/Cramer's V to test the strength of the relationship and the practical significance (Ellis, 2003). Data were analysed using Excel, correlation tests (non-parametric) and categorical testing (crosstabs) were done using the Statistical Package for the Social Sciences - SPSS 21.0.0 (2013). The Mann–Whitney test was not used due to the small sample size (not being a true representative sample of the population) and the sample sizes between <5 years experience and >5years experience not being equal in size.

This cross-sectional survey was made available to the study population at a particular time point (one questionnaire per participant from the survey which was available for a month). Groups that were compared within the sample comprised of categorical/nominal variables (job titles within the regulatory field, years experience) compared with ordinal/quantitative variables (using the ranking of what is considered as important if a TPA are to be included in the review process – see Appendix 6 question 6). The space created in the questionnaire for general comments or thoughts on the TPA-concept (question 9) and question options of 'Other' (where it was requested to specify if this option was selected), allowed confounding variables to surface. Although not optimal, this was used purposefully to enrich results and ensure that all variables are considered to successfully establish the need of - and construct a desired body to provide relief to the current dossier review dilemma experienced and to be of benefit to the regulatory industry as a whole.

The data from this questionnaire feedback was quantified to produce conclusions that can be generalised to a certain extent (Bell, 2010: 5).

3.3 Mixed Method Analysis

The data from the qualitative and quantitative arm of the study were used to attain an insight and appreciation of the local regulatory industry's perception of the TPA-concept. This form of exploratory research allows for new discoveries and minimise the probability of rejecting relationships that might exist. As the research problem, namely what the effect of the NMRA's review time will be if competent TPAs are used, has no similar studies to refer to, the exploratory approach assist in generating this new concept and assumptions, testing its feasibility, and assist in establishing what the research priorities are. Disadvantages to this design are the difficulty to generalize the results, data may seem unstructured and are difficult to draw a definitive conclusion (Labaree, 2013).

Methodological triangulation, which entails using qualitative and quantitative study methods, was used to add validity to the concept by testing if the two sets of results obtained was consistent and increase confidence in

the conclusions (Guion, Diehl and McDonald, 2011). A disadvantage to this method is that new lines of enquiry emerged. An example of this was the structure of the TPA in terms of management – being a company with a CEO, or following the structure of Partners (as seen in law or consulting firms) which enjoys the benefit of ensuring that diligence remains in the proposed company and that the lack of competition would not cause indolence and returning to a review backlog again. The concept however was designed around a CEO (refer to the organogram in Appendix 3). Other disadvantages of triangulation are not only the increased time-consumption and planning that is required, but that the results may diverge. Although this may be considered as disadvantageous, theories can only be developed more and on a deeper level if challenged to obtain a more unambiguous concept by exploring through innovation to overcome inconsistencies. The study also made use of theoretical triangulation in the survey by using participants from different positions within the regulatory discipline that gave feedback from different perspectives. This was guided by the inclusion criteria of the questionnaire (refer to Appendix 6 question 1) these professionals in the regulatory sector would influence feedback and decrease bias.

Chapter 4: Findings, Analysis and Discussion

4.1 Qualitative Analysis

4.1.1 Establishment and Purpose

In the formulation of the TPA-framework, international health bodies (n=7) that form part of a third party or alternative regulatory program were explored to determine the need or gap that existed, fulfilling its primary purpose for its establishment:

- **Notified Bodies (NBs)**

  NBs were established in the early 1990's from a form of self-regulation as a result of conscientious manufacturers assessing medical devices (MD) and the quality of systems, developing into EU legislation. This allowed these bodies to grant pre-market approval using a recognised regulatory procedure. This delegation was mainly due to the lack of MRA resources in relation to MD regulation, to enable assessment of MD-conformity. The international review timelines depending on the type/class MD are one to 36 months (see Appendix 7).

- **Accredited Persons Program (APP) / Third Party Program (TPP)**

  The original purpose for this program was to reduce cost to stakeholders, yet after the FDA's Modernization Act (FDAMA) was signed into law in 1997, the agreement to have Accredited Persons (APs) perform specific FDA tasks on its behalf for MDs, reduced the inspectors' burden while ensuring compliance with regulatory requirements. Fulfilling the purpose of prompt decisions while ensuring confidence in the APP, the scope of practices were divided to have the APs assess low to moderate risk MDs while the FDA continued assessing high-risk devices. The approval process takes an average of 72 – 109 days (see Appendix 8).

- **Generic Drug User Fee Act Program (GDUFA)**

  Implemented in 2012, with the aim on safety, access and transparency, GDUFA was established to provide additional human resources, to ensure that patients receive faster access to quality medicine that is inexpensive, to further provide increased predictability with regard to timelines and the review process for generic products. The FDA uses a risk-based method to inspect GDUFA biennially and this allowed them to perform their vital purpose using FDA freed-up resources. The stipulated timeline for this process is 10 months (see Appendix 9).

- **Tentative Approval (TA)**

  TA was designed to accelerate generic medicine availability for PEPFAR (the President's Emergency Plan for AIDS Relief) and took effect as an accredited FDA review process in 2004. TA indicates that the product meets standards of safety, efficacy and manufacturing quality. MAs were welcomed from international applicants for single ingredient, fixed-dose combination (FDC) and co-packed ARVs. With quality submissions, the target review time of two to six weeks are met.

- **WHO's Prequalification Programme (WHO PQP)**

  The WHO PQP has facilitated developing countries in enhancing their regulatory capacity through regulator engagement and training. The programme first focused on quality vaccines (1987), expanding to include medicines from 2001. PQP focus on preventing scientific assessment duplication using a condensed review process for products already approved by recognised MRAs e.g. EMA and FDA. The mission of PQP is to increase the availability of quality medicinal products to patients. The median time determined in 2010 for prequalification approval of generic and innovator products were 4.3 and 31.6 months (WHO, 2011).

- **Article 58**

  Laid down by the European Parliament in 2004 (Regulation (EC) No 726/2004), Article 58 was established in response to protecting public health and in support of WHO, to provide timely access to medicinal products. The review process is aligned with the standard regulatory MA review, but the EMA's CHMP (Committee for Medicinal Products for Human Use) gives a scientific opinion and advice instead of final approval. The rapid, yet thorough process takes an average of 2.5 months (Appendix 10).

- **Benchmarking of European Medicines Agencies (BEMA)**

  BEMA was established in 2004 following UK and Germany's proposal of implementing a benchmarking project for human and veterinary MRAs, where standards would be set, gaps identified and best practices shared in the public and private sector to encourage performance improvement. BEMA is a collective approach between NRAs and consultants fulfilling EC-legislative responsibilities, augmenting self-assessment (BEMA, 2012: 8). Part of BEMA's aims is to supplement the decision-making processes with pragmatic intelligence, while increasing transparency and responsibility during the approval process.

A trend observed from these bodies is that a regulatory partnership was established after a need was identified within the regulatory process, to enable an increase in available resources for regulatory responsibilities and to reduce the time spent on assessments, ensuring increased compliance, transparency and performance, and to ultimately accelerate the availability of a quality product to the patient population.

4.1.2 Advantages

The advantages of the international health models (n=7) were assessed, coded and compared.

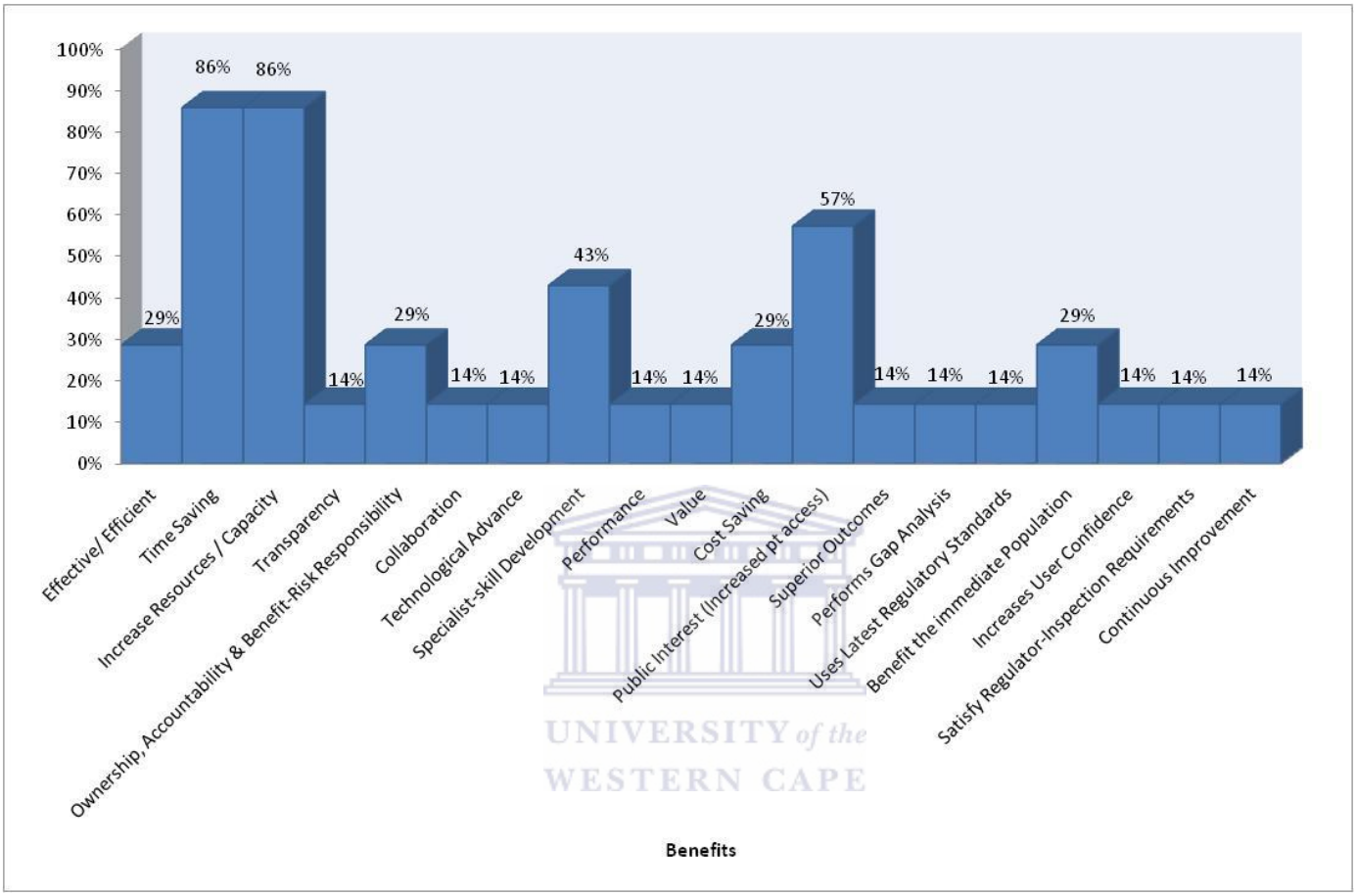

Figure 9: Percentage of international models with comparative advantages

From the data in Figure 9 it is evident that 86% of the bodies present the benefit of reducing the time spent towards approvals, as well as an increase in the available resources and the regulator's capacity, reducing the assessment burden, which leads to a further benefit of making MRA-resources available to perform their other critical functions. The third highest benefit from the study showed that the third party bodies act in favour of public interest, increasing earlier patient access to medicinal products.

When this data was compared with the benefits for Public Private Partnerships (PPPs) recorded in the literature (n=12) commonalities were observed. During the '*Post-2015 Development Agenda: Setting the Stage'* UN General Assembly, John Sanbrailo, Executive Director of the Pan American Development Foundation (2013) supported that PPPs provide a unique answer to hurdles countries face, especially for partnerships with shared objectives and accountability, and synergistic interactions and decision-making. In a PPP workshop held on food and nutrition (Pray and Pillsbury, 2012), it was concluded from participants feedback that complex societal health issues can be addressed successfully during public-private collaborations where resources, skills and perspectives are employed in unison.

