# An Evaluation of the Regulatory Environment in South Africa: Improving the Review Process and Patients' Access to Medicines

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IF YOU THINK YOU ARE TOO SMALL TO MAKE A DIFFERENCE, YOU HAVEN'T SPENT A NIGHT WITH A MOSQUITO

(African Proverb)

*Image Source:* https://media.istockphoto.com/vectors/ Retrieved January, 26, 2020

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# ABSTRACT

National regulatory authorities (NRAs) are responsible for the evaluation of medicines and for ensuring that only those products which meet the requirements of quality, safety and efficacy are registered and made available to patients. The NRAs are required to effect such regulatory mandates efficiently and ensure timely patients' access to medicines. Many NRAs, especially in resource-limited settings or emerging markets face challenges in fulfilling these mandates as resources are stretched to capacity. Adopting a risk-based approach to medicine evaluation can provide relief for NRAs striving towards improved regulatory performance. The NRAs may implement facilitated regulatory pathways, appropriate frameworks for benefit-risk (BR) assessment and abridged review processes in order to leverage reliance mechanisms and good regulatory practices to improve regulatory efficiencies.

The aim of this research was to evaluate the regulatory environment in South Africa with a view to improve the review process for medicines and to ensure their timely access by patients. This was achieved through a review of the legislative framework and historical context supporting the new regulatory environment in South Africa and the transition from the Medicines Control Council (MCC) to South African Health Products Regulatory Authority (SAHPRA). The regulatory performance of the South African regulatory authority and how it compared to that of other agencies was evaluated and the strategies supporting enhanced BR assessment and reliance mechanisms were appraised.

Various methodologies were considered in determining an appropriate study design and a mixed method approach, including a combination of self-administered questionnaires, focus groups and a case study, was adopted to support achieving the study objectives. A questionnaire was used to evaluate the review process of the MCC and the results demonstrated that the MCC was not able to meet target timelines for the review of new active substances (NASs). A comparison was made between the MCC and other similar NRAs using the same questionnaire. The results indicated that the MCC had similar requirements to other agencies and all the NRAs conducted a full assessment of applications for the registration of NASs. However, the approval

times for the MCC were considerably longer. Further investigation into these lengthy timelines resulted in the analysis of the performance metrics of the MCC between 2015-2017 and of SAHPRA in 2018. A case study approach and focus group were used to evaluate strategies for enhanced communication of BR assessments and a questionnaire and two focus groups were conducted to understand the implications of the application of an abridged review in the evaluation of NASs. The results of these studies culminated in the development of a proposed improved model for the regulatory review process of new active substance (NASs) for SAHPRA.

This programme of research has presented, in a seminal piece of work, key recommendations for the improvement of the regulatory review process as it may be applied by SAHPRA. The results from this work provide, for the first time, a baseline against which future improvements, implemented by SAHPRA, may be measured. The implementation of these recommendations will contribute towards an enhanced regulatory performance, underpinned by good regulatory, good review and good reliance practices. This will result in a stream-lined review process, improved regulatory responsiveness, consistency, transparency and accountability and ultimately patients' timely access to medicines.

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| | |
|---|---|
| ACSS | Australia, Canada, Switzerland and Singapore |
| AMA | African Medicines Agency |
| AMRHI | African Medicines Registration Harmonization Initiative |
| ANOVA | Analysis of Variance |
| ANVISA | Agência Nacional de Vigilância Sanitária |
| APEC | Asia-Pacific Economic Cooperation |
| API | Active Pharmaceutical Ingredient |
| ARPP | Abridged Review Process Profile |
| ASEAN | Association of Southeast Asian Nations |
| ATC | Anatomical Therapeutic Classification |
| AusPAR | Australian Public Assessment Report |
| BR | Benefit-Risk |
| BRAIN | Benefit-Risk Assessment in New and Old Drugs |
| CEO | Chief Executive Officer |
| CFO | Chief Financial Officer |
| CHMP | Committee for Medicinal Products for Human Use |
| CIRS | Centre for Innovation in Regulatory Science |
| CMC | Chemistry, Manufacturing and Control |
| COBRA | Consortium on Benefit-Risk Assessment |
| CPP | Certificate of Pharmaceutical Product |
| CRT | Clinical Full Review Report Template |
| CTD | Common Technical Document |
| EAC | East African Community |
| EDL | Essential Drugs List |
| EDMS | Electronic Document Management System |
| EM | Emerging Market |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Reports |
| EU | European Union |
| FRP | Facilitated Regulatory Pathway |
| GBT | Global Benchmarking Tool |

| | |
|---|---|
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| GRelP | Good Reliance Practice |
| GRevP | Good Review Practice |
| GRP | Good Regulatory Practice |
| HPTTT | Health Products Technical Task Team |
| HSA | Health Sciences Authority |
| HTA | Health Technology Assessment |
| ICDRA | International Conference of Drug Regulatory Authorities |
| ICH | International Conference on Harmonization |
| ICT | Information and Communication Technology |
| IPRP | International Pharmaceutical Regulators Programme |
| ISO | International Standardization Organization |
| ITG | Industry Task Group |
| MA | Marketing Authorisation |
| MCC | Medicines Control Council |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| MLE | Major Line Extension |
| NAS | New Active Substance |
| NCE | New Chemical Entity |
| NRAs | National Regulatory Authorities |
| PAHO | Pan American Health Organization |
| PAR | Public Assessment Report |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PFMA | Public Finance Management Act |
| PhRMA BRAT | Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team |
| PIC/S | Pharmaceutical Inspection Co-operation Scheme |
| PMA | Pharmaceutical Manufacturers Association |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PRISMA | Preferred Reporting Items for Systematic Reviews And Meta-Analyses |

| | |
|---|---|
| PrOACT-URL | Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk tolerance, Linked decisions |
| PSUR | Periodic Safety Update Report |
| QDMPs | Quality Decision-Making Practices |
| QMS | Quality Management System |
| QoDoS | Quality of Decision-Making Orientation Scheme |
| RAC | Regulatory Advisory Committee |
| RS | Regulatory System |
| SADC | South African Development Community |
| SAHPRA | South African Health Products Regulatory Authority |
| SAMMDRA | South African Medicines and Medical Devices Regulatory Authority |
| SBD | Summary Basis of Decision |
| SBR | Summary Basis for Registration |
| SCoRE | Summary of Critical Regulatory Elements |
| SOP | Standard Operating Procedure |
| TGA | Therapeutic Goods Administration |
| TORS | Technical Operations and Regulatory Strategy |
| UMBRA | Universal Methodology for Benefit-Risk Assessment |
| USA | United States of America |
| USFDA | United States Food and Drug Administration |
| WHA | World Health Assembly |
| WHO | World Health Organization |
| ZAPAR | South African Public Assessment Report |

# CHAPTER 1

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# General Introduction

The intersection of legislative frameworks and medicines dates back to antiquity (Halwani & Takrouri, 2006) while the systemic failings in the regulation of medicines, publicised extensively with the advent of the thalidomide scandal (McBride, 1962), were the catalyst for rigorous medicine regulation in many countries (Rago & Santoso, 2008). Today governments remain responsible for safeguarding their citizens from the use of ineffective, poor quality and harmful medicines and national regulatory authorities (NRAs) have been established to ensure that medicines are regulated effectively through the implementation of laws, evidence-based scientific evaluation and safety monitoring programmes (Rago & Santoso, 2008). The regulation of medicines is realised through several activities that mutually contribute to promoting and protecting public health (WHO, 2003). These principal functions include inspection and licensing of manufacturers and distributors of medicines, control of the advertising, post-market surveillance and vigilance activities as well as the scientific evaluation of medicines and the issuing of market authorisation for approved medicines (WHO, 2003).

**Global perspective for regulatory requirements**

Emanating from the sixty-seventh World Health Assembly (WHA) in 2014, WHA Resolution 67.20, identified the need for effective regulatory systems and emphasised the importance of strengthening regulatory processes and the regulatory performance of NRAs (WHA, 2014). This includes developing strong legal foundations with a clear focus on transparency in decision-making and recognising the importance of collaboration to promote greater access to quality, safe and effective medical products (WHA, 2014). The role of the World Health Organization (WHO) in the regulation of medical products has been demonstrated through regulatory capacity-building for NRAs in Member States, ensuring the safety, quality and efficacy of medical products through the WHO prequalification programme, as well as the support provided for monitoring and pharmacovigilance activities and the establishment of norms and standards by the WHO Expert Committees (WHO, 2014a).

As regulatory authorities around the world enforced legislative mandates; differences and increases in regulatory requirements were observed. The rising need for harmonisation brought together pharmaceutical associations and regulators from Europe (EU), the United States of America (USA) and Japan. The efforts of these

three regions resulted in the establishment of the International Conference on Harmonization (ICH) in 1990 (ICH, 2019). The work of the ICH aimed to address the scientific and technical issues related to the harmonisation of medicine registration. Initially the ICH focused on new active substances (NASs) and biotechnology products however, over time, the recommendations of the ICH have been applied to generic medicines. The efforts of the ICH have enabled mutual acceptance of data across ICH countries and have also influenced non-ICH countries (ICH, 2019).

One of the key initiatives of the ICH was manifested in the establishment of a common technical document (CTD). The CTD made provision for the assembly and presentation of the quality, safety and efficacy data required for the scientific assessment of market authorisation applications in a common format. The CTD is organised into five modules. Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions. For industries, the CTD has eliminated the need to reformat the information for submission to the different ICH regulatory authorities. For regulators, the CTD has helped to pave the way for the implementation of reliance and recognition strategies.

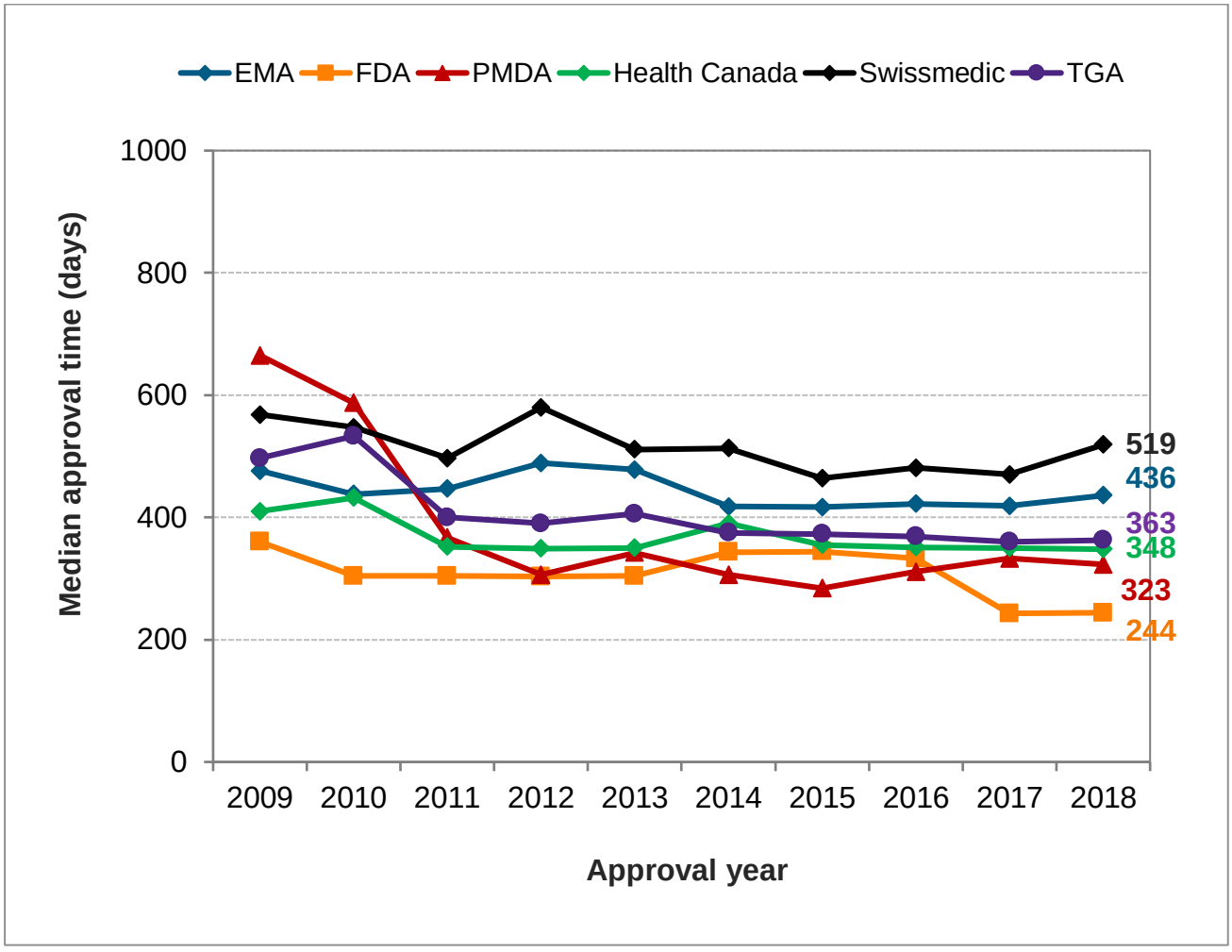
**Challenges in the regulatory review process**

Global trends of continuing pressure on NRAs, of all sizes and capacity, have been noted, due to the increased volumes of applications received, the complexity of the submissions and the increased categories of medical products (WHO, 2014b). Efforts to address these challenges, especially for NRAs in low and middle-income countries, have focused on strategies for identifying and performing core regulatory functions that have to be undertaken directly by NRAs, to meet country or regional needs (WHO, 2014b). The WHO has encouraged NRAs to consider regulatory convergence and to collaborate with and recognise the work carried out by other agencies in order to ease the regulatory burden (Ward, 2014).

The time taken to review and evaluate applications for NASs is a common measure of the performance of a regulator (CIRS, 2019a). The Centre for Innovation in Regulatory Science (CIRS) has studied market approval timelines for medicines for the past three decades. The latest data published by CIRS provided insight into the improvements made in the regulatory environment. Over the last decade, six major NRAs, namely

the European Medicines Agency (EMA), the United States Food and Drug Administration (USFDA), the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Swissmedic and the Australian Therapeutic Goods Administration (TGA) have achieved shortened timelines for the review and approval of NASs despite the increase in the number of registrations for NASs (CIRS, 2019a). The median approval time for the review of NASs by these six regulatory authorities in 2008-2017 is displayed in Figure 1.1 (CIRS, 2019a).

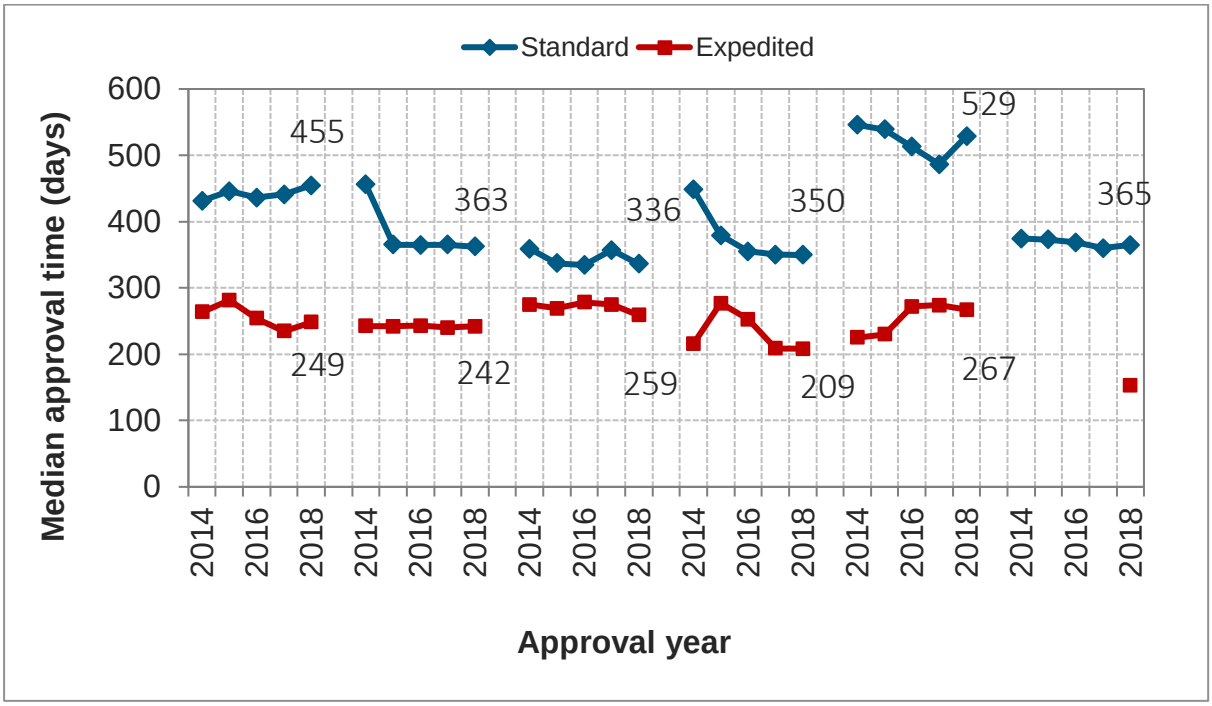
**Figure 1.1 New active substance (NAS) median approval times for six regulatory authorities in 2009-2018**




*Adopted from CIRS, 2019a*

The median approval times for NASs, achieved by these six agencies for the period 2014-2018, have been further stratified by review type (standard or expedited) (CIRS, 2019a) and the results thereof are displayed in Figure 1.2.

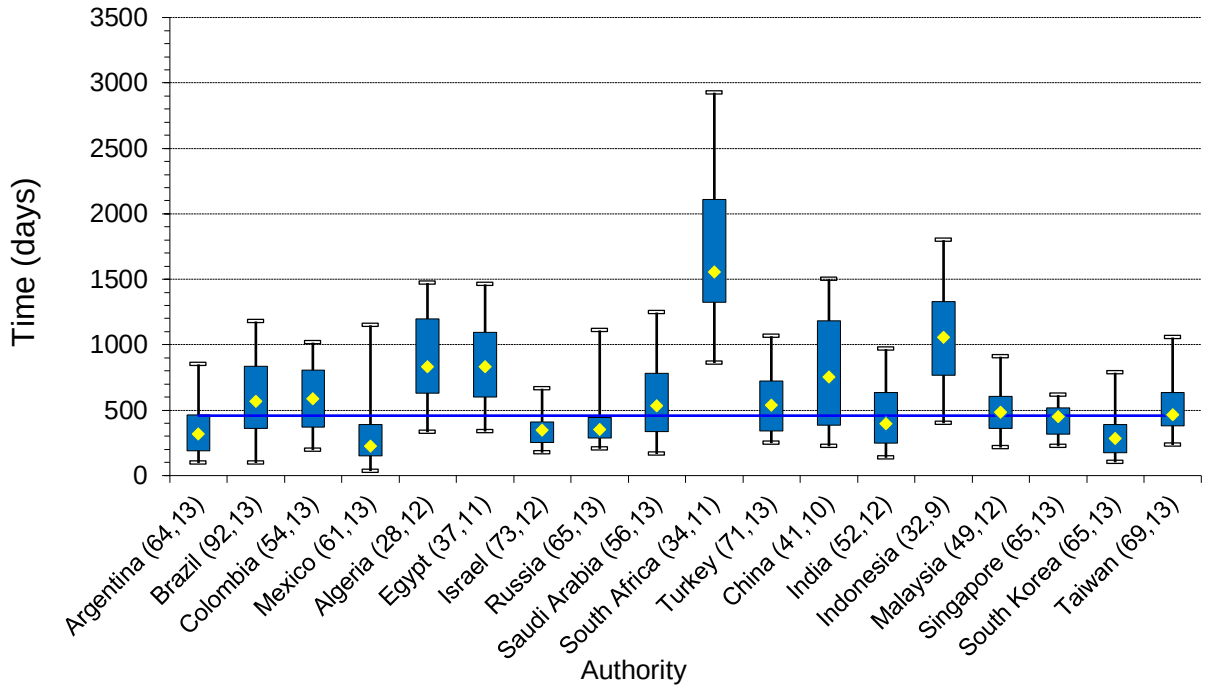
**Figure 1.2 New active substance (NAS) median approval times by review type for six regulatory authorities in 2014-2018**




*Adopted from CIRS, 2019a*

Similar data were collected to reflect the median approval times for the review of NASs by NRAs in the emerging economies for the period 2014-2018 (CIRS, 2019b). The data presented in Figure 1.3 is based on the median approval times for NASs in each country. Inherent variability in approval times was noted as a result of differences in the type of review assessments used by the NRAs. For example, Argentina makes use of a verification review while South Africa and Turkey perform a full review of applications for NASs. At the time of this study, the review times for the approval of NASs in South Africa were the longest out of the countries represented in the data set.

**Figure 1.3 Regulatory approval times from date of emerging markets submission to date of approval for new active substances (NASs) approved between 2014-2018**




Data are shown for NASs that were approved between 01/01/2014 and 31/12/2018.

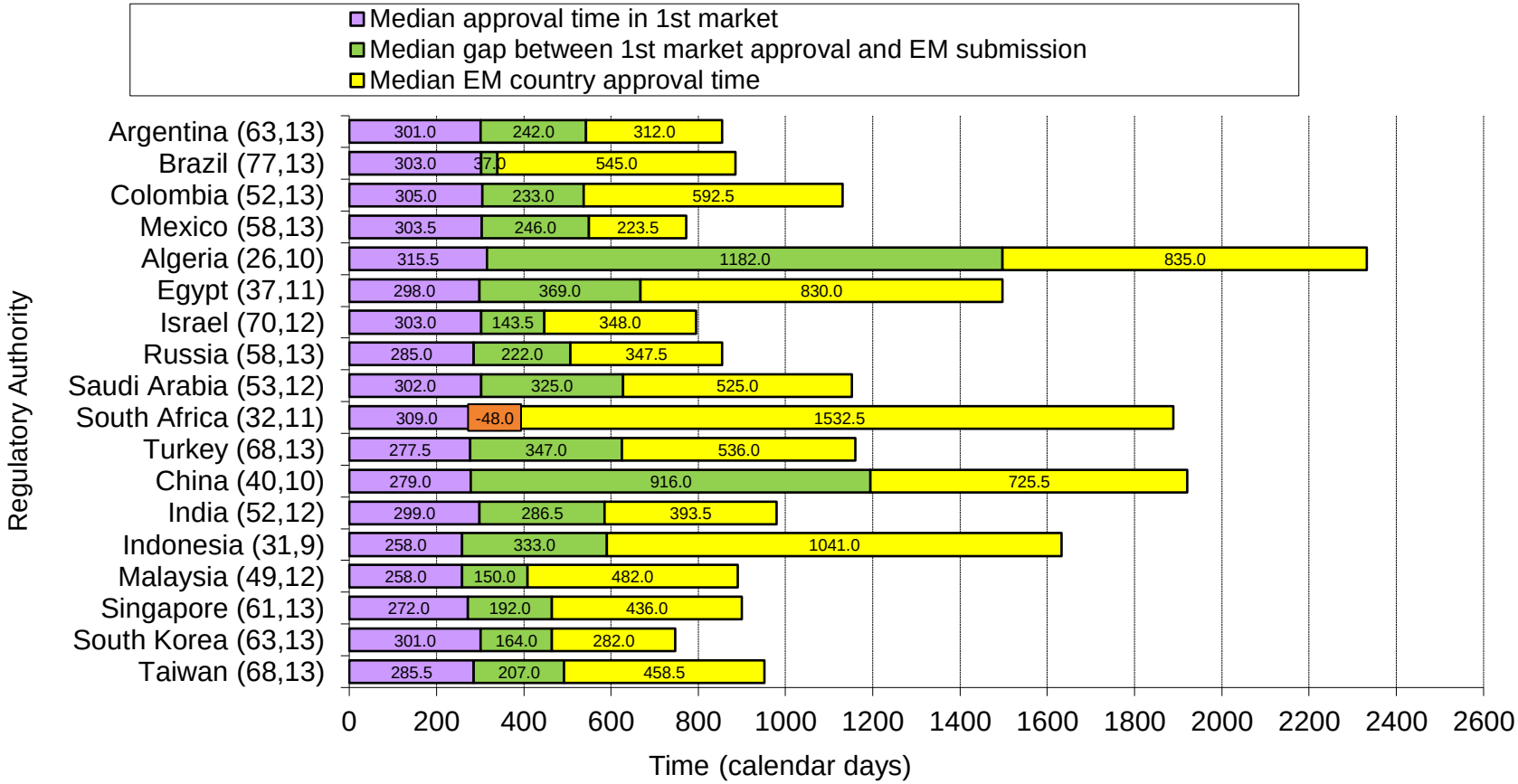
(n1) = number of drug applications, (n2) = number of companies providing data.