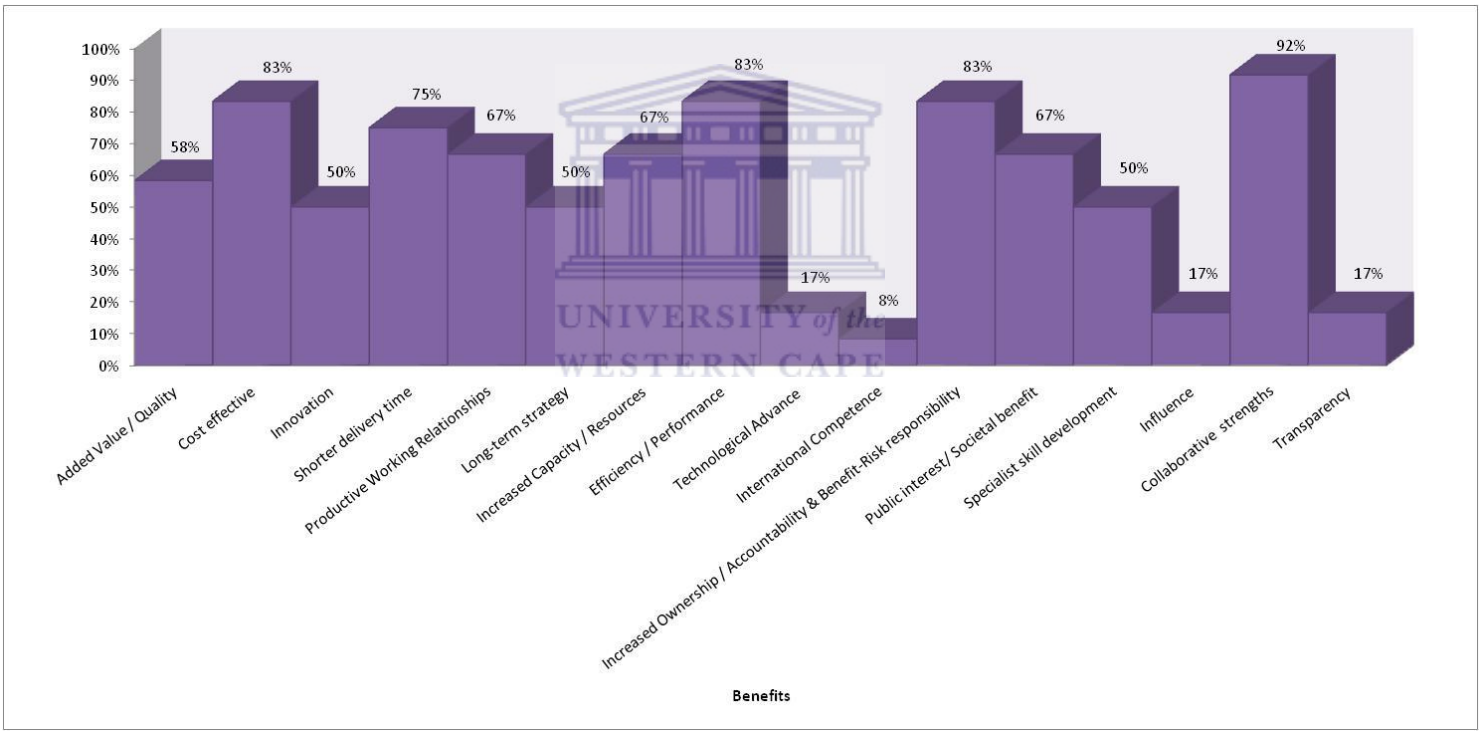

Figure 10: Percentage of PPPs' advantages per category

It is apparent from Figure 10 that the majority of the benefits from a PPP are collective, with collaborative strengths peaking at 92%, followed by 83% for being cost effective, PPPs resulting in increased efficiency and performance, as well as increased ownership, accountability and a shared benefit-risk responsibility. 75%

reported shorter project delivery times and are favoured for its increased resource availability to perform its functions.

Important from these findings is that with the reduced costs and waiting time, PPPs still owned the advantage of adding value and delivering high quality projects, to further provide a positive impact in favour of public interest.

The benefits of transparency and technological advance were parallel to the findings from Figure 9, with results below 20%.

A process-flow can be established by combining the positive correlations between Figure 9 and 10 in Figure 11:

Figure 11: A process-flow stipulating the progression of benefits with a partnership agreement

4.1.3 Concerns and disadvantages

In order to successfully construct the TPA concept, the concerns around - and disadvantages experienced with the International Health models and PPPs were considered. Table 4 depicts these challenges:

Table 4: Concerns and possible disadvantages of intermediary models currently in operation

Model	Bias / Conflict of interest / Favouritism	Incompetence / Substandard Assessment	Lack in transparency	Finance driven	Increased cost	Process gaps	Time-consuming	Patient safety concerns
International Health Bodies								
Notified Bodies (NBs)	•	•	•	•				
Accredited Persons Program (APP)		•			•	•		
Generic Drug User Fee Act Program (GDUFA)						•	•	
Tentative Approval (TA)								•
Prequalification Program (WHO PQP)							•	
Article 58						•		
Benchmarking of European Medicines Agencies (BEMA)	•				•			
PPPs	•		•	•	•			

Concerns around PPP's were mainly finance-related (which directly relates to bias), but also included complex contracts and negotiations, risk-baring, potential imbalance in data access, intercompany culture gaps, short-term rigidities, and a lack of competition causing inefficiencies in the long-term.

The disadvantage of favouritism observed for NBs are due to the fact that a large number of these bodies are in existence, where applicants have the freedom of choice which NB to use and can change to a different NB in the case of a MA rejection. Some NBs have been involved in the MD-development, which causes conflict of interest, and the financial drive of both parties, together with market competition have caused bias. This process defect encouraged substandard assessments, which means poor quality and unsafe MD's were approved. Standardization of the review process by the Advanced Medical Technology Association (AdvaMed) and European Commission (EC), tightened regulations and a Code of Conduct were applied with strategies to improve consistency, competency and objectivity during assessments. This highlighted the importance during the construction of the TPA-concept to have a single TPA-entity, which would act as an extension of the NMRA, to eliminate bias and conflict of interest.

Favouritism seen in PPPs was mainly due to the fact that a partnership exists on a temporary contract basis. The issue of temporary staff was also emphasized by the MCC Registrar (as discussed in Chapter 2) as being one of the main setbacks leading to the review backlog experienced. The international health bodies discussed above were all adopted into the relevant countries' legal framework, which eliminated the temporary staff-factor, and also supports the appointment of permanent staff. This approach would be applicable to the TPA structure and partnership with the MRA.

This may lead to the next concern of a lack of competition causing inefficiencies in the long-term (as seen above with PPPs). Yet, with the overwhelming existence of new applications and the inexhaustive demand from industry for MA reviews and approvals, in addition to pre-established review timelines, TPA efficiency and performance will be assured. This also signifies the value of the TPA being a registered company driven by performance appraisals (as discussed in Chapter 1) to ensure competent staff and institutional integrity.

With the introduction and implementation of new initiatives, short-term rigidities and challenges (as seen with PPPs) will be inevitable. This supports a phased approached, as well as comprehensive, unambiguous TPA-NMRA requirements and responsibilities specified in contractual and technical agreements. Vital contractual inclusions will be addressing and demonstrating relationships between potential conflict of interest, transparency and non-disclosure agreements.

4.2 Quantitative Analysis

To assess the susceptibility of a TPA performing pre-approvals for the MRA and reduce the dossier review time a questionnaire was used (Annexure 5).

According to the respondents (n=26) the main reason for the current backlog experienced (as seen in Figure 12) is that the MCC does not have enough reviewers (88%) followed by different MCC members handling dossiers with every resubmission (if changes are needed to the application) (32%).

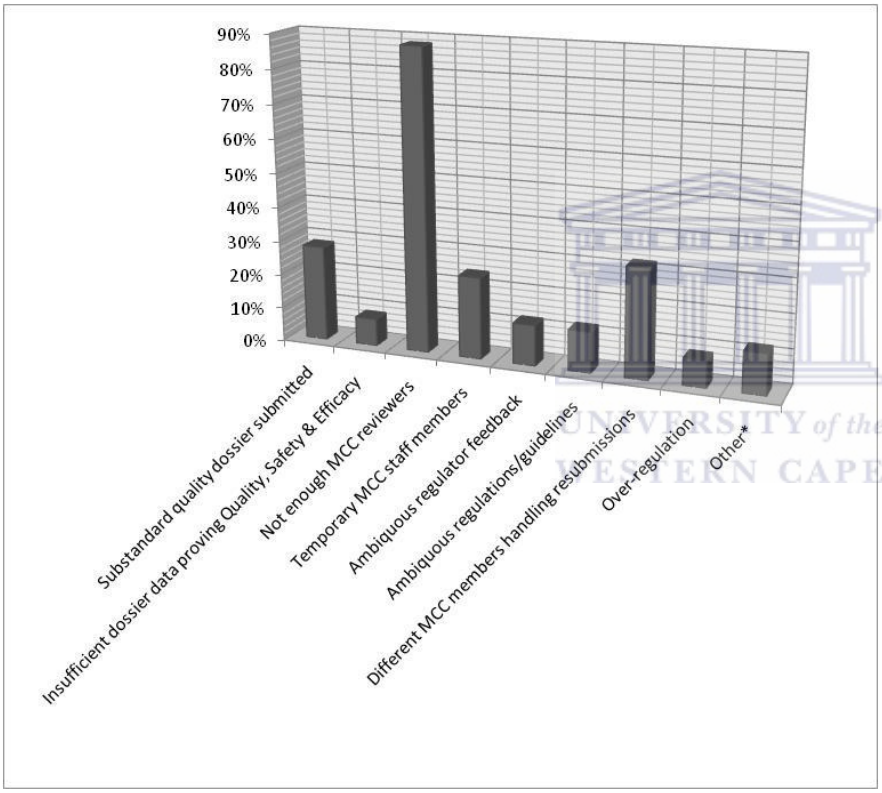

Figure 12: Reasons for the current backlog

The 12% feedback received for the *Other** category reported that the backlog is due to maladministration, political reasons, not enough experienced reviewers and MCC misplacing applications and resubmissions.

Uncertainty remains as to when exactly SAHPRA will take over from the MCC and the Amendment Bill has given a basic outline to their functions and structure, as reported in the Literature Review, but is was evident from the

results depicted in Figure 13 that an improved strategy will be needed to provide relief to the current backlog, have optimal review time-frames and be compliant with these set time-frames.

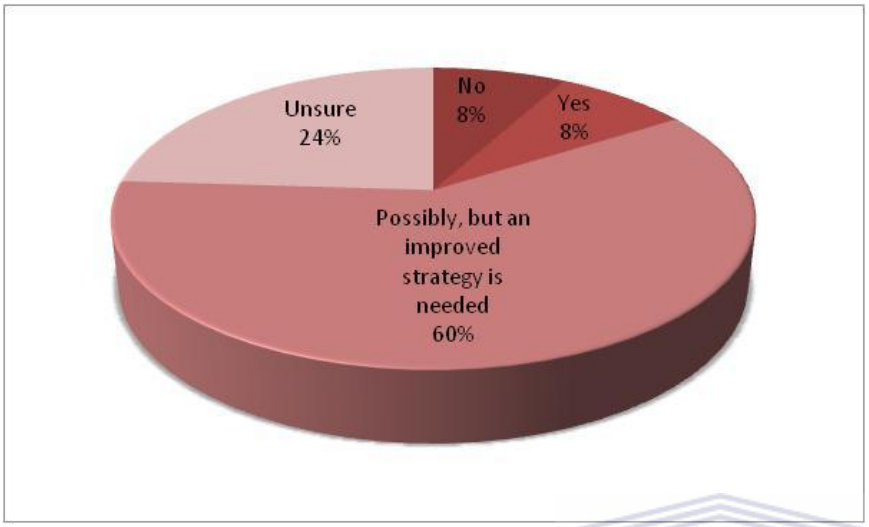

Figure 13: Respondent's opinion if SAHPRA will eliminate the backlog once implemented

The key variable considered in the questionnaire was the years' experience the respondents have in the regulatory industry. It was used to assess the validity of the answers, ensuring reasonable expectations based on knowledge and experience. 74% of the respondents had <1 - 5 years' experience and 26% more than 5 years experience in the regulatory industry.

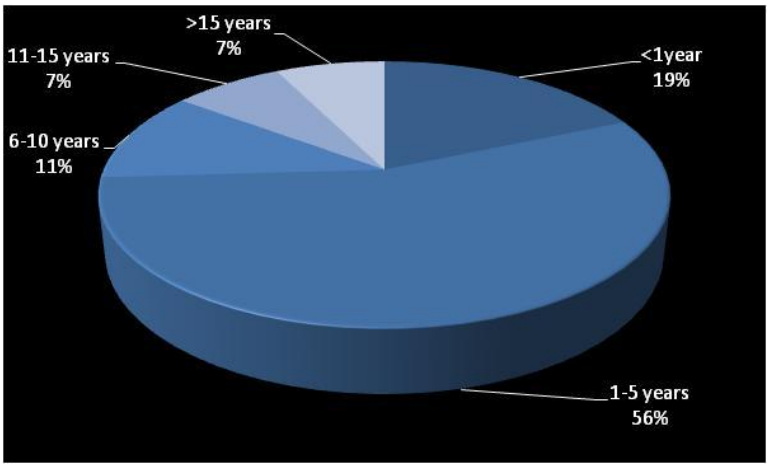

Figure 14: Respondents years experience in the regulatory industry according to questionnaire groups

The participants were asked to rate the importance of eight operational aspects and qualities that would be considered fundamental when functioning via the TPA towards accelerated market approval, with the rating of 1 being the least important and 10 being imperative:

1. The TPA is audited annually by the MRA;
2. The applicant can appeal against a decision made by the TPA and/or the MRA;
3. The applicant can anonymously rate the TPA based on the quality service received;
4. Transparency in decisions;
5. Intellectual property protection (signing a Non-Disclosure Agreement);
6. Constant communication between the applicant and the TPA;
7. No substantial additional application costs; and
8. Expedited reviews must still be reviewed by the MRA.

Table 5: Analysis of the ranking of operational aspects and qualities according to importance using descriptive statistics

	N	Minimum	Maximum	Mean	Std. Deviation
TPA_audited_annually	23	1	10	8.09	2.843
Applicant_can_appeal_vs_TPA_decision	23	3	10	8.70	2.077
Rating_the_TPA_anonymously	23	2	10	8.13	2.546
Transparency	23	2	10	8.83	2.289
NDA	23	1	10	8.78	2.679
Constant_communication	23	1	10	7.61	3.500
No_additional_costs	23	1	10	8.26	2.832
MCC_handling_expedited_reviews	23	1	10	7.35	2.964
Valid N (listwise)	23				

It can be seen from the data in Table 5 that all eight aspects and qualities were considered important with the means between 7.35 and 8.83. The highest score was for transparency in decisions with a mean value of 8.83 (2.289), followed by the non-disclosure agreement with a mean value 8.78 (2.679) and that the applicant can

appeal with a mean value of 8.70 (2.077) – having the lowest standard deviation. Constant communication between the assessor, MRA and applicants received the second lowest average score 7.61 with the highest standard deviation (3.5), showing a higher inconsistency between the answers submitted. This may be due to the idea that communication between the reviewer and the applicant may interfere with the judgement of the reviewer, causing bias. Comments from respondents in this regard included that communication should remain at the level of the MRA and applicant, and that the applicant should not be in direct contact with the TPA. It was also stated that the MRA's logging and tracking system should enable the applicant to follow up on the status of the application, not allowing communication between the applicant and the TPA to eliminate corruption.

Practical initiatives from BEMA with the focus on transparency, consistency in interaction and advice, quality, robustness, and encouraging good practices, included Agency Scorecards, Good Review Management Principles (GRMP) (Cone and Walker, 2005: 3) and key performance indicators (KPIs) (BEMA, 2012: 21).

Interestingly, in a question where respondents were asked if the quality of the dossier submitted will increase as a result of this intercommunication between the applicant, TPA and the MRA, 82.6% (n=23) confirmed that the quality will increase. One of the respondents stated in the comments section that the quality of the dossier submitted is upon the individual compiling the dossier and the standards of the company (applicant). The significance in these findings considering communication are that applicants covet clear communication to enable their dossier submission's quality to increase in accordance with the MRA's expectancy, clearing ambiguities and unnecessary delays to effectively accelerate the process for both the reviewer and applicant.

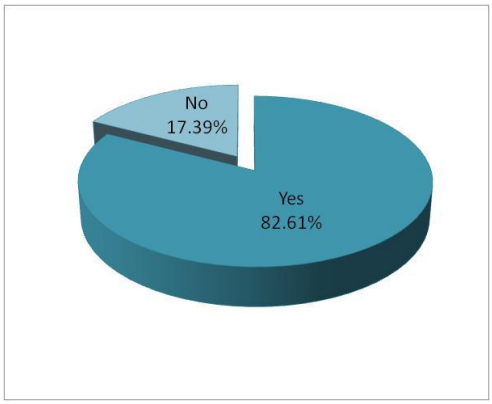

Figure 15: The quality of dossier increase as a result of Applicant-TPA-Regulator intercommunication

To assess correlations between the years experience and the answers on the importance (of each point when functioning via the TPA with the value 10 being imperative), the Spearman's rho test was used for this ordinal data (instead of the Kendall's tau test).

Table 6: Spearman's rho correlation between the years experience and the importance of the eight categories of Question 6

Correlations

			Experience	TPA audited annually	Applicant can appeal vs TPA decision	Rating the TPA anonymously	Transparency	NDA	Constant communication	No additional costs	MCC handling expedited reviews
Spearman's rho	Experience	Correlation Coefficient	1.000	.133	.063	.449*	.320	.168	-.029	.005	.234
		Sig. (2-tailed)		.545	.774	.032	.137	.444	.895	.981	.282
		N	23	23	23	23	23	23	23	23	23
	TPA audited annually	Correlation Coefficient	.133	1.000	.701**	.363	.756**	.335	-.043	.168	.367
		Sig. (2-tailed)	.545		.000	.088	.000	.118	.847	.444	.085
		N	23	23	23	23	23	23	23	23	23
	Applicant can appeal vs TPA decision	Correlation Coefficient	.063	.701**	1.000	.574**	.599**	.618**	.243	.559**	.505*
		Sig. (2-tailed)	.774	.000		.004	.003	.002	.265	.006	.014
		N	23	23	23	23	23	23	23	23	23
	Rating the TPA anonymously	Correlation Coefficient	.449*	.363	.574**	1.000	.441*	.633**	.410	.429*	.682**
		Sig. (2-tailed)	.032	.088	.004		.035	.001	.052	.041	.000
		N	23	23	23	23	23	23	23	23	23
	Transparency	Correlation Coefficient	.320	.756**	.599**	.441*	1.000	.386	.210	.314	.363
		Sig. (2-tailed)	.137	.000	.003	.035		.069	.336	.145	.089
		N	23	23	23	23	23	23	23	23	23
	NDA	Correlation Coefficient	.168	.335	.618**	.633**	.386	1.000	.546**	.606**	.718**
		Sig. (2-tailed)	.444	.118	.002	.001	.069		.007	.002	.000
		N	23	23	23	23	23	23	23	23	23
	Constant communication	Correlation Coefficient	-.029	-.043	.243	.410	.210	.546**	1.000	.430*	.409
		Sig. (2-tailed)	.895	.847	.265	.052	.336	.007		.040	.053
		N	23	23	23	23	23	23	23	23	23
	No additional costs	Correlation Coefficient	.005	.168	.559**	.429*	.314	.606**	.430*	1.000	.723**
		Sig. (2-tailed)	.981	.444	.006	.041	.145	.002	.040		.000
		N	23	23	23	23	23	23	23	23	23
	MCC handling expedited reviews	Correlation Coefficient	.234	.367	.505*	.682**	.363	.718**	.409	.723**	1.000
		Sig. (2-tailed)	.282	.085	.014	.000	.089	.000	.053	.000	
		N	23	23	23	23	23	23	23	23	23

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

It is apparent from Table 6 that there is no significant correlation, with p (Sig.) >0.05, between the years experience and the importance of the eight categories. The small sample size (n=23) also influences the validity of the results.

To explore the dependent variable of the hypothesis, namely optimal review times for MAs, the participants were given an open question in the survey to state what they consider an optimal and fair review time would be for assessors to review new chemical entities (NCEs) and generic product applications. From the descriptive analysis (Table 7) it was seen that the participants' (n=19) opinion varied significantly.

Table 7: Descriptive Statistics table for the minimum and maximum time considered favourable and fair for NCE and generic MAs

Descriptive Statistics

	N	Minimum	Maximum	Mean	Deviation
NCE_Min	19	3.00	62.00	20.2105	14.54716
NCE_Max	19	3.00	62.00	21.6316	15.75934
Gen_Min	19	1	36	11.68	8.718
Gen_Max	19	1	36	12.00	9.062
Valid N (listwise)	18				

By making use of Frequency tables (Appendix 8) it was found that NCEs' desired review times are 12 – 24 months, and generic applications 12 months. On the histograms of these Frequency tables it is noticeable that the respondents have a more definite opinion of the required time of generic reviews with the histogram's normal distribution (Figure 14), than for NCEs which has a positively skewed distribution (Figure 13). The rationale behind this finding may be due to the fact that 70% of the current backlog is for generic applications allowing participants to have a better opinion considering the required review time. It may also show that applicants accept that NCEs have new hurdles specific to the product that may take longer or have varied review timeframes for the reviewers to confirm that the product approves of quality, safety and efficacy.

The outlier observed in the results may be due to the participant's misinterpretation of the question as the answer submitted was in accordance with the current time lines.

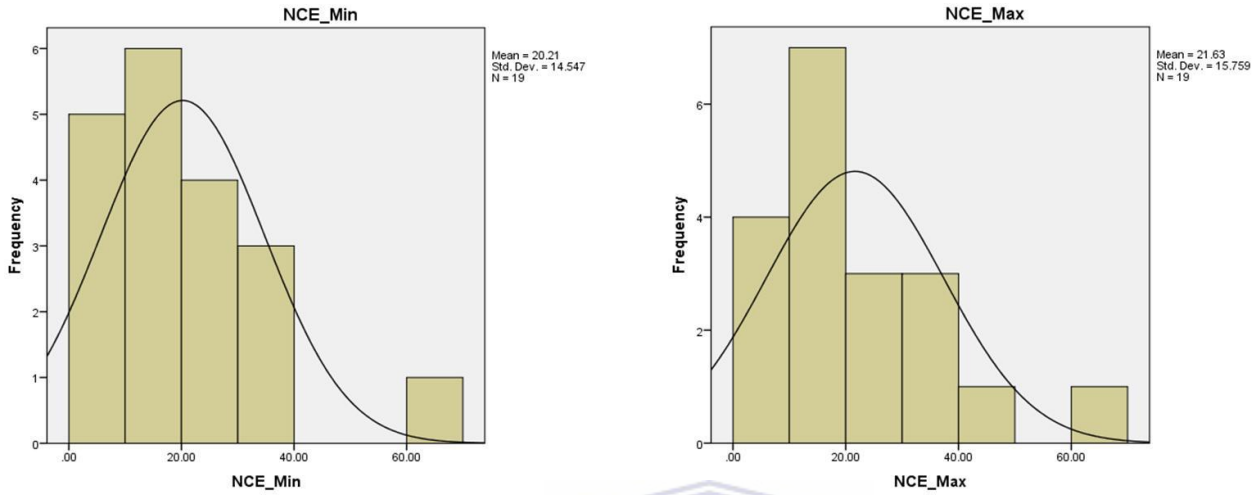

Figure 16: NCE minimum and maximum review time from Frequency tables showing a positively skewed distribution

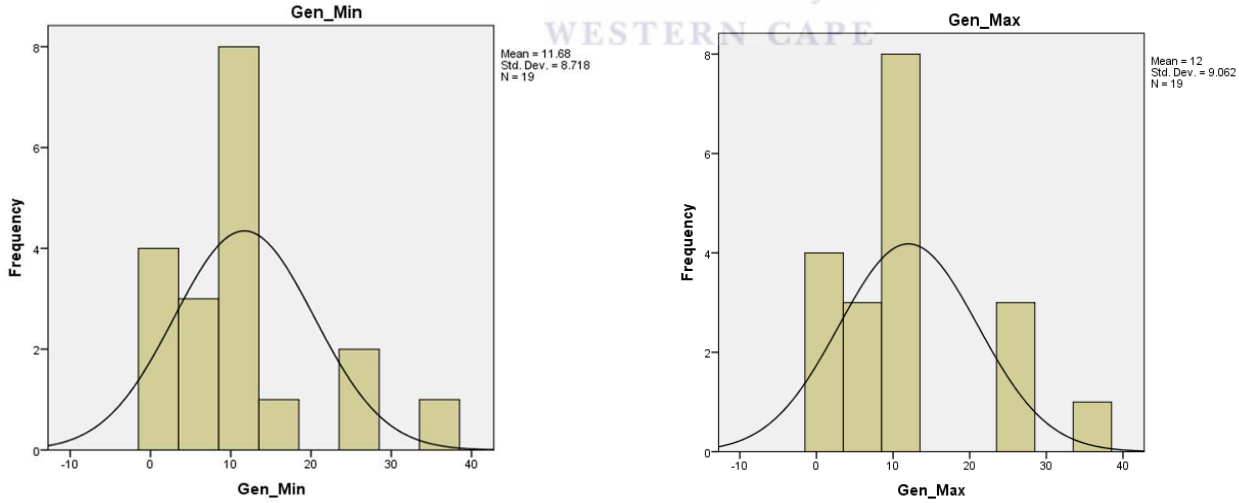

Figure 17: Generic application review time from Frequency tables showing a normal distribution

To assess the participant's years experience as a variable on the outcome of the expected time-frames, nonparametric correlations, crosstabs, Chi-Square tests and Symmetric measures (Phi and Cramer's V) were

used (Appendix 9). Participants were grouped into ≤5 years and >5 years experience in the Regulatory field. All results showed that p>0.05, which means that there was no correlation between the desired review time for NCEs and generic applications when compared with the respondent's years experience. This was also observed in the Spearman's rho Correlation Coefficient, used to indicate the practical significance of the relationship or effect sizes: The correlation coefficient of years experience compared with the desired review time (minimum and maximum) for NCEs and generic product applications were -0.154, -0.180, and -0.103, demonstrating that a small and no practical significant relationship exists between the variables having a Correlation Coefficient value below 0.1.