Box: 25th and 75th percentiles. Whiskers: 5th and 95th percentiles.

*Adopted from CIRS, 2019b*

Figure 1.4 provides an analysis and comparison of median interval durations for the first regulatory approval for an NAS anywhere in the world followed by submission and approval for the same compound to one of the emerging market authorities (CIRS, 2019b). The results depicted in Figure 1.4 reflect the extended approval timeline for NAS in South Africa. The results of the study illustrate the South African NRA's historical track record of slow decision making and delays in effecting regulatory mandates. Efforts to address the increasing volume of applications that were received by the Medicines Control Council (MCC), the previous South African NRA, were unsuccessful, as resources were stretched to capacity, resulting in the development of a significant backlog and extended timelines for product registration.

**Figure 1.4 Median time to roll out to emerging market (EM) countries for new active substance (NASs) approved 2014-2018**




Denotes the submission to emerging market country was prior to first world approval

*Adopted from CIRS, 2019b*

Similar research in this field has demonstrated that NRAs of varying sizes and capacity are able to improve their regulatory performance. Key elements for consideration include the application of risk-stratification approaches and facilitated regulatory pathways (FRPs) (Liberti, 2018). This would be an advantage when considered in line with the recommendations of the WHO (Ward, 2014; WHO, 2014b) to embrace regulatory harmonisation and/or convergence strategies and engage in reliance and recognition activities that allow NRAs, in resource-limited settings, to consider or accept the regulatory decisions made by other comparable NRAs. In addition, this would have the potential to reduce the regulatory burden on NRAs and to avoid duplication of regulatory effort (Ward, 2014). Furthermore, this could enable the application of an appropriate framework for benefit-risk (BR) assessment to enhance consistency in the clinical assessment of medicines (Leong et al., 2015a) as well as incorporating the principles of good review practices (GRevP) in routine regulatory undertakings (WHO, 2014b). Thus, the entirety of such an initiative would build quality into regulatory decision-making to reinforce transparency (Walker et al., 2014).

**Good review practices**

National regulatory authorities (NRAs) are responsible for the review of applications for medicine registration and for ensuring that the foundation for regulatory decisions is supported by the scientific and evidentiary requirements for safety, efficacy and quality (WHO, 2015). They are also responsible for ensuring timely access to medicines (WHO, 2015). Many NRAs strive towards goals of improved regulatory performance and strengthened regulatory systems (WHO, 2015). The implementation of GRevPs provides a mechanism for NRAs to enhance regulatory performance (WHO, 2015). GRevPs provide guidance on the best practices that may be applied by NRAs during the regulatory review of a medicine (WHO, 2015). GRevPs are a fundamental part of overall good regulatory practices (GRP) with a focus on the review of medicines (WHO, 2015). The application of GRevPs provides a platform for NRAs to effectively manage the regulatory review of medicines and to ensure the consistency, transparency and quality of the review process (WHO, 2015). The WHO has provided general guidance for NRAs, through the development of a guideline on GRevPs that provides insight into the ten key principles of a good review (Figure 1.5) (WHO, 2015).

**Figure 1.5 Ten key principles of good review practices (GRevPs)**

**BALANCED** A good review is objective and unbiased.

**CONSIDERS CONTEXT** A good review considers the data and the conclusions of the applicant in the context of the proposed conditions of use and storage, and may include perspectives from patients, health-care professionals and other RAs' analyses and decisions.

**EVIDENCE-BASED** A good review is evidence-based and reflects both the scientific and regulatory state of the art. It integrates legislative, regulatory and policy frameworks with emerging science.

**IDENTIFIES SIGNALS** A good review comprehensively highlights potential areas of concern identified by the applicant and the reviewers.

**INVESTIGATES AND SOLVES PROBLEMS** A good review provides both the applicant's and the reviewers' in-depth analyses and findings of key scientific data and uses problem-solving, regulatory flexibility, risk-based analyses and synthesis skills to devise and recommend solutions and alternatives where needed.

**MAKES LINKAGES** A good review provides integrated analysis across all aspects of the application: preclinical, nonclinical, clinical, chemistry/biocompatibility, manufacturing and risk management plan. It includes timely communication and consultation with applicants, internal stakeholders and, as needed, with external stakeholders who have expertise relevant to the various aspects of the application.

**UTILIZES CRITICAL ANALYSES** A good review assesses the scientific integrity, relevance and completeness of the data and proposed labelling, as well as the interpretation thereof, presented in the application.

**THOROUGH** A good review reflects adequate follow through of all the issues by the reviewers.

**WELL-DOCUMENTED** A good review provides a well-written and thorough report of the evidence-based findings and conclusions provided by the applicant in the dossier, and the reviewers' assessment of the conclusions and rationale for reaching a decision. It contains clear, succinct recommendations that can stand up to scrutiny by all the parties involved and could be leveraged by others.

**WELL-MANAGED** A good review applies project and quality management processes, including clearly defined steps with specific activities and targets.

*Adopted from WHO, 2015*

The consistent application of these principles should be underpinned by a quality management system (QMS) supported by standardised procedures. Intentions to establish these systems are shared by NRAs across the world as agencies recognise the importance of improved GRevPs as the basis for good decision-making (McAuslane et al., 2011). Commonalities in the functions performed by NRAs and the processes applied in the review of medicines provide an opportunity for regulatory convergence and for building mutual confidence, among NRAs, in regulatory practices (Liu et al., 2013).

A survey was conducted among NRAs of the Asia-Pacific Economic Cooperation (APEC) member economies to assess the current use of GRevPs to support quality

decision-making (Liu et al., 2013). This survey was the first step of the APEC Best Regulatory Practice Project that was initiated following the APEC GRevP Workshop on Medical Products in 2010. Fourteen of the NRAs in the APEC member economies including Australia, Canada, Chile, Indonesia, Japan, Mexico, Malaysia, New Zealand, Peru, the Philippines, Singapore, South Korea, Chinese Taipei and the USA participated in the survey. Participants provided information pertaining to the size of the agency, the scope of responsibilities and the types of reviews conducted (Liu et al., 2013). Quality measures undertaken by the agencies were described and insight into the progress made and satisfaction with the implementation of GRevPs, QMSs and available training mechanisms was provided. The majority of the APEC regulatory agencies responding to this survey recognised the need for employing quality measures in the regulatory review of medicines driven by objectives of ensuring consistency and improving efficiencies as shown in Figure 1.6 (Liu et al., 2013).

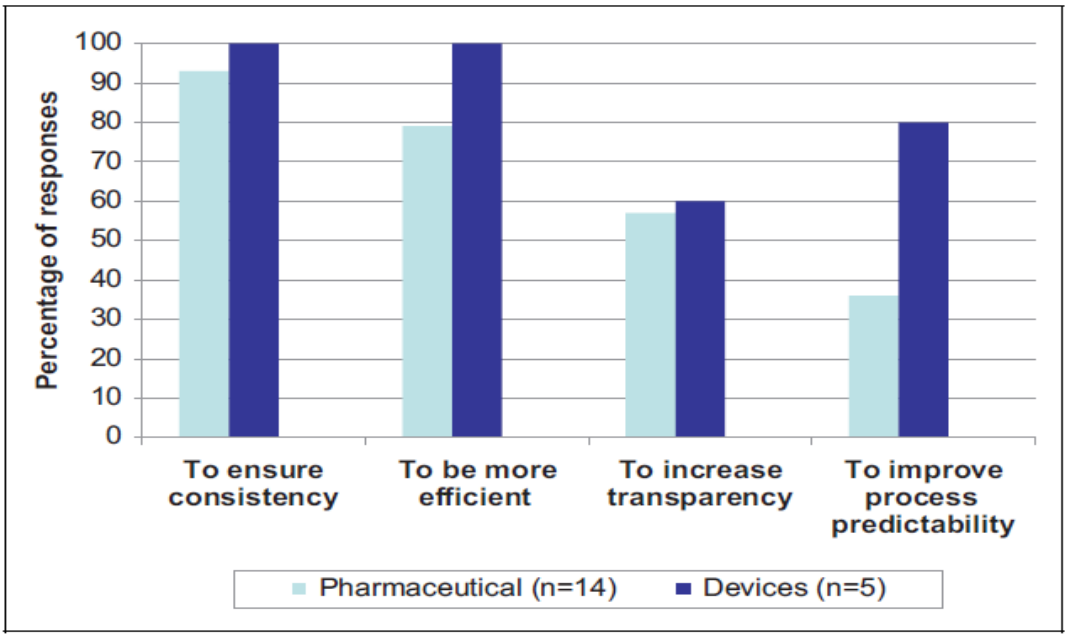
Many NRAs have implemented systems to ensure the consistent application of GRevPs and continue to work towards the evaluation and improvement of such systems. It is hoped that mutual confidence will be cultivated among NRAs as they progress and share their experiences as well as lessons learned and best practices for the effective application of GRevPs. In turn, such practices will contribute to the movement towards regulatory convergence and the reliance on, or recognition of, the assessment reports and decision-making of reference agencies; ultimately leading to improved regulatory performance and timely patient access to medicines.

**Harmonisation, reliance and recognition**

The challenges faced by NRAs in meeting demands for improved regulatory performance are more acute in low and middle income countries (Ward, 2017). The WHO has supported these NRAs through the development of norms and standards, promoting regulatory convergence and harmonisation as well as the optimum use of limited resources through collaboration, reliance and recognition (Ward, 2017). At the core of harmonised regulatory activities lies the need to reach convergence in regulatory requirements and a prerequisite for NRAs, within participating countries, to function at the necessary maturity level. Through harmonisation initiatives, technical requirements on safety, quality and efficacy may be standardised and the regulatory

burden, faced by many NRAs, may be reduced and the duplication of regulatory efforts may be avoided (Ward, 2014).

**Figure 1.6 Top reasons given by the Asia-Pacific Economic Cooperation (APEC) regulatory agencies for employing quality measures in the regulatory review**

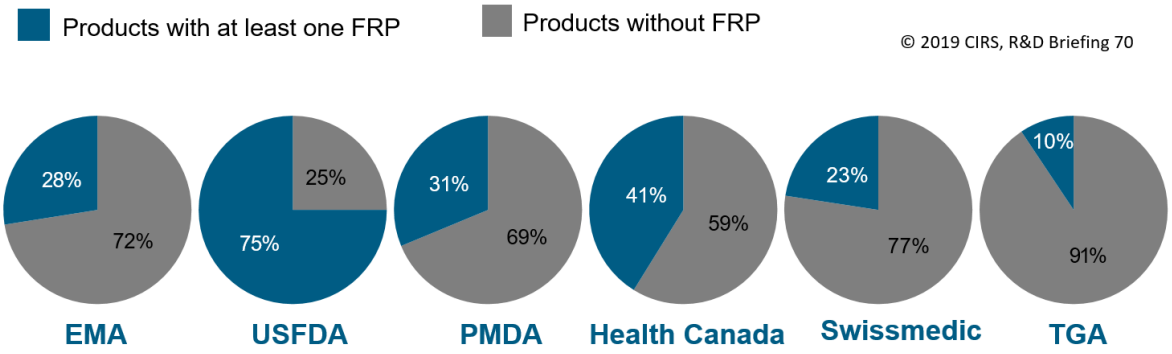



*Adopted from Liu et al., 2013*

The use of facilitated review practices (FRPs) may be considered as a mechanism to expedite regulatory decision-making in the review of applications for the registration of NASs. Primary FRPs are defined as pathways that are typically used by mature NRAs, during the first review of a medicine, to decrease the timeline for the development or the regulatory review of a product (Liberti, 2018). Secondary FRPs can be used to expedite regulatory decisions made by NRAs and contribute towards decreasing median approval times for medicines resulting in improved patient access to medicines. Secondary FRPs are based on the reliance or recognition of the prior review and regulatory decision made by another NRA (Liberti, 2018). Reliance is defined as the act whereby, in making a regulatory decision, an NRA in one jurisdiction considers, and in some cases, gives significant weight to the regulatory decision made by another NRA (Ward, 2017). Recognition is defined as the routine acceptance of the regulatory decision made by another NRA (Ward, 2017). Data on the proportion

of NASs approved by each NRA in 2017 that benefited from at least one FRP are provided in Figure 1.7 (CIRS, 2019a).