With the focus on the hypothesis, participants were asked if, in their opinion, by reducing the MRA's burden in terms of performing full dossier reviews, the concept of TPA's taking over the review process, will reduce the review time of applications from the date of submission to market approval. 88.5% (n=23) of the total participants (n=26) answered this question (Figure 18), of which all (100%) stated that the review time will decrease.

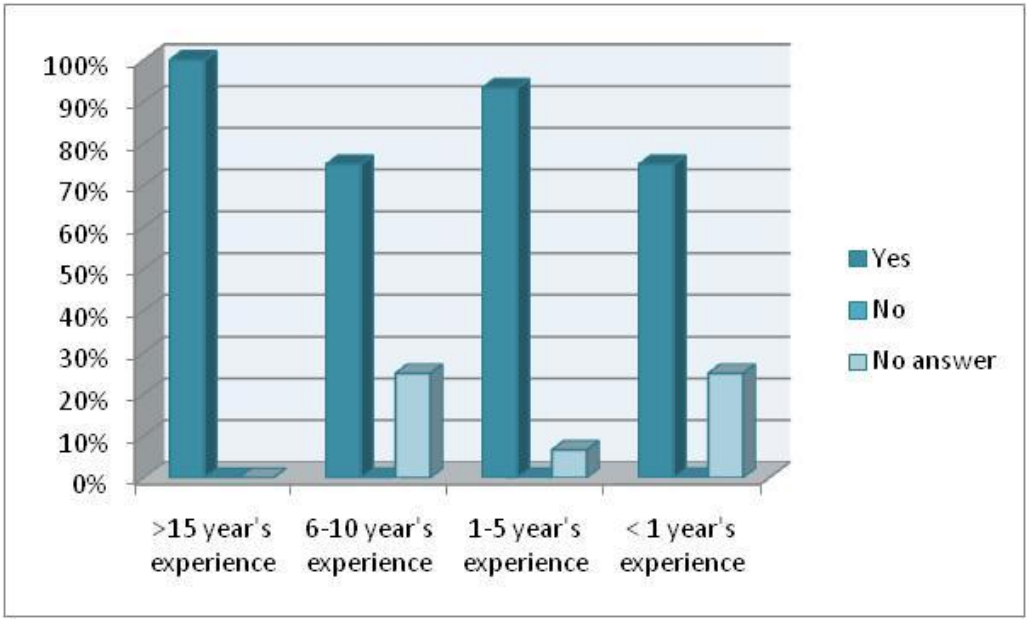

Figure 18: TPA reducing the review time of MA's according to respondents (n=26)

The respondents' feedback demonstrated that applicants were in favour of the TPA concept with 75% of the sample (n=12) being positive on the concept's viability (Figure 16), and 82.6% of the sample (n=23) in favour of implementing a validated pilot project (Figure 17) of which 47.8% were confident that it can be fully implemented, assessing NCEs and generic dossiers for all categories as set out in the medicines and related substances act (Act 101 of 1965), where 34.8% supported a phased implementation, considering that the body consists of skilled and licensed members with a clear understanding of MRA's aims and requirements for MAs.

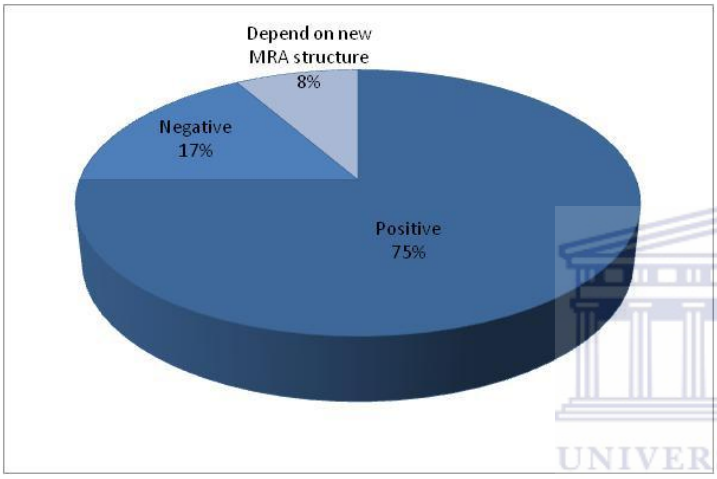

Figure 19: The consideration of the viability of the TPA

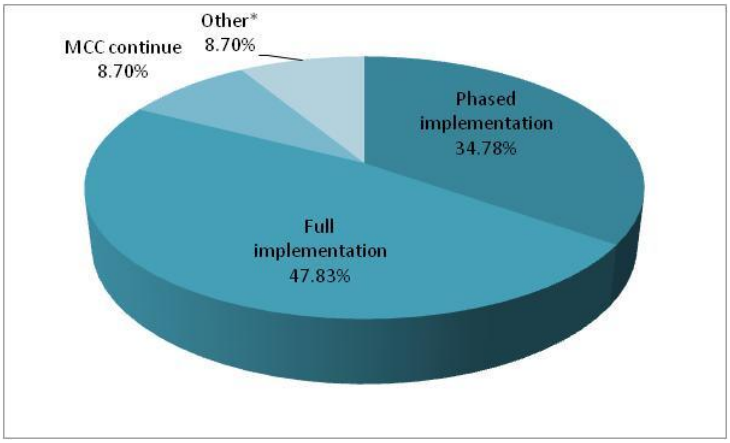

Figure 20: TPA pilot project implementation to be full or phased approach, or have the MCC continue

4.3 Triangulation

The following variables were evaluated by means of theoretical and methodological triangulation:

Time

The results on investigating review times (the hypothesis' dependant variable) were consistent across the three mixed-method analysis sections, with 86% of the investigated international health bodies and 75% of PPPs presented the benefit of reducing time spent, being coherent with the questionnaire feedback where 100% of the respondents affirmed that the TPA concept will reduce the review time for MAs.

The optimal review time established from the questionnaire (which demonstrated that no practical significant relationship exists between the years experience and the optimal expected time, $p>0.05$) were 21 months (638 days) for NCEs and 12 months (365 days) for generic applications (Figure 16 and 17). When this was compared with the international health bodies, those with the disadvantage of an increased time were still within the desired optimal time of the respondents: GDUFA 10 months (304 days) and WHO PQP 4.3 months (131 days) for generics. WHO PQP for NCEs were however outside this timeframe with 31.6 months (961 days). Those bodies with the benefit of reduced review times were well within the expected time-frames.

From the results it was also evident that having pre-established timelines ensured realistic expectations, which are beneficial for the applicant, assessor and regulatory body monitoring the assessors.

Skilled resources

The benefit of reduced review times were not limited to an accelerated process for the specified product-review groups, but enabled more resources to be available within the NMRA to provide its critical functions. NBs, GDUFA and WHO PQP were established for the purpose of increasing capacity in terms of regulatory human

resources. The advantages in terms of increased resources and capacity for the international health bodies were applicable to 86% of those assessed. This benefit was consistent with PPPs' 67% increased resources.

Each of the third party's examined not only had criteria for designation, specified requirements and qualification standards, but the study also revealed that the partnership itself resulted in increased efficiency and performance, specialist-skill development, technological advance, innovation and continuous improvement, and superior outcomes, as well as satisfying regulatory requirements. The collaborative strengths from each department are the cornerstone of this evolving asset to public health. These factors together with PPPs benefit of added quality confirm that quality would not be compromised in the process of accelerated reviews.

Transparency

Transparency is fundamental in the regulatory sphere and a goal of the International Conference of Harmonisation. Transparency is part of BEMA's purposes and one of three main aims of GDUFA, improving MRA communication and feedback to accelerate access to medicines. Reasons for the current backlog from respondents included ambiguous regulatory feedback and guidelines. In the ranking of TPA-operational qualities that would be imperative (with 10 being the maximum value), transparency had a mean of 8.83 and the second lowest standard deviation in the range with 2.289, showing that respondents concurrently and highly value transparency. Although a benefit in both the international health bodies and PPPs, findings of transparency were inconsistent in terms of importance, revealing applicability to only 14% and 17% consecutively.

Constant communication and bias

Transparency raised the question if constant communication between the applicant, TPA and MRA would provide a solution, but the concern was that it may lead to bias. 82.6% of the respondents stated that the quality of the submissions will improve as a result of increased intercommunication, showing that a need exists for unambiguous and more frequent communication from the regulators and assessors. Article 58 has pre-

submission EMA meetings where applicants can obtain advice on procedures, legal and regulatory matters, to ensure MA conformance and to interact with assessors. With the highest standard deviation (3.5) in the feedback regarding the rating of constant communication, an inconsistency were revealed in the findings, and illustrated that there is an awareness of a fine line between increased communication and it affecting assessor judgement.

Phased approach

Respondents' feedback on the implementation of a TPA showed that 47.8% were in favour of its full implementation, and 34.7% for a phased implementation. In the question where participants rated the importance of the MRA still being responsible for handling expedited reviews, it had a high mean in relation to the ranking scale (7.35), yet a mean lower than the average mean in this 8-point question, and the second highest standard deviation (2.964), showing inconsistency. When further triangulated with the international health bodies a trend is observed in support of a phased approach. WHO's PQP commenced with a focus on vaccines before expanding its scope to include medicines. BEMA underwent phases in the form of cycles – the first establishing the methodology for benchmarking, the second focusing on assessments and organisation, and the third to include all medicine agencies. NBs and APP are responsible for certain regulatory classes in the approval process, GDUFA focusing on generic product applications, and TA on generic products specific to PEPFAR. From the results in analysing the concerns and disadvantages, process gaps and short-term rigidities may exist with the implementation of the new initiative, supporting a phased approach.

Chapter 5: Conclusions and Recommendations

This research dissertation has given an account of and the reasons for the backlog and the protracted review times for MA assessments and approvals by the NMRA. It has explained the central importance of constructing a partnership between the regulator and industry to solve complex issues by the collaboration of each sector's specialists and resources, to be of benefit to the immediate population by increasing patient access.

The aim of the study was to establish the need and to formulate a framework around the use of a TPA; to examine the advantages and possible disadvantages of the TPA concept in its purpose to decrease the NMRA's burden and reduce the time between MA submission and approval, without compromising the quality of the assessment process.

It can be concluded from the study that there will be a reduction in the time spent if a TPA is introduced, accepting or proving the hypothesis. This was evident from the results during the evaluation of the international health models, PPPs and in the feedback from the participants. The optimal review times confirmed by the participants were within the international review timelines for the partnership-entities investigated, thereby illustrating realistic expectations, and showed that no significant variance exists between the participant's years experience and the optimal anticipated timeframes. The study suggests that pre-established review timelines and benchmarking are required to ensure realistic expectations for all concerned during the review process, to provide a tool for measuring outcomes and to identify gaps and areas of improvement to overcome unnecessary delays.

The study has shown that a PPP makes skilled resources available to reduce the time spent on a project, e.g. dossier review, and further enables an increased capacity within the NMRA to perform its critical functions. The TPA-concept was designed to reinforce that the final decision on MA approvals or rejections lies with the NMRA, while ensuring that ownership and accountability is maintained on both sides of the partnership. This was also a

benefit observed for both the existing international health bodies assessed and the PPPs. The qualitative arm of the study also found that the benefits are not restricted to better timelines and an increased capacity, but that efficiency, performance, skills, innovation, and superior outcomes increased as a result of a PPP.

While this study revealed inconsistent findings when transparency, constant communication and bias were triangulated, it did substantiate that a need exists from the regulatory industry's perspective for increased communication from the regulator, and that the quality of the submissions will increase as a result of transparency in requirements.

Although an inconsistency in survey findings on the subject of a phased or full approach were observed for the implementation of the TPA, the qualitative arm of the study proved that challenges in the implementation phase can be addressed and overcome using a phased approach.

The results from this research revealed that an improved strategy is needed and supports the concept of a TPA. The most important limitation to the study lies in the fact that theoretical problem solving was used and TPA remains a concept, which was evaluated in the light of similar concepts in existence such as international health bodies e.g. NBs, APPs etc. and PPPs. This form of extrapolation may proof to be inaccurate when applied in an actual setting. Validation of the concept is therefore needed to assess its practicality and gaps that may exist in the concept. This study was designed to introduce the concept of a TPA and investigate its effect on the MA review time, but further studies could assess the true cost implications and sustainability, the strategy and process that would be required to enable an effective implementation, TPA-staff criteria for designation and qualification standards, the contractual agreements that would be essential in this agreement, together with the stipulation of the benefit-risk responsibility. As seen in this research, and an implication, is that a PPP needs to be incorporated into legislation, which will mean possible amendments to acts, regulations and guidelines. It is worthy of noting that this is not impracticable or unattainable as it has been effectively implemented in other countries as proved in this research. Participants of this study also considered TPA as a viable option.

Another limitation of the study was that the number of survey participants was very small and made use of convenience sampling. This allowed the possibility of inaccurate assumptions and sampling errors as the participants may not necessarily be a true representation of the study population; in this research the target population was regulatory professionals from both industry and the NMRA. The sample was more representative of the industry's regulatory professionals, but no NMRA responses were received, which may increase biased survey conclusions. The findings, analysis and discussion chapter did take this limitation into consideration and discussed the findings accordingly.

Finally, a limitation when performing qualitative research is that primary data sources are not always readily or freely available. The process of coding involves that categories are saturated after data collection and constant comparison were applied until the hypothesis can be tested. This suggests that the accessibility to more or different primary sources may produce variations in findings.

These study results and information can be used to develop targeted interventions aimed at providing lasting relief to the current review backlog, reducing the review time for MAs, while fulfilling its purpose of ensuring that medicine and medicinal products that approves of quality, safety and efficacy are available to patients and consumers.

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Appendices

Appendix 1
Research Proposal

Research Proposal: The Impact Accredited Third Party Assessors will have on the Regulator's Response Time

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MRESC007

Research Proposal submitted in partial fulfillment of the award of M.Sc. in Pharmacy Administration and Pharmacy Policy Specialising in Regulatory Sciences
Hibernia College
2014

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The Impact An Accredited Third Party Assessor will have on the Regulator's Response Time

1. Introduction

Globally Medicine Regulatory Authorities (MRAs) have been under scrutiny for delayed Market Approvals, and have implemented different approaches to reduce consequential stakeholder tensions. In South Africa MRA strategies have been beneficial in reducing the backlog, but a proactive approach is still needed to ensure sustainability, especially with rapid pharmaceutical and biopharmaceutical advances, and the newly released CAMS regulations.

1.1 The Regulator's Function

The function of MRAs is to ensure the quality, safety and efficacy of medicine and medical devices, and promote health through "scientific excellence in the evaluation and supervision of medicines" (EMA, 2011: 30) by establishing a positive benefit-risk ratio. This involves various elements as set out in Figure 1. Regulators also have the responsibility of ensuring that medicines are made available to patients in a timely manner (Redmond, 2004).

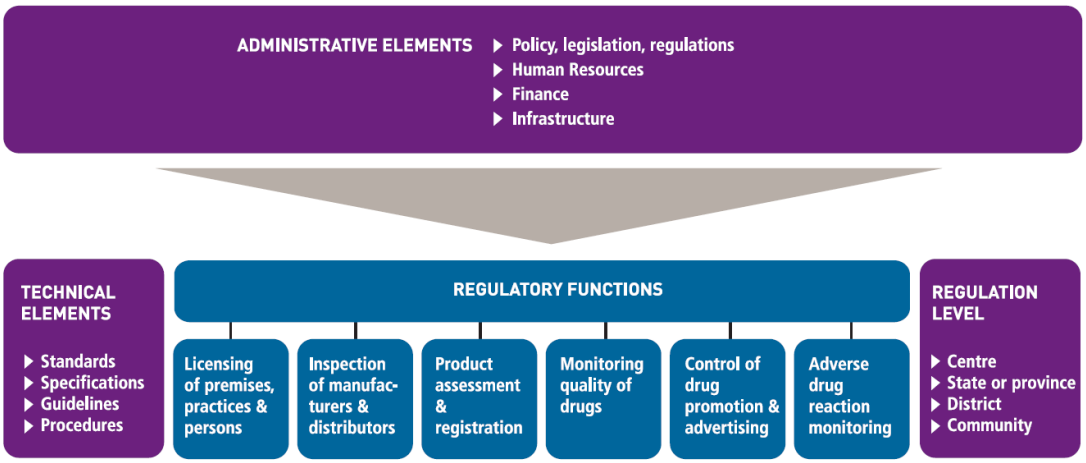


Figure 21: MRA Functions (Moran, 2010)

Challenges in successfully fulfilling these functions and responsibilities exist such as limited human resources (and a high key-staff turnover); the need for public and financial support (especially for governmentally financed MRAs); more complex medicine and scientific advances; and often the quality of Market Applications (or dossiers) submitted that is sub-standard. Stakeholder tensions increase as the review-times increase causing a delay in patient access (especially in illnesses where novel treatment is necessary, such as cancer and HIV/AIDS) and slowing pharmaceutical companies' revenues. A proactive approach, with a transparent methodology and tools that remain current, is required to regulate effectively (Lumpkin, 2012).

1.2 Timelines and Backlogs experienced

An international comparison on review-times showed that Switzerland's IKS is one of the most efficient agencies (Vozeh, 1999), while the FDA and EMA are often under scrutiny for approval times (Roberts, 2011).

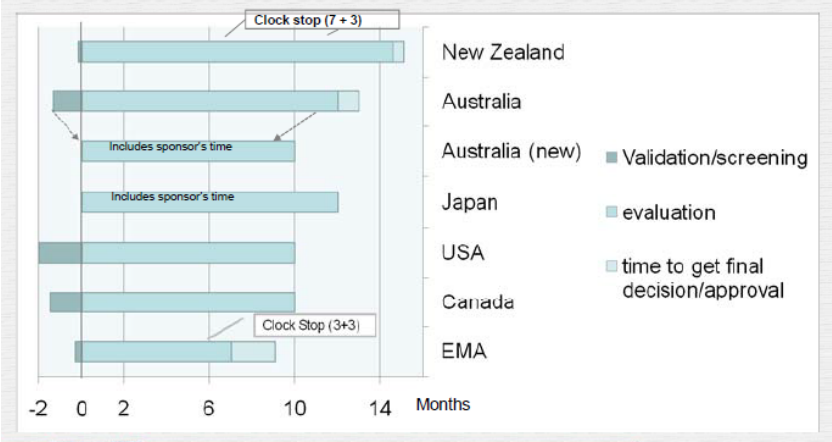


Figure 2: An overview of NCE review timelines for different MRAs (Melchior, 2011)

Severe delays were however caused by the MCC, which had sub-optimal registration timelines: In 2008 the 'Backlog Project' reduced the 4500 application-backlog (with submissions from 2001) to 1500 (by June 2010) by the Department for International Development's (DFID) support (SARRAH, 2010). In 2013, 26 evaluators were contracted to accelerate generic registration during the first quarter (SARRAH, 2013). The backlog however is not cleared and an average of 48-52 month waiting period from first submission to registration still exists.

1.3 Steps taken and Problem statement

Some of the benefits of harmonization and the global use of CTD and eCTD are the increased transparency and reduced time in the review and approval process (Molzon, 2010). In SA the pilot project for eCTD is in the final stages, but teething problems are experienced and more applicant training is needed. The new regulatory body, SAHPRA, will have 400 instead of 150 members (Reuters, 2012), and the submission costs will increase, but the newly published CAMS guidelines (requiring a similar process as medicine approval) (MCC, 2013), and its local industry worth R2.5 billion (HPA, 2013) will necessitate increased and competent assessors.

This leads to the problem of using a reactive approach by involving external reviewers, increasing funds needed, causing inconsistent reviews and uncertain review timeframes, which is not a sustainable long-term solution – a proactive approach is required.

1.3.1 Research Question

Will the MRA's review time for Market Applications decrease if permanently appointed, competent Third Party Assessor are used, who are trained by an MCC/SAHPRA accredited trainer and program?

1.3.2 Hypothesis

If MRAs make use of skilled Third Party Assessor, optimal review times for Market Applications will exist.

2. Aim

The aim of this study is to:

- Formulate a framework around the use of Third Party Assessor;

- Examine the benefits and possible drawbacks the concept of using accredited and competent Third Party Assessor will have on providing relief to the backlog currently experienced by SA's MRA (MCC/SAHPRA), reduce the time between submission and approval, increase the quality of applications to the MCC and be of benefit to all associated stakeholders.

- Establish a foundation for my anticipated doctorate in this subject, where the concept can be further explored and validated.

3. Limitations

The limitation to the study lies in the fact that it remains a concept based on a combination of evaluations from similar global model-types (e.g. Notified Bodies – see section 4.4), extrapolating it to medicine and SA's regulation; performing theoretical problem-solving. Validation processes will be needed to assess the practicality and gaps of this initiative of introducing Third Party Assessor.

4. Methodology

4.1 Research design

This dissertation will be a qualitative study exploring the variable's significant facets such as scope of practice, bias, qualifications, processes, performance, etc. to structure this framework within the existing regulatory framework. A concise quantitative survey will evaluate the industry's receptiveness to the concept, producing a mixed method research approach. Although this will not increase validation or generalization to the study, it will add richness to the data, testing the hypothesis (facilitation).

4.2 Research subjects or participants

As this is primarily a qualitative study, research subjects will not be involved. The research will however have a small quantitative arm by using a short questionnaire. This will be distributed to pharmacists in January 2014 to evaluate the susceptibility of the concept. The questionnaire, not exceeding 10 questions, will contain a combination of closed and open-ended questions and will be designed in such a way that it will be submitted anonymously. The option of providing an email address will be presented, for the purpose of dissemination - should the participant wish to be informed of the questionnaire outcome.

Inclusion criteria:

1. Pharmacists directly affected by registrations (Regulatory Affairs Pharmacists, Consultants, Quality Assurance Pharmacists, Regulators and Inspectors);
2. Non-pharmacists involved in the registration process.

Exclusion criteria:

1. Retail pharmacists;
2. Other individuals not directly involved in the medicine registration process.

4.3 Sample size

For the quantitative survey, the sample size will depend on the amount of individuals willing to complete and submit the questionnaire. It will therefore be a nonprobability sample, making use of convenience - and snowball samples. This will limit the results in terms of generalization as it may not be a true representation of the specific population, but will give valuable feedback from pharmacists currently challenged with this problem in the industry.

4.4 Study instruments, collection of data and analysis

Qualitative data will be obtained from published literature (e.g. journals and regulations). Theoretical sampling (from grounded theory) has already commenced by collecting data generating the theory. This will further be used to collect more data, code and analyse the information during the process, leading towards the development and exploration of the theory. Different aspects in this theory will be categorised using coding (open, axial and selective coding). Using a conceptual analysis the relationship between equivalent international models will be assessed which include:

- Notified Bodies for medical devices (MHRA, 2013)

- Third party Programs for medical devices (FDA CDRH, 2001)

- Tentative approval (FDA, 2013)

- Prequalification Programme (WHO, 2011)

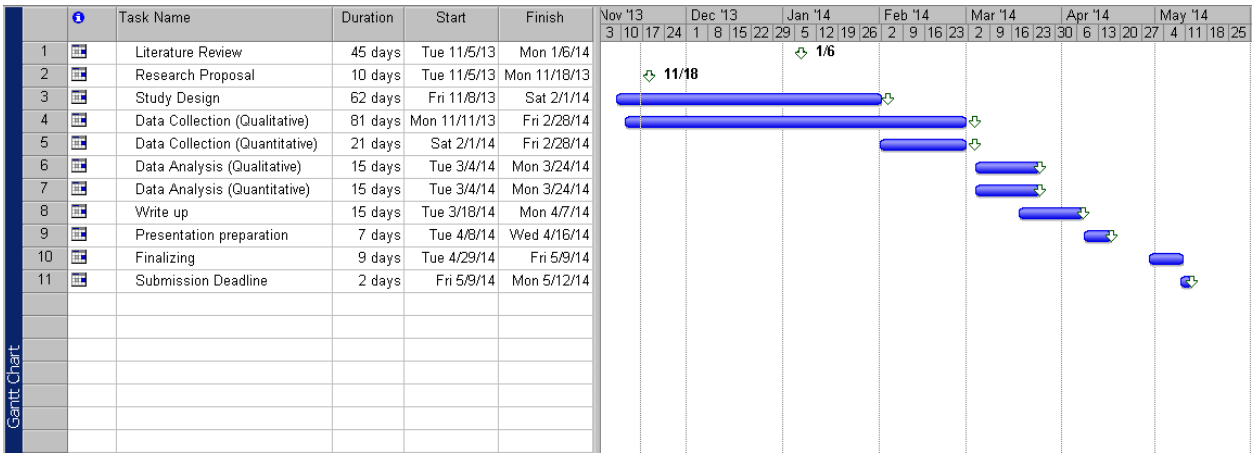
- ICH Global Cooperation Group (EMA, 2011)

- European, TGA and Asian Benchmark Agencies (e.g. BEMA) (HMA, 2012)

A quantitative survey (self-completion questionnaire) will be done via internet research methods using on-line tools such as SurveyMonkey™. The pharmaceutical sector in South Africa, excluding retail, is small and the majority of industry pharmacists belong to an association accessible via an email-database, making it a representative sample.