**Figure 1.7 Proportion of New Active Substances (NASs) approved by each agency in 2018 that benefited from at least one facilitated regulatory pathway (FRP)**




*Adopted from CIRS, 2019a*

### Key milestones of the regulatory review process

A workshop on "The Emerging Markets: Regulatory issues and the impact on patients' access to medicines" was organised in Geneva, Switzerland in March 2006 with the aim to discuss the data assessment methods used by NRAs to perform a scientific review of applications for NASs (Walker et al., 2006). The outcomes of the workshop informed the identification of three review models that were agreed by the global representation of NRAs in attendance at the workshop. The three scientific review models of NAS applications are described below:

#### *Review assessment type I - Verification model*

The verification model is used by NRAs that lack the resources to perform full scientific assessments of applications for NASs. This model allows the NRA to authorise the registration of the NAS provided that marketing authorisation for the NAS has been obtained, in the form of a Certificate of a Pharmaceutical Product (CPP), from at least two recognised NRAs. The verification model is built on the premise that the NRA has verified the data submitted, for compliance with the reference country(s) authorisation(s), including the product characteristics (formulation, composition and strength) and the proposed labelling information (use, dosage, precautions) for local

marketing. For this model, it is a pre-requisite that the CPP or alternative documentation of approval be provided on submission of the application for authorisation.

***Review assessment type II – Abridged model***

The abridged model makes provision for a truncated review focused on the evaluation of clinical data (BR assessment) as well as country specific requirements related to quality data. Requirements pertaining to quality data are generally associated with evidence of product stability in the local climatic zone and the suitability of distribution networks within the country. Provided that the scientific data submitted has been evaluated and approved by a recognised NRA, local authorities can avoid duplication of effort and can forgo the re-assessment of such data. This model does not require the submission of the CPP on application, but may require submission of the CPP or alternative documentary evidence of approval, prior to product authorisation.

***Review assessment type III - Full review model***

The full review model is intended for use by NRAs that have the necessary resources to perform a full independent scientific review of applications for NASs. This model entails a "full" assessment of quality, pre-clinical and clinical data by internal and external experts. The full review model does not require evidence of marketing authorisation from any other NRA at the time of submission and thus allows for parallel or prior review to first applications worldwide.

Historically, the MCC in South African utilised the full review model in the assessment of all applications including NASs and generics for orthodox, biological, complementary, and veterinary medicinal products. A full independent assessment of quality, efficacy and safety data was performed for each application received. The MCC had access to reviewers who had the relevant qualification and technical experience to perform a full assessment of the data provided. The majority of the reviewers were external consultants. Reviewers were responsible for preparing a detailed assessment report, that was peer-reviewed and then submitted to the relevant Scientific Committee for discussion. The Scientific Committees then made a recommendation to the Council for ratification.

**Benefit-risk assessment**

The assessment of the benefits and risks in the context of an application for a NAS is a complex process that requires evaluation of a large amount of data (EMA CHMP, 2008). Whilst the same data on quality, safety and efficacy could be submitted in support of the registration of a new medicine, NRAs may have different views on the authorisation of the product. A report in 2008, by a working group of the EMA Committee for Medicinal Products for Human Use (CHMP) stated that there was no accepted, universal approach on the methodology to estimate the overall BR balance or on how to describe the way the evidence was weighed and balanced (EMA CHMP, 2008). However, since 2008, there have been a number of publications supporting the BR assessment of medicines (Walker et al., 2014; McAuslane et al., 2017; Leong et al., 2015a). National regulatory authorities (NRAs) have recognised the need for a structured, standardised, systematic approach to BR assessment of medicines using a framework that should ideally be feasible and practical within the regulatory review process. The NRAs are also under increased pressure to improve transparency, consistency and accountability and to establish appropriate documentary governance for decision-making processes.

Over the past decade, current global practice frameworks, implemented by both pharmaceutical companies and NRAs, have been evaluated (Walker et al., 2014). Such models included those recommended by pharmaceutical companies as well as the Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT), the Benefit-Risk Assessment in New and Old Drugs (BRAIN), as well as frameworks advanced by NRAs, including the USFDA 5-step framework and the EMA Problem, Objectives, Alternatives, Consequences, Trade-Offs, Uncertainty, Risk Tolerance, Linked Decisions (PrOACT-URL) (Walker et al., 2014). Through this work the need for applicants to submit safety, quality and efficacy data in a standardised, well-structured manner was identified and, therefore, the submission of intuitive BR assessments, resulting in inconsistent narratives, could be avoided.

In 2008, four regulatory agencies namely the Australian TGA, Health Canada, the Health Sciences Authority (HSA) in Singapore and Swissmedic collaborated in the development of a universal model for BR assessment. The development of this model was intended to facilitate shared or joint reviews of new medicines submitted

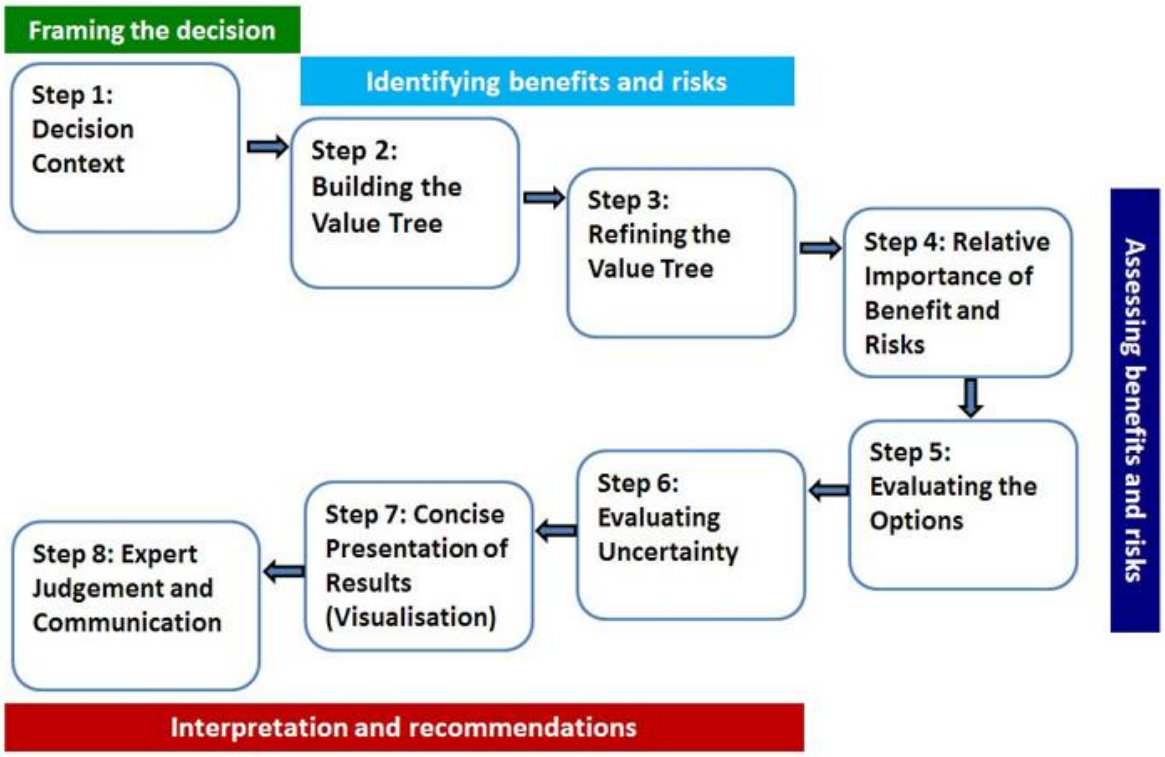
simultaneously to each of the four agencies. The initiative became known as the Consortium on Benefit-Risk Assessment (COBRA) initiative and was subsequently renamed Australia, Canada, Switzerland and Singapore (ACSS). Through the facilitation of this collaboration, a BR assessment template was developed based on the EMA reflection paper of 2008 (EMA CHMP, 2008). The template was constructed and then evaluated in three phases: a feasibility study, a retrospective pilot study and a prospective study (McAuslane et al., 2017; Levitan et al., 2014). The final template, named the Universal Methodology for Benefit-Risk Assessment (UMBRA) was developed (Levitan et al., 2014) and incorporated appropriate methodologies for evaluating the BR assessment of medicines, as well as tools for supporting transparent decision-making. The UMBRA overarching framework provided the basis for a common agreement on the principles for BR assessment of medicines taking into account the criteria influencing the quality of the framework, namely the logical soundness, comprehensiveness, acceptability of results, practicality, specificity and sensitivity, scope and visualisation (Walker et al., 2014). The EMA CHMP assessment report template was used as the basis in the development of UMBRA and the revised template included a structured list of benefit and risk criteria.

There was a consensus from regulators who were developing BR frameworks that there were eight steps either explicitly or implicitly undertaken in BR methodologies for assessing medicines (Leong et al., 2015a). These steps have been incorporated into the UMBRA eight step benefit risk framework (Figure 1.8).

The use of the UMBRA eight step benefit risk framework has potential benefits. The template facilitates consistency in BR assessment in that the template prompts evaluators to avoid lengthy narratives. Through the use of this template, reviewers are able to articulate each benefit and risk clearly which is an important mechanism for training new reviewers and a means for allowing comparisons with other medicines in the same class. Consequently, its use has the potential to enhance internal consistency and the quality of decision-making within the NRA (Walker et al., 2014; Bujar et al., 2016; Donelan et al., 2015). The template contributes towards the principles of GRevP in that it allows for transparent, documented decision-making,

resulting in a valuable tool that may be beneficial in engaging in joint reviews and collaborations with other NRAs.

**Figure 1.8 Universal Methodology for Benefit Risk Assessment (UMBRA) eight step benefit risk framework**




*Adopted from Leong et al., 2015a*

In the event that NRAs engage in such collaborations, it becomes essential that there is agreement with respect to the clinical template, with emphasis on the section of the template addressing the BR assessment. Standardisation of the BR assessment will facilitate effective exchange between partnered NRAs in communicating the reasons for views expressed and the regulatory decisions made. Further value would be gained, should such a universal, standardised model be received internationally, especially for those agencies, where reliance and/or recognition mechanisms are in place.

**Quality decision-making practices**

National regulatory authorities (NRAs) are responsible for making regulatory decisions that affect patients' access to medicines. Frameworks supporting the science of decision-making can be improved with a view to enhance consistency, transparency and accountability in decision-making practices. Ten quality decision-making practices (QDMPs) have been identified (Donelan et al., 2015) and can be linked to the science of decision-making as it unfolds in the review of medicines, particularly in the area of BR assessment (Bujar et al., 2016).

Any NRA that aims to improve its decision-making practices should ensure that the quality of such decision-making practices is monitored and measured. An assessment of the QDMPs applied by an NRA will provide insight into current strengths and gaps in current QDMPs and highlight commonalities and differences that may exist through the stratified forums for decision-making inherent within the NRA.

A study conducted by (Donelan et al., 2016) resulted in the development of a tool named the Quality of Decision-Making Orientation Scheme (QoDoS) that was validated using a standardised approach and qualitative as well as quantitative techniques. Through the application of the QoDoS in a regulatory environment, differences in decision-making between individuals and their organisation can be identified (Donelan et al., 2016).

**Review of the global regulatory environment**

The regulation of medicines is supported by a legislative framework that empowers NRAs to effect statutory mandates in ensuring patients' access to safe, effective, quality medicines. Patient-focused, evidence-based, risk-oriented, transparent, effective and flexible practices are the mainstay of medicines regulation (Azatyan, 2009). National regulatory authorities (NRAs) of various sizes and maturity levels have experienced challenges in the face of resource constraints and have had to revise legacy systems and processes in order to adapt to the new regulatory environment. As the demand on NRAs increases, regulators globally have had to re-engineer regulatory processes in an effort to increase the effectiveness of regulatory operations. International benchmarking, against mature NRAs has driven many NRAs

to strive towards the implementation of pragmatic solutions to address regulatory inefficiencies.

The WHO has developed a global benchmarking tool (GBT) that has been used to perform an evidence-based assessment and comparison of NRAs. The WHO GBT is used by the WHO to assess the regulatory systems of NRAs in Member States, as mandated by the WHA Resolution 67.20 on regulatory system strengthening for medical products (WHA, 2014; WHO, 2020). The benchmarking methodology embedded within the WHO GBT enables the WHO to identify both strengths and areas for improvement within the NRAs' regulatory system. The GBT is used to evaluate each of the nine component regulatory functions of the regulatory system against a series of sub-indicators. These functions include national regulatory systems, registration and marketing authorisation, vigilance, market surveillance and control, licensing establishments, regulatory inspection, laboratory testing, clinical trial oversight and lot release. Fact sheets have been developed to describe the scope and requirements for each sub-indicator. During the assessment, NRAs are required to provide evidence supporting the implementation of each of the sub-indicators. A number of the sub-indicators highlight the importance of formalising the implementation of the QMS and GRevPs. The sub-indicators require NRAs to demonstrate the effective application of QDMPs in regulatory decision-making and support the publication of regulatory decisions in the public domain. The sub-indicators endorse the measuring and monitoring of regulatory performance, making use of effective electronic document management systems (EDMS) and participation in regional and/or global networks to promote harmonisation and collaboration. Each sub-indicator is linked to a 'maturity level' rating. The measure of 'maturity level' is based on the concept adapted from the International Standardization Organization (ISO) 9004 standard that provides guidance on quality management and the quality of an organisation to achieve sustained success (WHO, 2020). The GBT facilitates an assessment of the maturity level of an NRA on a scale of 1 (existence of some elements of regulatory system) to 4 (operating at advanced level of performance and continuous improvement). National regulatory authorities (NRAs) that are operating at a maturity level of 3 and above are considered to be competent in effecting regulatory mandates and are listed by the WHO as such. The application of the WHO GBT in the assessment of NRAs in WHO Member States provides an opportunity for

NRAs that are operating at lower maturity levels or NRAs in resource-limited settings to rely on or recognise the regulatory decisions of WHO-listed NRAs.

Technical support under-pinned by efforts promoting regulatory convergence has been provided by WHO to Member States. The WHO has initiated collaborative activities between various countries and regions and through these harmonisation initiatives participating NRAs have been able to exchange consolidated information without challenging the sovereignty of the participants (Azatyan, 2009).

Global trends for convergence and reliance have filtered down into the African region as reflected through the informal consultations initiated at the International Conference of Drug Regulatory Authorities (ICDRA), held in Bern, Switzerland, in September 2008. As a result of these discussions a WHO concept paper was developed to institute the African Medicines Registration Harmonization Initiative (AMRHI) to support the harmonisation of medicine registration within and across Africa (Azatyan, 2009). It is further anticipated that the African Medicines Agency (AMA) may be established in order to further support the regulatory systems of NRAs and build regulatory capacity within the region (Ndomondo-Sigonda et al., 2017).

The drive for the establishment of a more effective regulatory framework in South Africa has been evident for the past two decades. In June 2017 the Medicine and Related Substances Act, 1965 (Act 101 of 1965), was amended to allow for the transition of the MCC to the South African Health Products Regulatory Authority (SAHPRA). This new era, promising regulatory re-form, provided an opportunity to study the past practices of the South African NRA, with a view to enhancing regulatory operations and the responsiveness of the NRA to the advancing new regulatory landscape. Similarly, to other NRAs, SAHPRA is working towards the development and improvement of its regulatory capacity. At a workshop convened by the CIRS, on the Risk-Based Evaluation of Medicines, held in Sao Paulo, Brazil in 2017, many NRAs expressed an interest in applying risk-based evaluation approaches focused on reliance models that leveraged on the work by other trusted NRAs. Steps for the practical implementation of such models are key to understanding how NRAs may apply these mechanisms and is something that SAHPRA is also exploring. As SAHPRA moves forward with its objective for regulatory reform it is important that the

agency has the relevant capabilities and decision-making frameworks in place to ensure the efficient application of resources, with a view to improve median approval times and patients' access to medicines.

# AIM AND OBJECTIVES OF THE STUDY

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**AIM**

The aim of the study is to evaluate the regulatory environment in South Africa with a view to improve the review process and patients' access to medicines.

**OBJECTIVES**

- Review the historical context supporting the new regulatory environment in South Africa and the transition from the MCC to SAHPRA;
- Evaluate the regulatory review process for NASs in South Africa through consideration of key milestones, timelines and scientific assessment models;
- Evaluate trends in the review of approved NASs in South Africa during the period: 2015-2018;
- Compare the regulatory review practices of SAHPRA with other similar emerging economy NRAs;
- Determine how the implementation of an appropriate benefit-risk framework may support a streamlined review process, coupled with improved timeliness and increased consistency and transparency;
- Provide recommendations for the implementation of an abridged review process and a framework for GRelPs; and
- Develop a proposed improved model for the regulatory review process of NASs for SAHPRA.

# CHAPTER 2

## Study Rationale and Methodological Framework

**STUDY RATIONALE**

National regulatory authorities (NRAs) are tasked with the evaluation of the safety, quality and efficacy of medicines. Following a successful assessment, a medicine will be registered by the NRA and given market authorisation. Timely patients' access to new medicines is a key pillar in any health care system. NRAs are responsible for their regulatory performance and ensuring assessment of new medicines within target timelines. Many NRAs face challenges in meeting these targets and this undoubtedly affects patient's access to new medicines. The NRA in South Africa has faced similar challenges and a large backlog has developed in the registration of new medicines in South Africa. As such, key elements for consideration in this research include the application of strategies, frameworks and systems that may be applied to improve the regulatory performance of the South African NRA and ensure timely patients' access to new medicines. These include: risk-stratification approaches and facilitated regulatory pathways which would be an advantage when considered in line with the recommendations of the WHO; embracing regulatory harmonisation and convergence strategies; engaging in reliance and recognition activities, that allow NRAs in resource-limited settings to consider or accept regulatory decisions made by other comparable NRAs in an effort to reduce regulatory burden and avoid duplication of regulatory effort; the application of an appropriate framework for benefit-risk assessment to enhance consistency in the clinical assessment of medicines; ingraining the principles of GRevPs in routine regulatory undertakings and building quality into regulatory decision-making to reinforce transparency. Similar research in this field has demonstrated that NRAs are able to improve their regulatory performance and accelerate the timelines for the approval and registration of new medicines.

The first chapter of this programme of research has described the emergence of the regulatory system and has provided a review of the global regulatory environment. The fundamental elements of the regulatory review process have been explored and strategies for regulatory system strengthening have been identified. The regulatory environment in South Africa has been reviewed and insight into the historical challenges and opportunities experienced by the MCC has been provided. It has provided an account of the evolution of the legislative framework, supporting the regulatory system, in South Africa and the developments that led to the establishment of SAHPRA. Previous studies evaluating the regulatory performance of mature NRAs

have been conducted and comparisons between NRAs of similar scope and size have been performed.

This programme of research will be the first to provide a review of the historical context and legislative amendments that have supported the regulatory system in South Africa and driven the movement for the establishment of a new NRA in South Africa. This research will also be the first to evaluate the regulatory review process applied by the MCC and the juxtaposition thereof against comparable NRAs. This review will be the first to be carried out in determining the current practices of NRAs in performing an abridged review of a NAS while considering the practicality of the implementation of good reliance practices (GRelPs) and how these principles and practices may be applied in the South African context. An assessment of the approach initiated by SAHPRA to document and communicate the BR decision will be coupled with these studies.

Following a review of the published literature, an analysis of the progression and proactive legislative amendments of the regulatory framework in South Africa and a critical analysis of eight years of experience working within the NRA of South Africa, it became evident that the focus of this study will be to evaluate the regulatory landscape in South Africa with a view to improve patients' access to medicines.

Based on the information reviewed so far, it is proposed that studies will be carried out to:

- Review the evolving legislative regulatory landscape in South Africa over the past two decades and the quintessential statutory drive that lead to the establishment of the newly established SAHPRA (Study 1)
- Assess the organisation of the MCC and the regulatory review process applied by the MCC and identify the GRevPs actively codified within the MCC's regulatory system (Study 2)
- Evaluate the regulatory performance of the South African NRA during the period 2015-2017 under the auspices of the MCC and 2018 during the transition to SAHPRA (Study 3)
- Compare the MCC registration process with that of similar NRAs in Australia, Canada, Singapore and Switzerland (Study 4)

- Evaluate the BR framework and decision-making practices (Study 5)
- Assess the framework for an abridged review using GRelPs and how the application of such a framework may optimise the regulatory review process in South Africa (Study 6)
- Develop recommendations for a proposed improved model for regulatory review for SAHPRA

These areas of focus have led to the design of six studies that are to be completed through this programme of research. The results from these studies will be analysed and will culminate in the development of a set of recommendations that may be adopted by SAHPRA with a view to enhance its regulatory performance and ensure timely patients' access to medicine. The study rationale and methodological framework applied in conceptualising these studies have been documented throughout this chapter.

**Conceptual framework**

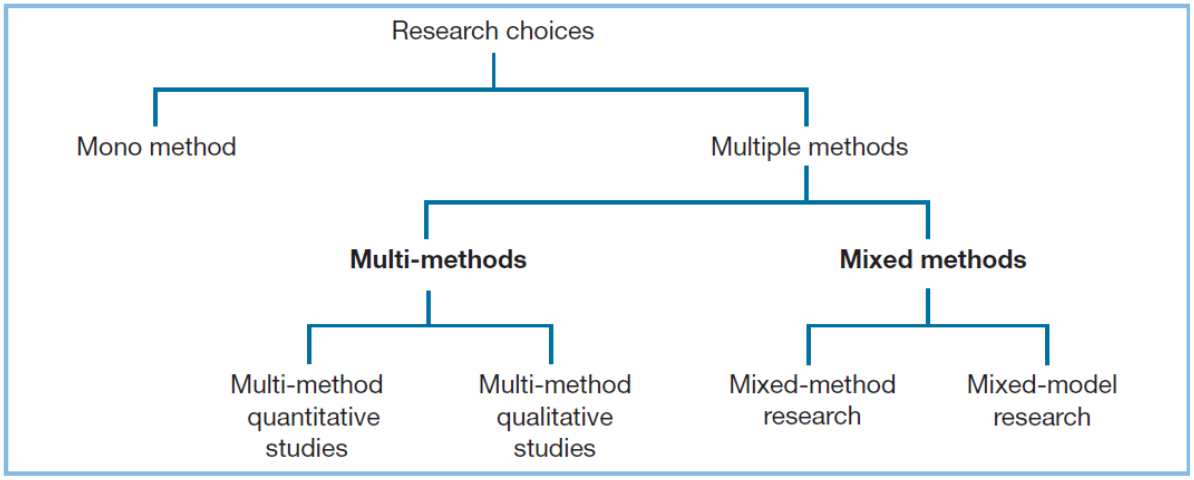
The purpose of research may be either exploratory, descriptive or explanatory (Saunders et al., 2009). Exploratory studies are used in order for the researcher to gain a better understanding of a problem (or research question) that has been identified. Exploratory research may be conducted by means of literature reviews, focus group discussions or interviews with the relevant experts in order to identify the precise nature of the problem (Saunders et al., 2009). Through the use of exploratory studies, the researcher may be able to narrow the initially broad focus of the research as it progresses. The main advantage of exploratory studies is the inherent flexibility lent to the enquiry without the loss of direction to the enquiry (Saunders et al., 2009). Explanatory studies require the researcher to draw conclusions based on the relationships identified between variables, as supported by quantitative or qualitative data (Saunders et al., 2009). Descriptive studies require the researcher to identify the data to be described before collecting the data. Descriptive studies require the researcher to draw further conclusions from the descriptive data that has been collected (Saunders et al., 2009). Descriptive studies are often considered to be supplementary to exploratory or explanatory studies. Considering the paucity of the research topic identified, this research project will be exploratory in nature in a manner that supports hypothesis generation as opposed to hypothesis testing.