The objective of this meta-analysis will be to structure a strategy for using a Third Party Assessor, evaluating validity of arguments, performing a gap analysis and establishing general guidelines on how to introduce this concept into the existing regulatory framework.

4.5 Gantt chart



4.6 Budget

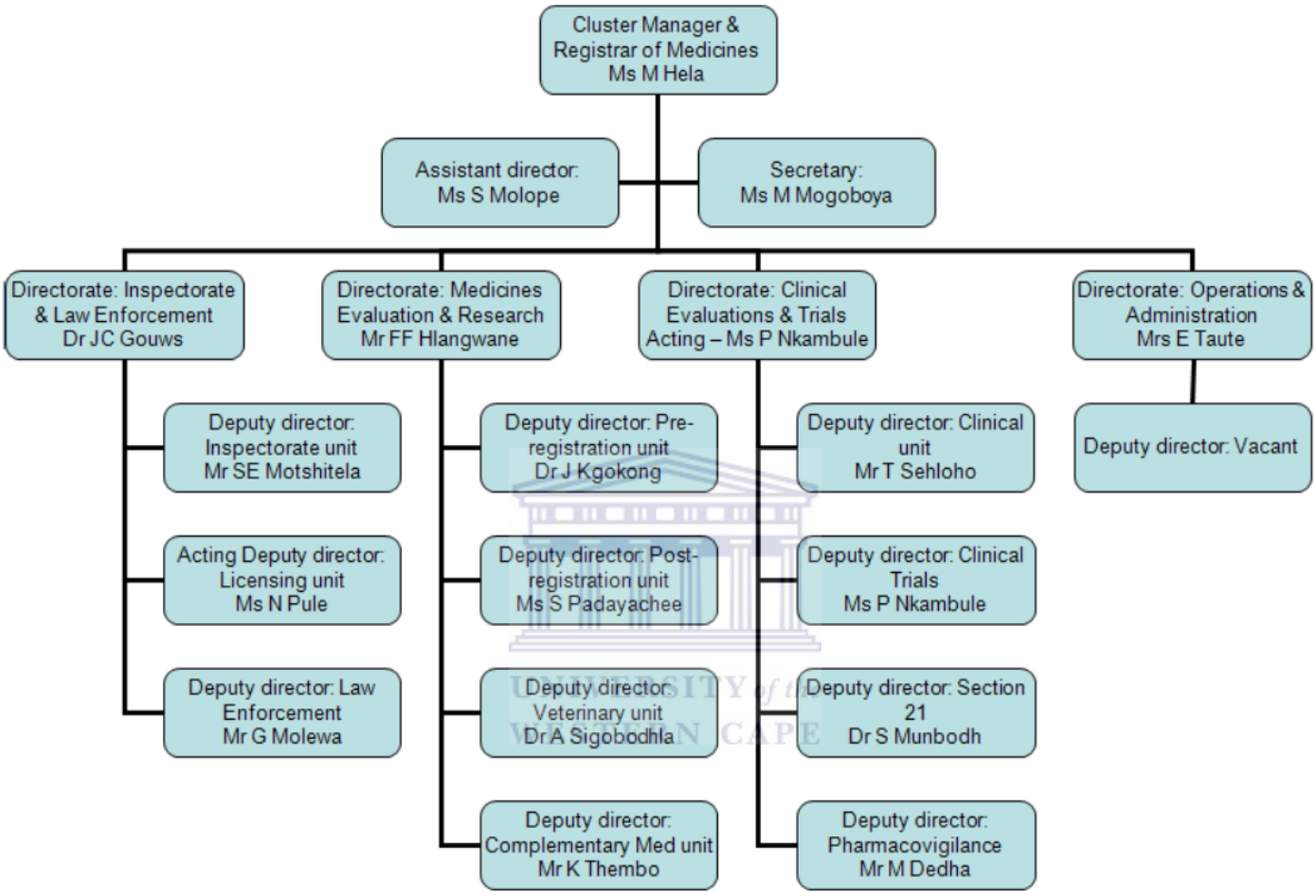
Financial resources for the qualitative study will not be required, as all data will be obtained from published literature. In the event where articles need to be purchased to obtain more in-depth data, this will be self-funded. The quantitative arm of the study will also be done by via internet research methods using tools such as SurveyMonkey™ with minimal costs associated, that will be self-funded.

5. Ethical Considerations

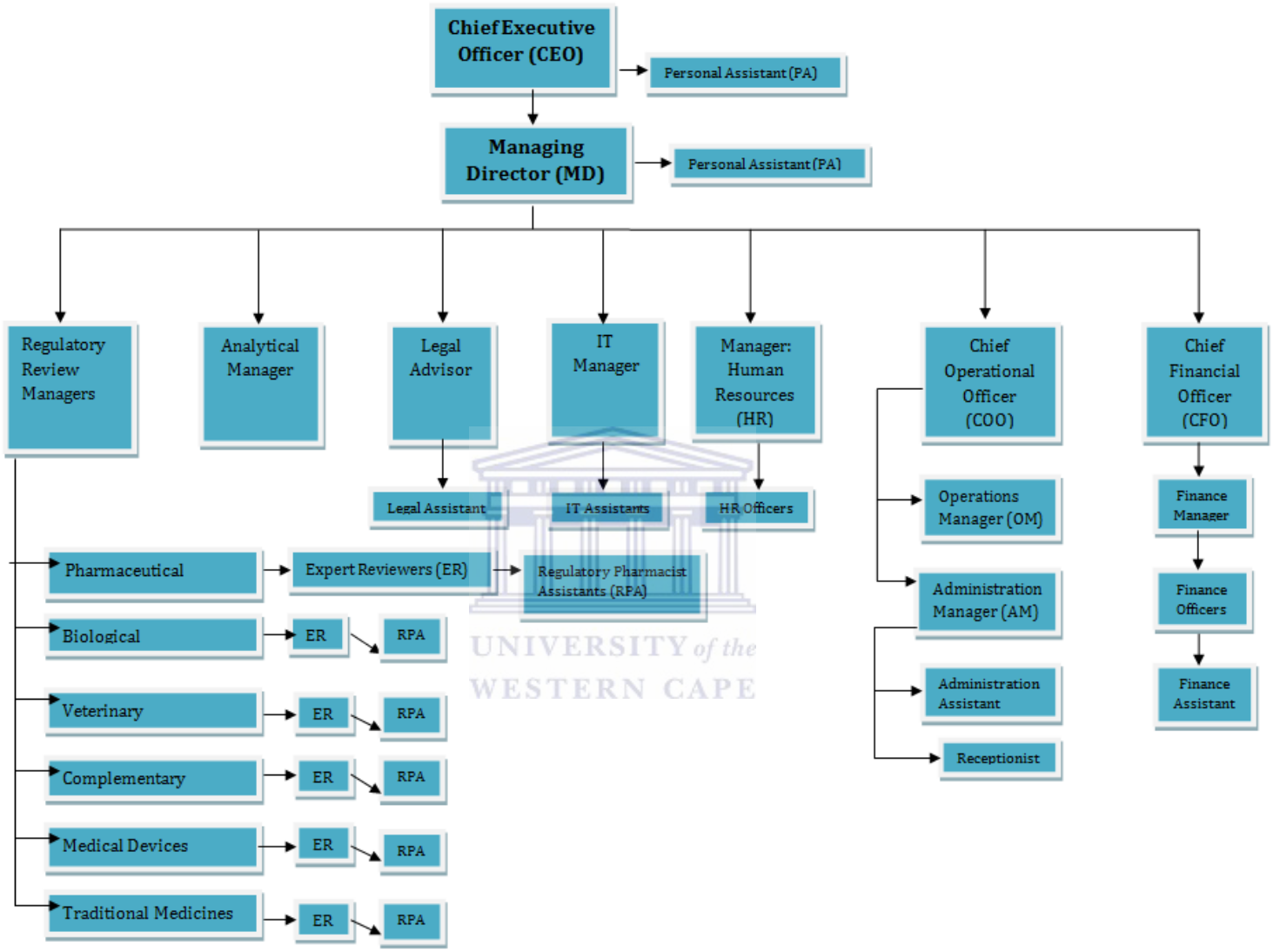
No research subjects will be used. A succinct questionnaire will be completed voluntarily and anonymously, meaning that confidentiality and welfare will be respected. See attached for the Ethics Forms.

Appendix 2
MCC Structure

MCC Structure: Pharmaceutical & Related Product Regulation & Management (MCC, 2003-2013)



Appendix 3
TPA Organogram



Appendix 4
TPA SOP for the procedure from dossier submission to final applicant communication

Third Party Assessor – Standard Operating Procedure

SOP title:	The Operational Procedure from Dossier submission to Final communication to the Applicant		
SOP number:	01	**Effective date:**	01.02.2015
Version number:	V01	**Review date:**	01.02.2017

1. Purpose

The purpose of this procedure is to ensure that each Applicant dossier submission is handled with urgency, managed within the allowed time-frames by each relevant department within the Third Party Assessor (TPA), following the procedure as outlined herein.

2. Procedure

2.1 The Applicant submits the Market Application (MA)/dossier (and a copy) with the proof of payment to the Administration Assistant.

2.2 The Administration Assistant logs the dossier receipt and provides a log number per application to the Applicant.

2.3 The dossier is then allocated to the relevant Regulatory Review Manager's department where an Expert Reviewer is assigned with the dossier for the first phase namely screening.

2.4 If the dossier complies the next phases of evaluation and review can proceed. The Expert Reviewer must inform the Administration Manager (AM) that the dossier passed the screening phase. The AM will in turn inform the Applicant that the dossier is successfully progressing to the next review phase.

2.5 If the dossier does not comply during the screening process, the AM informs the Applicant. When the corrected dossier is resubmitted, the dossier would not fall at the back of the line, but will be handed to the same Expert Reviewer. A chargeable penalty fee would exist to the non-compliant Applicant.

2.6 After the Expert Reviewer evaluated and reviewed the dossier according to the latest regulations and guidelines, a report is constructed in favor of or against preliminary approval.

2.7 The Expert Reviewer meets with the Regulatory Review Manager to discuss findings and the report, after which a decision is taken in favor of or against preliminary approval based on Quality, Safety and Efficacy.

2.8 The final report which contains the following is submitted to the Medicines Control Council (MCC) and its committees for final approval:

2.8.1 The preliminary approval report signed by the Regulatory Review Manager and the Expert Reviewer;

2.8.2 A copy of the dossier;

2.8.3 Proof of payment to the MCC;

2.8.4 Any other relevant information that the Third Party Assessor may deem important.

2.9 The applicant is then informed via the AM that the preliminary approval report is submitted to the MCC.

	Prepared by:	Checked by:	Authorised by:
Signature:			
Date:			

2.10 The MCC and its committee members review the report and meet as per schedule to discuss if the product can be accepted or rejected.

2.11 It is the TPA Regulatory Pharmacist Assistant's responsibility to do follow-ups with the MCC to establish the progress and status of the application.

2.12 If accepted, the product receives a registration number.

2.13 The letter of acceptance with the registration number is sent to the Third Party Assessor.

2.14 The Third Party Assessor then informs the Applicant of the outcome and supply the letter of approval.

3. Responsibility

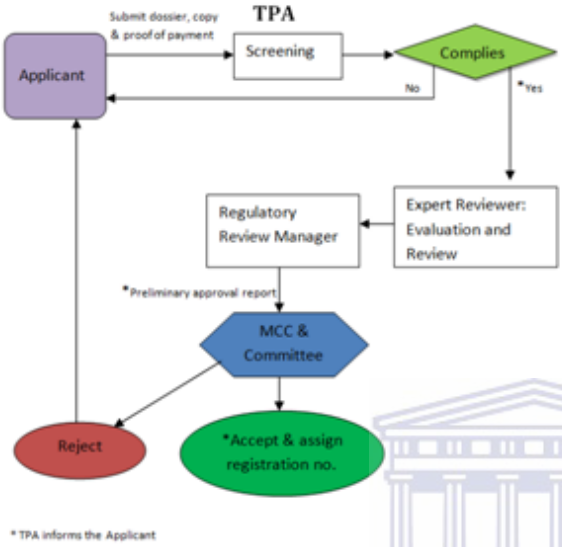
- Administration Assistant
- Administration Manager
- Regulatory Review Manager
- Expert Reviewer
- Regulatory Pharmacist Assistant
- MCC and its Committees

4. History of updates

Reason for revision	Name & Signature	Date
N/A		

5. Attachments

Attachment 1: Flow-chart



6. Record of employees trained on SOP

Trainer: Name	Trainee: Name	Job Title	Signature	Date of training

Appendix 5
Email to industry

Dear Regulatory Colleague,

In an effort to look at ways to provide relief to the backlog experienced for review or approvals of Market Applications, a survey is conducted to test the susceptibility of the concept of a Third Party Assessor who will perform pre-approvals for the MCC (or for SAHPRA that will be introduced and replace the MCC in the coming year(s)), to effectively supply a support function to the MCC/SAHPRA and reduce the dossier review time.