## METHODOLOGICAL FRAMEWORK

### Research methods

The choice of a research method is related to how the researcher uses quantitative and qualitative data, or the combination thereof, in the collection and analysis of data. Quantitative research relates to the collection of numerical data and the analysis thereof using statistical tests in the case of “hypothesis testing” design and descriptive statistics and graphs in the case of the “exploratory or hypothesis generating” design (Saunders et al., 2009). Whilst, qualitative research relates to the collection of non-numerical data and the analysis thereof in order to generate descriptions and opinions (Saunders et al., 2009). Such approach could also be exploratory or hypothesis generating. Furthermore, the research method choice relates to the decision to use a mono-method (the single use of either quantitative or qualitative methods) or multiple-method (the mixed use of quantitative or qualitative methods) (Saunders et al., 2009). The different choices of research methods are illustrated in Figure 2.1.

**Figure 2.1 Research method choices**




*Adopted from Saunders et al., 2009*

### *Selected research method*

A mixed methods approach, incorporating both quantitative and qualitative research methods will be applied. The mixed methods approach was selected in order to harness the strengths of both qualitative and quantitative research methods and provide a broader perspective on the research question. This research method

provides an opportunity for observational exploration through qualitative research which may then be validated or invalidated using analytical tools provided by quantitative research methods. Quantitative research methods will be used in Study 3 to perform a statistical analysis of the data collected on the overall approval time lines achieved by the MCC and SAHPRA, for NASs between 2015-2017 and 2018, respectively. The results from the quantitative research will provide a baseline for assessing the changes and improvements within SAHPRA going forward.

Qualitative methods including questionnaires and focus groups will be conducted as follows:

- A systematic and narrative literature review will be considered as part of Study 1 to identify prior initiatives aimed at establishing an improved regulatory framework in South Africa as well as risk stratification approaches adopted by other NRAs
- A questionnaire (McAuslane et al., 2009; CIRS, 2019) will be used in:
    - Study 2 to evaluate the MCC in terms of the requirements and the current model used for the regulatory review, the process for managing timelines, current review times and the application of GRevPs; and
    - Study 4 in the evaluation of the MCC's regulatory review process as compared with the regulatory agencies in Canada, Australia, Switzerland and Singapore
- A questionnaire (CIRS, 2017; McAuslane, 2019) will be used in Study 6 to identify the criteria and current practices that were applied by NRAs for implementing an abridged review process
- Focus group discussions will be conducted as part of Study 5 and Study 6.

**Study participants**

While there are six studies within this programme of research, only four of the studies required the recruitment of study participants. An overview of the study participants recruited for this research is summarised in Table 2.1.

## Table 2.1: An overview of the study participants

| Study | Study Participants |
|---|---|
| **STUDY 2**<br>Evaluation of the regulatory review process in South Africa | QUESTIONNAIRE<br>▪ Registrar of Medicines for the MCC |
| **STUDY 4**<br>Comparison of regulatory review processes of the MCC as compared with the regulatory agencies in Canada, Australia, Switzerland and Singapore | QUESTIONNAIRE<br>▪ Therapeutic Goods Administration (Australia)<br>▪ Health Canada (Canada)<br>▪ Health Science Authority (Singapore)<br>▪ Swissmedic (Switzerland)<br>▪ MCC (South Africa) |
| **STUDY 5**<br>Assessment of a benefit–risk framework and decision making practices | FOCUS GROUP<br>▪ Moderator<br>▪ Rapporteur<br>▪ Approximately 12 participants representing regulatory authorities, industry, health technology assessment groups and patient groups |
| **STUDY 6**<br>Evaluation of the implementation of a framework for an abridged review using good reliance practices | QUESTIONNAIRE<br>▪ Therapeutic Goods Administration (Australia)<br>▪ Health Canada (Canada)<br>▪ ANVISA (Brazil)<br>▪ Gulf Health Council (Gulf Cooperation Council)<br>▪ Ministry of Health (Israel)<br>▪ Thai Food and Drug Administration (Thailand)<br>FOCUS GROUP<br>▪ Moderator<br>▪ Rapporteur<br>▪ Approximately 12 participants representing regulatory authorities, industry, health technology assessment groups and patient groups |

Abbreviations: ANVISA=Agência Nacional de Vigilância Sanitária; MCC=Medicines Control Council

### Study design

When considering the study design to be employed for this research it is critical to ensure that the selected study design will yield suitable evidence upon which appropriate logical and scientific conclusions, relating to the research question and objectives, may be drawn.

### Time horizon

The time horizon relates to the timescale within which the research will be conducted. Cross-sectional research refers to the "study of a particular phenomenon at a particular time" (Saunders et al., 2009, p.148). Longitudinal research refers to the collection of data over an extended period of time resulting in a rich, comprehensive and representative source of data (Saunders et al., 2009).

#### *Selected time horizon*

The cross-sectional study approach was selected as it allows the researcher to collect data at a single point in time and employs a survey technique (Saunders et al., 2009) to achieve the aims and objectives of this programme of research. In addition, a retrospective approach will be applied in the data collection and analysis of the regulatory performance metrics of the MCC (2015-2017) and SAHPRA (2018).

## DATA SOURCE

In order to achieve the objectives of this research, data will be collected from the public domain as well as directly from representatives from NRAs, industry, Health Technology Assessment (HTA) groups and patient groups from different jurisdictions. The inclusion and exclusion criteria for data sources have been determined as follows:

### Inclusion criteria

A questionnaire technique (see Appendix 1) will be used to collect the data required to evaluate the MCC regulatory review process and compare the MCC registration process with that of similar NRAs.

For the evaluation of the regulatory performance of the South African NRA the primary inclusion criteria were related to data for NASs, including NCEs, biologicals and MLEs, only. The data will be obtained directly from the NRAs and reflect the timelines

between the various milestones of the review process, including dossier validation and queue time, scientific assessment as well as the overall approval times for NASs registered by the South African NRA during the period 2015-2018. Another questionnaire technique (see Appendix 2) will be used to obtain data directly from a number of NRAs in order to assess the framework for an abridged review using GRelPs and how the application of such a framework may optimise the regulatory review process in South Africa.

**Exclusion criteria**

Data related to generic medicines, complementary medicines and veterinary medicines will be excluded from this study.

**Public domain sources**

Published literature, available in the public domain, will be obtained through various search engines such as bibliographic databases (e.g. PubMed), Open Access and Google Scholar. Scientific journal articles and textbooks will be examined and the information obtained from the websites of NRAs, guidelines of organisations such as the WHO, Pan American Health Organization (PAHO) and ICH as well as presentations made during regulatory conference proceedings will be surveyed for the purposes of this research.

## DATA COLLECTION TECHNIQUES

Techniques for both quantitative and qualitative data collections have been appraised. The most appropriate data collection techniques considered for this research were selected based on a review of their strengths, weaknesses and the applicability of such techniques to achieve the research objectives for each of the studies that will be conducted throughout this programme of research.

**Literature review: systematic and narrative**

A literature review will be performed in order to gain an understanding of the global and local regulatory environment and the challenges and opportunities identified in the regulatory review of medicines. Conducting a literature review will allow for an exploratory search of other studies related to the enhancement of regulatory

performance and obtaining validated tools such as surveys or questionnaires, from the public domain, that may be used to contribute to the studies within this research.

The advantages and disadvantages of both systematic and narrative literature reviews were considered. The comparison of these two types of literature reviews is outlined in Table 2.2.

**Table 2.2 Comparison between systematic and narrative literature reviews**

| | Systematic reviews | Narrative reviews |
|---|---|---|
| Hypothesis | Clearly-defined or well-formulated clinical or basic research topic or question. | Broad overview of a topic-related research area. |
| Search method | Predefined protocol-based | Not predefined protocol-based: involving subjective selection bias |
| Inclusion of studies for review | Predefined selection criteria as per the authors' hypothesis | Authors' intuition and research experience |
| Search media | Diverse search engines | Mainly PubMed or Medline data base |
| Data extraction | Protocol-based: Continuous or categorical statistical values | Not protocol-based: Simple description of study findings |
| Data synthesis | Based on data extraction and synthesis guidelines such as PRISMA | Overall description of each study, mainly focusing in studies that authors selected |
| Data quality | Grading by guidelines available in multiple resources | Partially objective grading by anecdotal resources |
| Interpretation | Based on data included | Easily biased by authors' subjective intention |

Abbreviation: PRISMA=Preferred Reporting Items for Systematic reviews and Meta-Analyses
*Adopted from Chi-Un, 2015*

- A **systematic literature review** may be used to summarise a large volume of information and provide an explanation of the differences observed amongst studies examining the same question (Cook et al., 1997). Scientific strategies are employed during a systematic review in order to ensure an unbiased appraisal of the relevant studies that address the research question (Cook et al., 1997).
- A **narrative literature review** relies on the use of informal methods. Narrative reviews allow the researcher to gain a more comprehensive overview of the research topic however subjective selection bias may be evident in the collection and interpretation of data (Chi-Un, 2015).

***Selected data collection using a narrative literature review***

Following a consideration of the advantages, disadvantages and relevance of both systematic and narrative literature reviews, it was decided that a narrative literature review would be best suited for the purpose of this research. A narrative literature review will be conducted as part of an exploratory search of the global regulatory landscape and the challenges faced by NRAs in achieving goals for enhanced regulatory performance. The learnings from the narrative review will be developed into Chapter 1: General Introduction. Bibliographic databases will be searched and key search words to be included are: GRPs, regulatory performance, milestones, regulatory review process, risk-based review and best practices. The results from the initial narrative review will serve to pre-empt the refined search criteria applied to a more complex narrative review. Diverse search engines, including bibliographic databases and Google will be used to conduct a systematic review. The review will be conducted using a protocol-based search method to answer the pre-defined research question. The review will be conducted in order to identify existing tools, questionnaires and studies that may be applied to evaluate the regulatory performance of an NRA and the review practices of NRAs. The review will be limited to articles available in the English-language.

Structured search terms will be developed and used in the search of databases against the following criteria:

- For inclusion: (1) All articles related to a specific tool, questionnaire or study used to evaluate the regulatory review process and regulatory review practices; (2) studies that assess the regulatory performance of NRAs; (3) studies that draw comparisons between NRAs of similar size and scope.
- For exclusion: (1) General discussions relating to GRPs; (2) tools, questionnaires or studies that are not directly related to the regulation of medicines.

In order to prevent any bias stemming from the author's subjective intention, an independent secondary review will be performed. The secondary review will inform objective article selection and data collection.

**Questionnaire techniques and focus groups**

Data collection tools such as questionnaires, interviews and focus groups will be employed to collect data from representatives of NRAs, HTA groups, industry and academia:

***Questionnaires***

Saunders et al. (2009) describe a questionnaire technique as a research technique "that involves the structured collection of data from a sizeable population" (p.640). A questionnaire is a data collection technique in which the sample set is required to respond to a series of standardised questions in a pre-determined order, thus enabling the researcher to draw comparisons from the results obtained within the sample set (Saunders et al., 2009). For the purpose of this research, self-administered questionnaires will be used and will be distributed electronically to study participants (Figure 2.2). The use of self-administered questionnaires is beneficial in terms of the limited resources required to facilitate distribution, the large sample size that may be reached and minimises bias (Saunders et al., 2009). The disadvantage of this type of questionnaire is the risk of a low response-rate and the limitations experienced by participants who might need to seek clarification for certain questions in an attempt to provide the most accurate response.

*Questionnaire development*

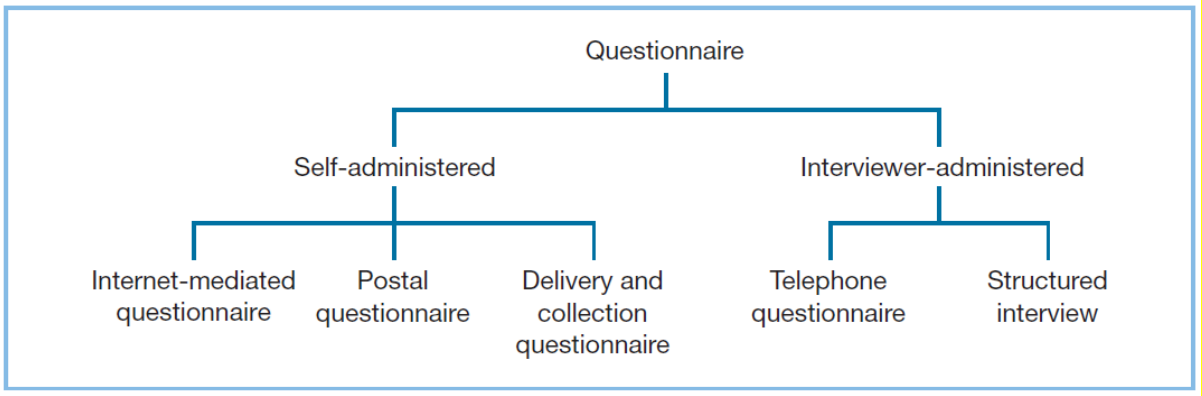
Two different validated questionnaires will be used for the purpose of this research (McAuslane et al., 2009; CIRS, 2019). The questionnaires will be completed by representatives from NRAs.