We would like you to be part of the survey, for us to obtain and construct an objective opinion in this regard from South Africa's Regulatory Industry.

Here is the link: https://www.surveymonkey.com/s/5KB69SZ , which consists of 10 questions and will take about 5 minutes to complete.

Any questions or comments can be directed to reviewtimesurvey@gmail.com .

Feel free to forward this email to any colleague in the Regulatory industry.

Disclaimer:

This is an anonymous survey, meaning you will not have to disclose your identity. By completing the survey you agree that you understand that you consent to participate voluntarily, and that you may withdraw at any time, without supplying any reason. The information collected from this study is kept anonymous and safe for reproduction in publications or reports. If you would like to receive feedback on the survey outcome you will have to supply an email address to reviewtimesurvey@gmail.com, which will remain confidential.

Appendix 6
Survey/Questionnaire

1. Your job title

- [ ] Regulatory Pharmacist
- [ ] Consultant
- [ ] Regulator
- [ ] Quality Assurance Pharmacist
- [ ] Inspector / Auditor
- [ ] Regulatory Pharmacist Assistant
- [ ] CEO / Director
- [ ] Lecturer
- [ ] Legal Advisor

Other (please specify)

***2. Years experience in the Regulatory field**

- ( ) < 1 year
- ( ) 1 - 5 years
- ( ) 6 - 10 years
- ( ) 10 - 15 years
- ( ) >15 years

3. The main reason (from your perspective) for the current backlog experienced for Market Application Approvals (or feedback) in South Africa

- [ ] Sub-standard quality dossiers submitted
- [ ] Insufficient dossier data to proof quality, safety & efficacy
- [ ] Not enough MCC reviewers
- [ ] Temporary MCC staff members
- [ ] Ambiguous regulator feedback
- [ ] Ambiguous regulations/guidelines
- [ ] Different MCC members handling dossiers every time
- [ ] Over-regulation
- [ ] Other (please specify)

4. Considering the current backlog, the implementation of the new CAMS guidelines and soon-to-be-released guidelines on Medical Devices - In your opinion, will the backlog be permanently eliminated by using SAHPRA (the National Regulatory body that will be replacing the MCC) with a CEO and 600 full-time employees, instead of MCC's current 150 members and temporary staff?

- ○ No
- ○ Yes
- ○ There might be some relief, but an improved strategy will be needed to diminish the backlog, have optimal review time-frames and comply with these set time-frames
- ○ Unsure as there are little information about the structure and strategy of SAHPRA available at this stage
- ○ Other (please specify)

5. Questions 5 - 9 will be based on this concept:
To assist the MCC/SAHPRA in reducing the review time of Market Applications while ensuring quality, safety & efficacy; a Third Party Assessor performs Market Application Assessments, granting pre-approvals in the form of a report to the MCC/SAHPRA per product within a set time-frame. This Third Party Assessor, who acts as an extension of the MCC/SAHPRA in terms of responsibility, will be a company led by a CEO, with full-time employees driven by performance appraisals. The Third Party Assessor will be independent from the industry, and therefore unbiased. It will be a competent body trained by the MCC/SAHPRA to effectively perform its functions. The final decision will be made by the MCC/SAHPRA based on the report.

In your opinion, if the concept is validated by a pilot project, legislation is adjusted to incorporate the Third Party Assessor and this body consists of skilled and licenced members, with years of regulatory experience and a clear understanding of the MCC/SAHPRA's aim and requirements for Market Applications, will you as an applicant:

- ○ Want the Third Party Assessor to be implemented through phases, where the first phase is only assessing and pre-approving applications for generic products, before progressing through the phases to New Chemical Entities
- ○ Be content with the Third Party Assessor assessing all applications (Category A to D) as they will be specialists in the field, and the final approval will ultimately remain with the MCC/SAHPRA
- ○ Would you prefer the MCC continue full evaluation and not allow third party assessment
- ○ Other (please specify)

6. Rank the importance of each point when functioning via/using the Third Party Assessor (with 1 being the least important and 10 being imperative)

	1	2	3	4	5	6	7	8	9	10	N/A
The Third Party Assessor is audited annually by the MCC/SAHPRA	○	○	○	○	○	○	○	○	○	○	○
You as the applicant can appeal to a decision made by the Third Party Assessor and/or the MCC/SAHPRA	○	○	○	○	○	○	○	○	○	○	○
You as the applicant can anonymously rate the Third Party Assessor based on the quality service received	○	○	○	○	○	○	○	○	○	○	○
Transparency in decisions	○	○	○	○	○	○	○	○	○	○	○
Intellectual property protection (Third Party Assessor to sign Non-Disclosure Agreement)	○	○	○	○	○	○	○	○	○	○	○
Constant communication between you (the applicant) and the Third Party Assessor	○	○	○	○	○	○	○	○	○	○	○
No substantial additional application costs	○	○	○	○	○	○	○	○	○	○	○
Expedited reviews must still be reviewed by the MCC/SAHPRA	○	○	○	○	○	○	○	○	○	○	○

Other (please specify)

7. In your opinion, do you envisage that the quality of dossier submitted will increase as a result of this intercommunication between applicant, Third Party Assessor and the MCC/SAHPRA?

- ○ Yes
- ○ No

Other (please specify)

***8. In your opinion, by reducing the MCC/SAHPRA's burden in terms of performing full dossier reviews, will this concept Reduce the review Time from date of dossier submission to market approval?**

9. Your comments or thoughts on the viability of the Third Party Assessor (voluntary)

10. What would you consider to be an optimal and fair Market Application review time for:

New Chemical Entity:	
Generic Application:	

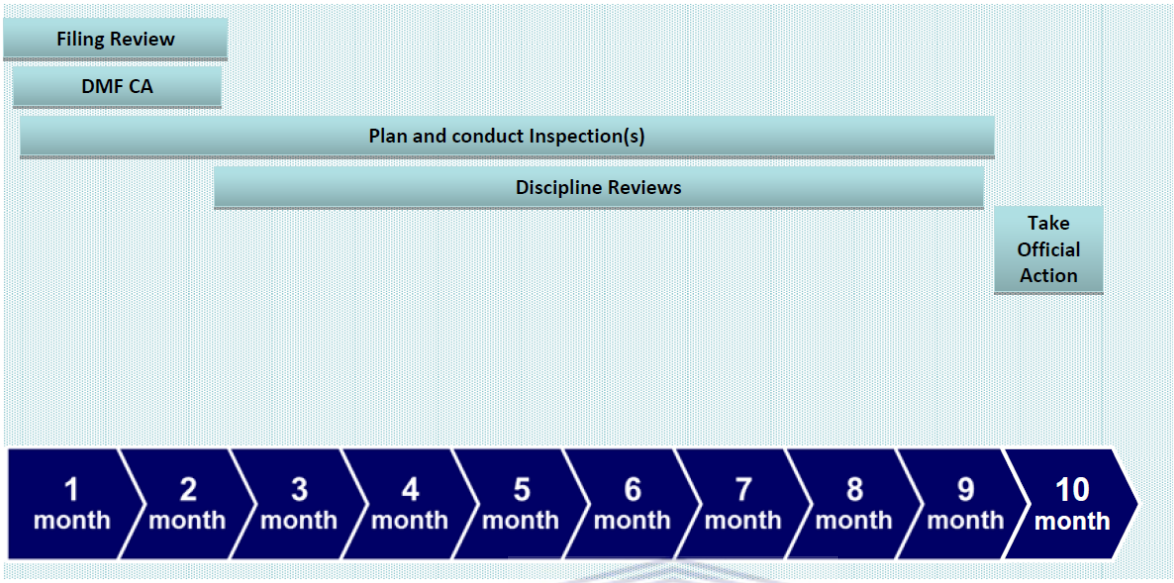
Appendix 7
Global MD review timelines*

Medical device category	Europe	USA	Canada	Australia	Costa Rica	Taiwan	South Korea	Mexico	Russia	China	Brazil	Columbia	Singapore	Saudi-Arabia
Class I			2-4		2-4	4-5	1-2		14-15	11-12	5-10 / 18-36	1		
Class I Exempt						1								
Class I - Devices exempt from 510(k) process		1												
Class I - Non-sterile, non-measuring	1			1										
Class I - Sterile or measuring	3-5			2-3										
Class II			2		2-4	8-17	1-2			17-30	5-10 / 18-36			
Class IIa	1-3			2-3		12-17			14-15			1		
Class IIb	2-6			2-3					14-15			4-7		
Class II - or any device subject to 510(k)		3-6												
Class II - Safety effectiveness Review							10-15							
Class II or III - new/high risk						14-24								
Class II - PMA or Class II devices without a predicate		18-30												
Class III	7-9		4-5	7-14	2-8		7-9		14-15	17-36	18-36	4-7		
Class III - Safety effectiveness Review							10-16							
Class IV			6-8		2-10		7-9				18-36			
Class IV - Safety effectiveness Review							10-15							
Class A (sterile devices)													1-2	
Class B													1-4	
Class C													7-10	
Class D													10-13	
Low Risk								3-4						3-5
Medium Risk														3-5
High Risk														3-5

* This table is a summary of the data obtained from the reference resource library for medical device regulatory process charts and approval timelines (Emergo, 2014).

Appendix 8
FDA Accredited Persons Program review timelines (Hass, 2011)

Appendix 9
GDUFA generic drug (ANDA) approval process (Uhl, 2013)



Appendix 10
Article 58 review time-lines (EMEA, 2009)

Day	Action
1	Start of the procedure
80	Receipt of the assessment reports from the Rapporteur and Co-Rapporteur by CHMP members and the EMEA. The EMEA sends the assessment reports to the applicant, making it clear that they only set out the preliminary conclusions, that they are sent for information only and that they do not yet represent the position of the CHMP.
100	Receipt of comments on the assessment reports from CHMP members (including peer reviewers) by the Rapporteur, Co-Rapporteur, other CHMP members, WHO experts, as appropriate and the EMEA.
115	Receipt of draft list of questions (including the CHMP recommendation and scientific discussion) from the Rapporteur and Co-Rapporteur, as discussed with the peer reviewers, by CHMP members, WHO Experts as appropriate, and the EMEA.
120	Adoption of the list of questions, overall conclusions and review of the scientific data by the CHMP. The EMEA sends these to the applicants and WHO Experts, as appropriate. Deadline for adoption of a request for a good manufacturing practice (GMP) or good clinical practice (GCP) inspection by the CHMP, if necessary, and start of inspection procedure.

The 'clock' is stopped at day 120. By analogy to the evaluation of centralised marketing authorisation applications, the same rules apply with regards the time allowed for applicants to respond to the list of questions and list of outstanding issues (EMEA/75401/2006 Rev. 2).

At day 121, responses are submitted by the applicant, including a revised summary of product characteristics (SPC), labelling and Package Leaflet in English. The clock is then restarted.

After receipt of the responses, CHMP adopts a timetable for the evaluation of the responses. The standard timetable is as follows:

Day	Action
150	Receipt of joint response assessment report from the Rapporteur and Co-Rapporteur by CHMP members and the EMEA. The EMEA sends the joint assessment report to the applicant, WHO Experts, as appropriate, making it clear that it only sets out their preliminary conclusions, that it is sent for information only and that it does not yet represent the position of CHMP. Inspection is carried out, if applicable.
170	Deadline for comments on joint assessment report from CHMP members and WHO Experts as appropriate. Responses are sent to the Rapporteur and Co-Rapporteur, the EMEA and other CHMP members.
180	CHMP discussion and decision on whether the applicant will need to attend an oral explanation. If an oral explanation is needed, the clock is stopped to allow the applicant to prepare. Deadline for submission of the final inspection report to EMEA, Rapporteur and Co-Rapporteur by the inspections team, if applicable.
181	Clock is restarted. Oral explanation takes place (if needed).
By 210	Final draft of SPC, labelling and package leaflet in English sent by the applicant to the Rapporteur and Co-Rapporteur, the EMEA and other CHMP members and WHO Experts, as appropriate. Adoption of CHMP scientific opinion and assessment report.

After adoption of a CHMP scientific opinion, the annexes to the opinion and European public assessment report on a scientific opinion in co-operation with WHO (EPAR) are prepared according to the following timetable:

Day	Action
By 240	The EMEA forwards the CHMP scientific opinion and its annexes to the applicant, the WHO, EU Member States, Norway and Iceland.

By 300	Finalisation of the EPAR in consultation with the Rapporteur, Co-Rapporteur and CHMP, and with the applicant to discuss issues related to commercial confidentiality.

Appendix 11
Frequency tables to survey Question 6

Experience

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	3	13.0	13.0	13.0
	2	14	60.9	60.9	73.9
	3	3	13.0	13.0	87.0
	4	1	4.3	4.3	91.3
	5	2	8.7	8.7	100.0
	Total	23	100.0	100.0	

1: <1 year experience

2: 1-5 years experience

3: 6-10 years experience

4: 10-15 years experience

5: >15 years experience

TPA_audited_annually

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	4.3	4.3	4.3
	2	2	8.7	8.7	13.0
	5	1	4.3	4.3	17.4
	7	1	4.3	4.3	21.7
	8	4	17.4	17.4	39.1
	9	3	13.0	13.0	52.2
	10	11	47.8	47.8	100.0
	Total	23	100.0	100.0	

Applicant_can_appeal_vs_TPA_decision

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	3	2	8.7	8.7	8.7
	6	1	4.3	4.3	13.0
	8	4	17.4	17.4	30.4
	9	4	17.4	17.4	47.8
	10	12	52.2	52.2	100.0
	Total	23	100.0	100.0	

Rating_the_TPA_anonymously

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	2	1	4.3	4.3	4.3
	3	1	4.3	4.3	8.7
	4	1	4.3	4.3	13.0
	5	1	4.3	4.3	17.4
	6	2	8.7	8.7	26.1
	8	4	17.4	17.4	43.5
	9	1	4.3	4.3	47.8
	10	12	52.2	52.2	100.0
	Total	23	100.0	100.0	

Transparency

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	2	1	4.3	4.3	4.3
	3	1	4.3	4.3	8.7
	6	1	4.3	4.3	13.0
	7	1	4.3	4.3	17.4
	8	2	8.7	8.7	26.1
	9	1	4.3	4.3	30.4
	10	16	69.6	69.6	100.0
	Total	23	100.0	100.0	

NDA

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	4.3	4.3	4.3
	3	2	8.7	8.7	13.0
	7	1	4.3	4.3	17.4
	8	1	4.3	4.3	21.7
	10	18	78.3	78.3	100.0
	Total	23	100.0	100.0	

Constant_communication

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	3	13.0	13.0	13.0
	2	2	8.7	8.7	21.7
	6	1	4.3	4.3	26.1
	8	3	13.0	13.0	39.1
	9	2	8.7	8.7	47.8
	10	12	52.2	52.2	100.0
	Total	23	100.0	100.0	

No_additional_costs

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	4.3	4.3	4.3
	2	1	4.3	4.3	8.7
	3	1	4.3	4.3	13.0
	5	1	4.3	4.3	17.4
	6	1	4.3	4.3	21.7
	8	2	8.7	8.7	30.4
	9	3	13.0	13.0	43.5
	10	13	56.5	56.5	100.0
	Total	23	100.0	100.0	

MCC_handling_expedited_reviews

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	4.3	4.3	4.3
	2	2	8.7	8.7	13.0
	5	4	17.4	17.4	30.4
	6	2	8.7	8.7	39.1
	8	3	13.0	13.0	52.2
	9	2	8.7	8.7	60.9
	10	9	39.1	39.1	100.0
	Total	23	100.0	100.0	

Appendix 12
Frequency tables for survey Question 10:
Optimal and reasonable review times for NCEs and generic product market applications

NCE_Min

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	3.00	1	3.8	5.3	5.3
	6.00	3	11.5	15.8	21.1
	9.00	1	3.8	5.3	26.3
	12.00	3	11.5	15.8	42.1
	16.00	1	3.8	5.3	47.4
	18.00	2	7.7	10.5	57.9
	24.00	4	15.4	21.1	78.9
	36.00	3	11.5	15.8	94.7
	62.00	1	3.8	5.3	100.0
	Total	19	73.1	100.0	
Missing	System	7	26.9		
Total		26	100.0		

NCE_Max

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	3.00	1	3.8	5.3	5.3
	6.00	3	11.5	15.8	21.1
	12.00	4	15.4	21.1	42.1
	16.00	1	3.8	5.3	47.4
	18.00	2	7.7	10.5	57.9
	24.00	3	11.5	15.8	73.7
	36.00	3	11.5	15.8	89.5
	48.00	1	3.8	5.3	94.7
	62.00	1	3.8	5.3	100.0
	Total	19	73.1	100.0	
Missing	System	7	26.9		
Total		26	100.0		

Gen_Min

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	3.8	5.3	5.3
	3	3	11.5	15.8	21.1
	6	2	7.7	10.5	31.6
	8	1	3.8	5.3	36.8
	9	2	7.7	10.5	47.4
	12	6	23.1	31.6	78.9
	18	1	3.8	5.3	84.2
	24	2	7.7	10.5	94.7
	36	1	3.8	5.3	100.0
	Total	19	73.1	100.0	
Missing	System	7	26.9		
Total		26	100.0		

Gen_Max

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	3.8	5.3	5.3
	3	3	11.5	15.8	21.1
	6	2	7.7	10.5	31.6
	8	1	3.8	5.3	36.8
	9	2	7.7	10.5	47.4
	12	6	23.1	31.6	78.9
	24	3	11.5	15.8	94.7
	36	1	3.8	5.3	100.0
	Total	19	73.1	100.0	
Missing	System	7	26.9		
Total		26	100.0		

Appendix 13
Crosstabs and correlations for survey Question 10 – assessing experience as a variable

Nonparametric Correlations

Correlations

			Experience	NCE_Min	NCE_Max	Gen_Min	Gen_Max
Kendall's tau_b	Experience	Correlation Coefficient	1.000	-.103	-.127	-.103	-.103
		Sig. (2-tailed)		.592	.509	.601	.600
		N	26	19	19	19	19
	NCE_Min	Correlation Coefficient	-.103	1.000	.968**	.887**	.879**
		Sig. (2-tailed)	.592		.000	.000	.000
		N	19	19	19	18	18
	NCE_Max	Correlation Coefficient	-.127	.968**	1.000	.902**	.901**
		Sig. (2-tailed)	.509	.000		.000	.000
		N	19	19	19	18	18
	Gen_Min	Correlation Coefficient	-.103	.887**	.902**	1.000	.993**
		Sig. (2-tailed)	.601	.000	.000		.000
		N	19	18	18	19	19
	Gen_Max	Correlation Coefficient	-.103	.879**	.901**	.993**	1.000
		Sig. (2-tailed)	.600	.000	.000	.000	
		N	19	18	18	19	19
Spearman's rho	Experience	Correlation Coefficient	1.000	-.154	-.180	-.103	-.103
		Sig. (2-tailed)		.529	.461	.676	.676
		N	26	19	19	19	19
	NCE_Min	Correlation Coefficient	-.154	1.000	.988**	.949**	.943**
		Sig. (2-tailed)	.529		.000	.000	.000
		N	19	19	19	18	18
	NCE_Max	Correlation Coefficient	-.180	.988**	1.000	.958**	.958**
		Sig. (2-tailed)	.461	.000		.000	.000
		N	19	19	19	18	18
	Gen_Min	Correlation Coefficient	-.103	.949**	.958**	1.000	.999**
		Sig. (2-tailed)	.676	.000	.000		.000
		N	19	18	18	19	19
	Gen_Max	Correlation Coefficient	-.103	.943**	.958**	.999**	1.000
		Sig. (2-tailed)	.676	.000	.000	.000	
		N	19	18	18	19	19

**. Correlation is significant at the 0.01 level (2-tailed).

Crosstabs

Table 8: Experience grouped against the minimum desired time for NCEs

Crosstab

			NCE_min_grouped					
			1.00	2.00	3.00	4.00	6.00	Total
Experience_grouped	>5	Count	0	3	1	1	0	5
		Expected Count	1.1	1.1	.8	1.1	.8	5.0
		% within Experience_grouped	0.0%	60.0%	20.0%	20.0%	0.0%	100.0%
	<=5	Count	4	1	2	3	3	13
		Expected Count	2.9	2.9	2.2	2.9	2.2	13.0
		% within Experience_grouped	30.8%	7.7%	15.4%	23.1%	23.1%	100.0%
Total		Count	4	4	3	4	3	18
		Expected Count	4.0	4.0	3.0	4.0	3.0	18.0
		% within Experience_grouped	22.2%	22.2%	16.7%	22.2%	16.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	7.200[a]	4	.126
Likelihood Ratio	8.454	4	.076
Linear-by-Linear Association	.479	1	.489
N of Valid Cases	18		

a. 10 cells (100.0%) have expected count less than 5. The minimum expected count is .83.

Symmetric Measures

		Value	Approx. Sig.
Nominal by Nominal	Phi	.632	.126
	Cramer's V	.632	.126
N of Valid Cases		18	

Table 9: Experience grouped against the maximum desired time for NCEs

Crosstab

			NCE_Max_grouped						
			1.00	2.00	3.00	4.00	6.00	8.00	Total
Experience_grouped	>5	Count	0	3	1	1	0	0	5
		Expected Count	1.1	1.1	.8	.8	.8	.3	5.0
		% within Experience_grouped	0.0%	60.0%	20.0%	20.0%	0.0%	0.0%	100.0%
	<=5	Count	4	1	2	2	3	1	13
		Expected Count	2.9	2.9	2.2	2.2	2.2	.7	13.0
		% within Experience_grouped	30.8%	7.7%	15.4%	15.4%	23.1%	7.7%	100.0%
Total		Count	4	4	3	3	3	1	18
		Expected Count	4.0	4.0	3.0	3.0	3.0	1.0	18.0
		% within Experience_grouped	22.2%	22.2%	16.7%	16.7%	16.7%	5.6%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	7.615[a]	5	.179
Likelihood Ratio	9.133	5	.104
Linear-by-Linear Association	.734	1	.391
N of Valid Cases	18		

a. 12 cells (100.0%) have expected count less than 5. The minimum expected count is .28.

Symmetric Measures

		Value	Approx. Sig.
Nominal by Nominal	Phi	.650	.179
	Cramer's V	.650	.179
N of Valid Cases		18	

Table 10: Experience grouped against the minimum desired time for generic applications

Crosstab

			Gen_Min_grouped					
			1.00	2.00	3.00	4.00	6.00	Total
Experience_grouped	>5	Count	1	3	0	0	0	4
		Expected Count	1.3	1.9	.2	.4	.2	4.0
		% within Experience_grouped	25.0%	75.0%	0.0%	0.0%	0.0%	100.0%
	<=5	Count	5	6	1	2	1	15
		Expected Count	4.7	7.1	.8	1.6	.8	15.0
		% within Experience_grouped	33.3%	40.0%	6.7%	13.3%	6.7%	100.0%
Total		Count	6	9	1	2	1	19
		Expected Count	6.0	9.0	1.0	2.0	1.0	19.0
		% within Experience_grouped	31.6%	47.4%	5.3%	10.5%	5.3%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.953[a]	4	.744
Likelihood Ratio	2.693	4	.610
Linear-by-Linear Association	.497	1	.481
N of Valid Cases	19		

a. 9 cells (90.0%) have expected count less than 5. The minimum expected count is .21.

Symmetric Measures

		Value	Approx. Sig.
Nominal by Nominal	Phi	.321	.744
	Cramer's V	.321	.744
N of Valid Cases		19	

Table 11: Experience grouped against the maximum desired time for generic applications

Crosstab

			Gen_Max_Grouped				
			1.00	2.00	4.00	6.00	Total
Experience_grouped	>5	Count	1	3	0	0	4
		Expected Count	1.3	1.9	.6	.2	4.0
		% within Experience_grouped	25.0%	75.0%	0.0%	0.0%	100.0%
	<=5	Count	5	6	3	1	15
		Expected Count	4.7	7.1	2.4	.8	15.0
		% within Experience_grouped	33.3%	40.0%	20.0%	6.7%	100.0%
Total		Count	6	9	3	1	19
		Expected Count	6.0	9.0	3.0	1.0	19.0
		% within Experience_grouped	31.6%	47.4%	15.8%	5.3%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.953[a]	3	.582
Likelihood Ratio	2.693	3	.441
Linear-by-Linear Association	.583	1	.445
N of Valid Cases	19		

a. 7 cells (87.5%) have expected count less than 5. The minimum expected count is .21.

Symmetric Measures

		Value	Approx. Sig.
Nominal by Nominal	Phi	.321	.582
	Cramer's V	.321	.582
N of Valid Cases		19	