- **Study 2 and Study 4:** The questionnaire (see Appendix 1) considered for these two studies (McAuslane et al., 2009; CIRS, 2019c) was initially developed to support the evaluation of the regulatory review process in emerging markets and the impact of these processes on patients' access to medicines (McAuslane et al., 2009). Prior to its use in this programme of research, it was reviewed and determined to be applicable in meeting the study objectives. The questionnaire will be distributed electronically to the representatives from the participating NRAs. The questionnaire is aimed to evaluate the structure and

organisation of NRAs, identify the milestones within the regulatory review process and determine the level of implementation of GRevPs. The data from the completed questionnaires will be analysed using descriptive statistics.

- **Study 6:** The second questionnaire (see Appendix 2) (CIRS, 2017; McAuslane, 2019) will be administered to identify the criteria and current practices applied by NRAs for implementing an abridged review process. Prior to use in this programme of research, this questionnaire was reviewed and determined to be applicable in meeting the study objectives.

**Figure 2.2 Types of questionnaires**




*Adopted from Saunders et al., 2009*

***Focus groups***

Focus groups are exploratory tools that may be used to collect an appropriate amount of data within a short time frame (Freitas et al., 1998). Focus groups may be used to generate qualitative data. The focus group consists of participants with homogenous research interests discussing a specific topic that is prescribed by the research objectives (Freitas et al., 1998). The advantages and disadvantages of using focus groups are described in Figure 2.3.

**Figure 2.3 The advantages and disadvantages of focus group**

| Advantages | Disadvantages |
|---|---|
| • It is comparatively easier to drive or conduct<br>• It allows to explore topics and to generate hypotheses<br>• It generates opportunity to collect data from the group interaction, which concentrates on the topic of the researcher's interest<br>• It has high "face validity" (data)<br>• It has low cost in relation to other methods<br>• It gives speed in the supply of the results (in terms of evidence of the meeting of the group)<br>• It allows the researcher to increase the size of the sample of the qualitative studies | • It is not based on a natural atmosphere<br>• The researcher has less control over the data that are generated<br>• It is not possible to know if the interaction in group he/she contemplates or not the individual behavior<br>• The data analysis are more difficult to be done. The interaction of the group forms a social atmosphere and the comments should be interpreted inside of this context<br>• It demands interviewers carefully trained<br>• It takes effort to assemble the groups<br>• The discussion should be conducted in an atmosphere that facilitates the dialogue |

*Adopted from Krueger, 1994 and Morgan, 1988*

Focus groups are typically made up of ten to 12 participants that are either experts in the discussion topic, or are knowledgeable and have experience with the discussion topic (Breen, 2006). Focus group discussions are led by a moderator that guides the participants through a set of pre-determined questions and in doing so facilitates the generation of qualitative data.

Self-administered questionnaires will be used during this research in order to obtain information from NRAs regarding their regulatory review processes (Study 2 and Study 4) (CIRS, 2019c) and their current practices in applying an abridged review of medicines (Study 6) (CIRS, 2017). The results obtained from the questionnaires will allow for ease of comparison amongst the NRAs participating in the studies. The questionnaires will be sent electronically to representatives from each of the identified NRAs. Given the geographical spread of the participants and the researcher, this method of distribution will conserve resources.

The focus group technique will be applied to explore and identify the use of PARs as potential knowledge management tools for stakeholders in understanding a reference agency's decision making (Study 5); and the practical implementation of an abridged review process for new medicines in the light of the WHO's GRelPs (Study 6).

**Case study**

The case study is defined as “a strategy for doing research which involves an empirical investigation of a particular contemporary phenomenon within its real life context using multiple sources of evidence” (Robson, 2002, p.178). Survey or experiment strategies are considered to be more scientifically rigorous than case studies, however case studies may be a valuable source in generating new research questions (Saunders et al., 2009). Case studies may be categorised into single case or multiple case. Multiple case studies are preferred over single case studies as often they are applied across multiple organisations or individuals and generalisations across the multiple cases can be made (Saunders et al., 2009).

***Selected case study***

A multiple case study approach will be applied in Study 5 when comparing the PARs from four reference agencies against the UMBRA BR template (Walker et al., 2014). Attempts will be made to identify generalisations across the four PARs and then will be compared with the approach initiated by SAHPRA to document and communicate the BR decisions.

***A summary of the selected data collection techniques***

Table 2.3 provides a summary of the data collection techniques that have been selected for the purpose of this research and the relevant research objectives and studies to which these will be applied.

**STUDY PLAN**

The study plan (Figure 2.4) illustrates the commencement of the research with a literature review (Study 1), followed by conceptualisation of the studies, coupled with the development of the study question and study design. A questionnaire (see Appendix 1) will be used to evaluate the regulatory review process for NASs in South Africa through consideration of key milestones, timelines and scientific assessment models (Study 2). The same questionnaire will also be used in the comparison of the regulatory review practices of SAHPRA with other similar NRAs (Study 4).

## Table 2.3 Summary of the planned data collection techniques

| Data collection technique | Research Objectives | Thesis Chapter |
|---|---|---|
| **Narrative literature review** | **General Introduction**<br>Review of the global regulatory environment | Chapter 1 |
| **Narrative literature review** | **Review of the regulatory environment in South Africa** | Chapter 3<br>**(Study 1)** |
| **Self-administered questionnaires** | **Evaluation of the regulatory review process in South Africa** | Chapter 4<br>**(Study 2)** |
| | **Comparison of the Medicine Control Council's Regulatory Review Processes with Australia, Canada, Singapore and Switzerland**<br>Evaluation of MCC'S regulatory review process as compared with the regulatory agencies in Canada, Australia, Switzerland and Singapore | Chapter 6<br>**(Study 4)** |
| | **Recommendations for the implementation of a model for regulatory reliance in South Africa**<br>An overview of the principles of good reliance practices and recommendations for the implementation of a model for good reliance practices in South Africa | Chapter 8<br>**(Study 6)** |
| **Focus Group** | **Assessment of a benefit–risk framework & decision making practices**<br>An evaluation of the UMBRA framework as applied in the South African context and the feasibility of incorporating quality decision-making practices within SAHPRA | Chapter 7<br>**(Study 5)** |
| | **Recommendations for the implementation of a model for regulatory reliance in South Africa**<br>An evaluation of the implementation of a framework for an abridged review using good reliance practices | Chapter 8<br>**(Study 6)** |
| **Case Study** | **Assessment of a benefit–risk framework & decision making practices**<br>An evaluation of the UMBRA framework as applied in the South African context and the feasibility of incorporating quality decision-making practices within SAHPRA | Chapter 7<br>**(Study 5)** |

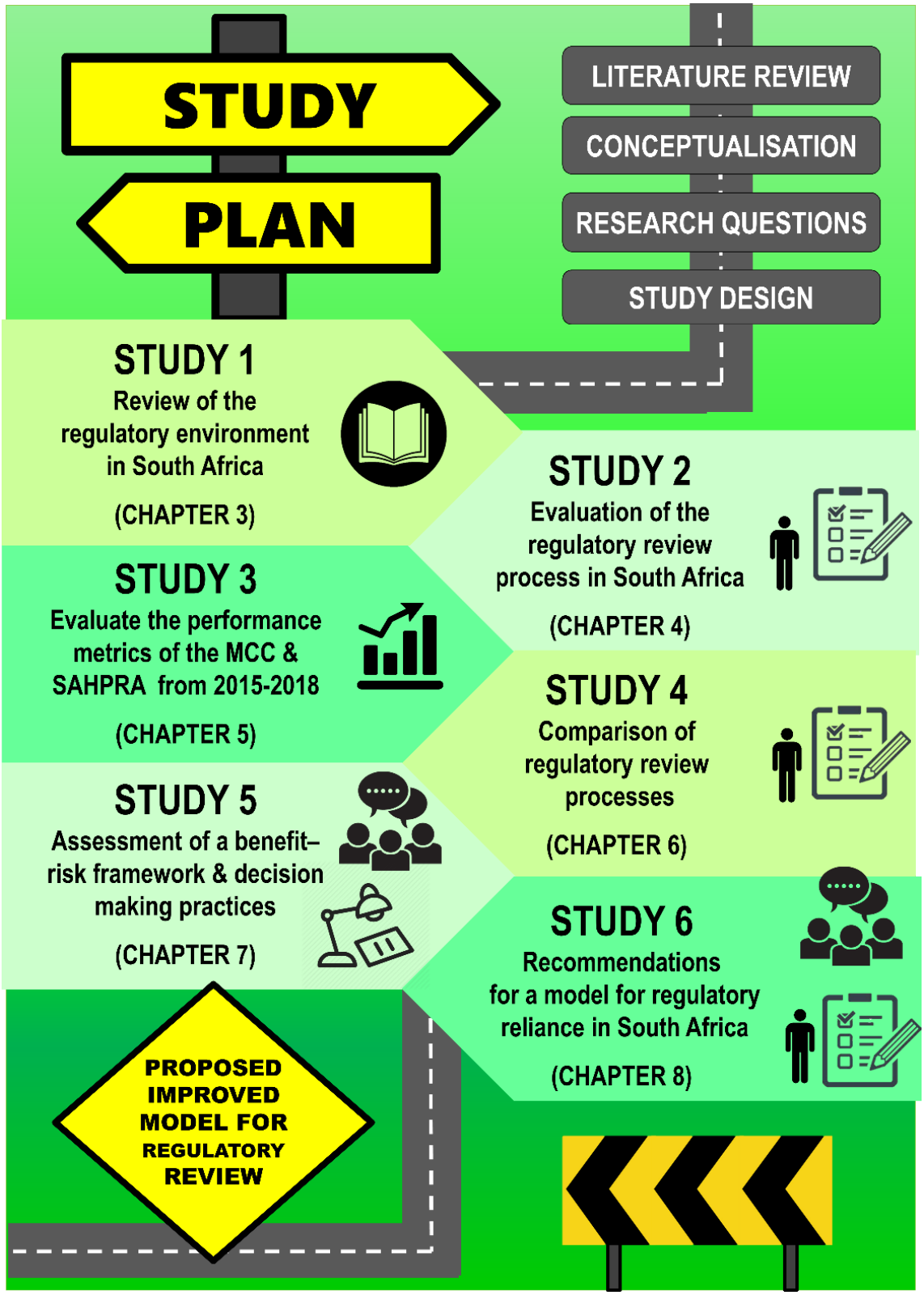
Abbreviations: MCC=Medicines Control Council; SAHPRA=South African Health Products Regulatory Authority; UMBRA=Universal Methodology for Benefit-Risk Assessment

Data collected directly from the South African NRA, in the form of performance metrics for the overall approval timeline for NASs will be used to evaluate trends in the review of approved NASs in South Africa during the period 2015-2018. A second questionnaire (see Appendix 2) will be used to identify the criteria and current practices that were applied by NRAs for implementing an abridged review process (Study 6). Focus group sessions will be held to explore the use of PARs as potential knowledge management tools for stakeholders in understanding a reference agency's decision-making (Study 5) and determine the practical implementation of an abridged review process for new medicines in the light of the WHO's GRelPs (Study 6). It is hoped that the analysis of the results from these six studies will culminate in a set of key recommendations for the proposed improved model for regulatory review for SAHPRA and improved patients' access to medicines. These recommendations will be further explored in Chapter 9, General Discussion.

**DATA PROCESSING AND ANALYSIS**

Qualitative data will be generated through the application of questionnaires and focus groups discussions. No statistical tests will be used to analyse the qualitative data collected in the exploratory studies (Study 1, 5 and 6). Conclusions drawn from hypothesis generating qualitative data may be considered for future research. The quantitative data collected in Study 2, 3 and 4 will be entered into Microsoft Excel for data analysis. The results of these analyses will be presented using descriptive statistics such as medians and upper and lower quartiles. The results may also be presented graphically in order to provide visual comparisons and illustrate relationships between variables. Time series analysis will be used to analyse the time series data collected in Study 3, which reflects the number of NASs registered by the MCC, per quarter, in the period 2015-2017. The ratio-to-moving-average method will be used to calculate seasonally adjusted indices for each quarter in the period 2015-2017. This method was selected because it is widely used to measure seasonal variation and integrate trends into forecasting. As the scope of Study 3 is exploratory in nature and not designed to support hypothesis testing, no further statistical analysis of the generated data will be performed.

**Figure 2.4 Study plan**



The data generated through the six studies contained within this programme of research will be processed and analysed using several methods. The data analysis for each study and the results thereof will be documented across six separate chapters. The key recommendations stemming from these chapters will be consolidated into a set of key recommendations for the proposed improved regulatory review model for SAHPRA.

**ETHICAL APPROVAL**

Ethics approval was obtained from the University of Hertfordshire. This programme of research did not require the national research ethics committee approval.

**SUMMARY**

- This chapter describes the study rationale and provides an outline of the six proposed studies that are to be conducted in order to achieve the research aim and objectives

- The study purpose was described to be exploratory in nature in a manner that supports hypothesis generation as opposed to hypothesis testing

- The data collection techniques used throughout this programme of research were described and valued in terms of the study objectives. As a result, the data collection techniques used included literature review, the use of validated questionnaires, a focus group approach and a case study

- The methodologies applied in the analysis of the data obtained from the South African NRA, comparable NRAs and focus group participants were described

- The data collected during this research was grouped and examined in three major areas, namely:
    - the regulatory review process and the associated milestones and timelines for review (Study 1-4);
    - the assessment of a benefit-risk framework and decision-making practices (Study 5); and
    - recommendations for the implementation of a framework for an abridged review using GRelPs (Study 6)

- A detailed study plan was outlined to illustrate the relationship between the six studies conducted and the aims and objectives of the research programme

# CHAPTER 3

## Review of the Regulatory Environment in South Africa

## INTRODUCTION

Ensuring effective medicine regulation through the strengthening of regulatory systems and improvement of regulatory performance has become a priority for both NRAs and governments worldwide. With the support of government, NRAs are responsible for protecting and promoting public health, implementing rigorous regulatory standards and maintaining an assured supply of medical products that are safe, effective and of good quality (Rägo & Santoso, 2008; WHO, 2018a; Ndomondo-Sigonda et al., 2017). Despite the critical role that NRAs play within national healthcare systems the importance of medical product regulation often goes under-recognised and is often under-funded (Rägo & Santoso, 2008). The WHO has indicated that almost a third of NRAs do not have the capacity to perform core regulatory functions and would not be able to sustain effective regulatory systems without adequate financial support (WHO, 2003).

Global trends toward increased pressure on NRAs of all sizes and capacity due to the increased volumes of applications received, the complexity of the submissions and the increased number of categories of medical products have been noted (WHO, 2014b). These trends and statistics resonate with many NRAs in low- and middle-income countries that have historically been faced with resource constraints (WHO, 2014a) and that have not participated in global harmonisation initiatives or development programs aimed at strengthening regulatory systems (Preston et al., 2012). Efforts to address the challenges faced by NRAs in resource-limited settings have focused on identifying and performing core regulatory functions that have to be undertaken directly by NRAs to meet country or regional needs (WHO, 2014b; Ward, 2014). National regulatory authorities (NRAs) have also been encouraged by the WHO to consider regulatory convergence and to collaborate with and recognise work done by other regulators to ease the regulatory burden (WHO, 2014b; Ward, 2014).

Resolution WHA67.20 emanating from the Sixty-seventh World Health Assembly (WHA) in 2014 identified the need for effective regulatory systems and highlighted that “inefficient regulatory systems create barriers for access to safe, effective and quality medical products” (WHA, 2014, p1). The drive for improved regulatory systems and the establishment of a more effective regulatory framework in South Africa has been

evident for the past two decades but despite political intentions and legislative revisions success has been limited to date.

It is suggested that while multi-factorial elements have resulted in a backlog in medicines registration, significant pro-access policies compounded by legislative requirements for the expedited review of medicines on the Essential Drugs List (EDL), most of which are generics, may be at the root of the problem (Leng et al., 2015). Efforts to address the increasing volume of applications that have been received have to date failed and resources have been stretched to capacity resulting in the development of a significant backlog and extended timelines for product registration. The median approval times for fast track applications approved by the MCC in 2015, 2016 and 2017 were 1218, 921 and 609 calendar days respectively. There was no target time set for the overall review time of new chemical entities (NCEs) and the median approval times for NCE marketing authorisation applications approved in 2015, 2016 and 2017 were 1175, 1641 and 1466 calendar days respectively. These data demonstrate that the MCC was not able to achieve the target timelines of 250 calendar days set for fast track applications nor meet the targets in 2015, 2016 and 2017 for the key milestones within the regulatory review process.

Pharmaceutical companies, private clinical research organisations, academic clinical research groups and civil society organisations have complained that delays and the backlog in medicines registration were harming patients' access to affordable medicines (Leng et al., 2015). It has been reported that prior to 2005 the number of applications received and the number of registration certificates issued were in equilibrium, however from 2005 the number of applications submitted more than doubled whereas the number of certificates issued remained approximately the same (Leng et al., 2015).

The South African NRA has a historical average of receiving approximately 4700 applications per year but has demonstrated that it can only process approximately 2550 applications per annum (SAHPRA, 2018a). SAHPRA inherited a backlog of approximately 16 000 applications that included all applications submitted up to 31 January 2018 which are yet to receive final approval (SAHPRA, 2018a). The SAHPRA Board aimed to clear the backlog within the next two years. Given that more than half

of the new registration applications were at least five years old, the industry were requested to indicate whether they would like to withdraw those applications submitted in 2013 or earlier. Submissions within the backlog need to be consolidated, updated and resubmitted to ensure that those requiring evaluation reflect current data (SAHPRA, 2018a). Applications will be segmented and prioritised according to public health priorities (SAHPRA, 2018a). SAHPRA is committed to operationalise reliance models for product review supported by optimal staffing solutions, implementation of a digitally powered approach to evaluation, effective change management and improved transparency and accountability (SAHPRA, 2018a).

The promulgation of the recently amended Medicines and Related Substance Act, 1965 (Act 101 of 1965) hereafter referred to as the Medicines Act triggered the establishment of SAHPRA as a separate juristic person outside of the National Department of Health to replace the former medicine regulatory authority the MCC. The amended Medicines Act saw the scope of the Authority's mandate extended to make provision for the regulatory oversight of medical devices and complementary medicines in South Africa and to make provision for the Authority to establish and strengthen collaborative initiatives with other regulatory authorities or institutions (Medicines and Related Substances Act 2017).

The aim of this chapter was to provide the historical context supporting the new regulatory environment in South Africa and the transition from the MCC to SAHPRA.

## THE MEDICINES CONTROL COUNCIL

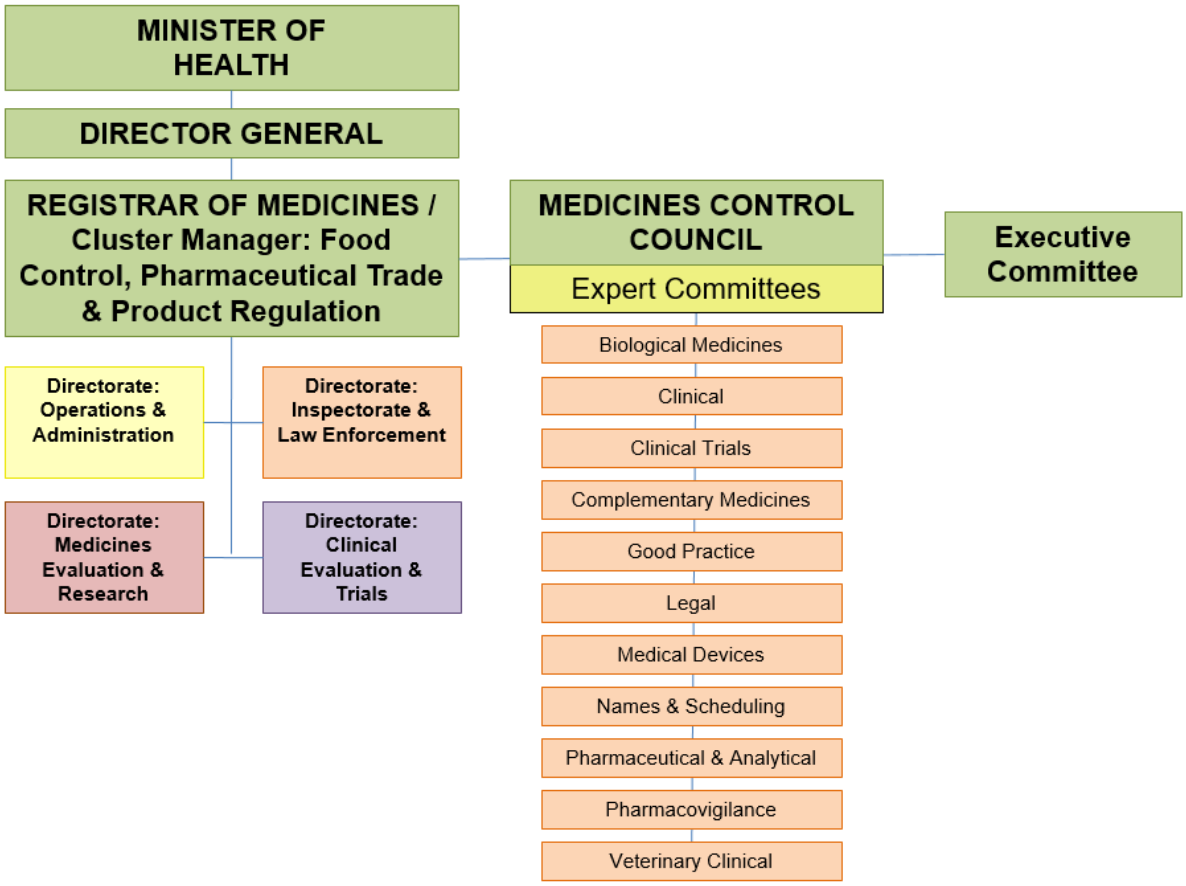
Prior to the establishment of SAHPRA in February 2018 the MCC was the national medicines regulatory authority of South Africa responsible in terms of the Act to provide for the monitoring, evaluation, regulation, investigation, inspection, registration and control of human and veterinary medicines, scheduled substances, clinical trials and related matters in the public interest. The statutory obligations of the MCC were to ensure that medicines that were available in South Africa met the required standards of quality, safety, and efficacy (MCC, 2006).

### Organisational structure

The MCC was a statutory body appointed by the Minister of Health consisting of not more than 24 members including the chairs of the expert committees. In addition, the council appointed external experts to serve on various expert committees overseeing medicine registration, regulation and control functions. Overall there were 11 active expert committees including the Biological Medicines, Clinical, Clinical Trials, Complementary Medicines, Good Practice, Legal, Medical Devices, Names & Scheduling, Pharmaceutical & Analytical, Pharmacovigilance and Veterinary Clinical Committees (MCC, 2017). The skills of the members of the council and its committees were written into law and included expertise in toxicology and medicine safety, basic and clinical pharmacology, biotechnology, pharmaceutics, internal medicine, virology, pharmaceutical chemistry, neonatology, paediatrics, immunology, veterinary science, complementary medicines and law (MCC, 2017).

The Office of the Registrar served as the Executive Secretary to the MCC and provided administrative and technical support to the Council and its activities. The Office of the Registrar was a Chief Directorate within the National Department of Health known as the Cluster: Food Control, Pharmaceutical Trade & Product Regulation. There were four Directorates within the Cluster namely, Operations & Administration, Inspectorate & Law Enforcement, Medicines Evaluation & Research and Clinical Evaluation & Trials. The staff complement of the Cluster included doctors, pharmacists, veterinarians, scientists and administrative staff (MCC, 2017). The MCC organisational structure is depicted in Figure 3.1.

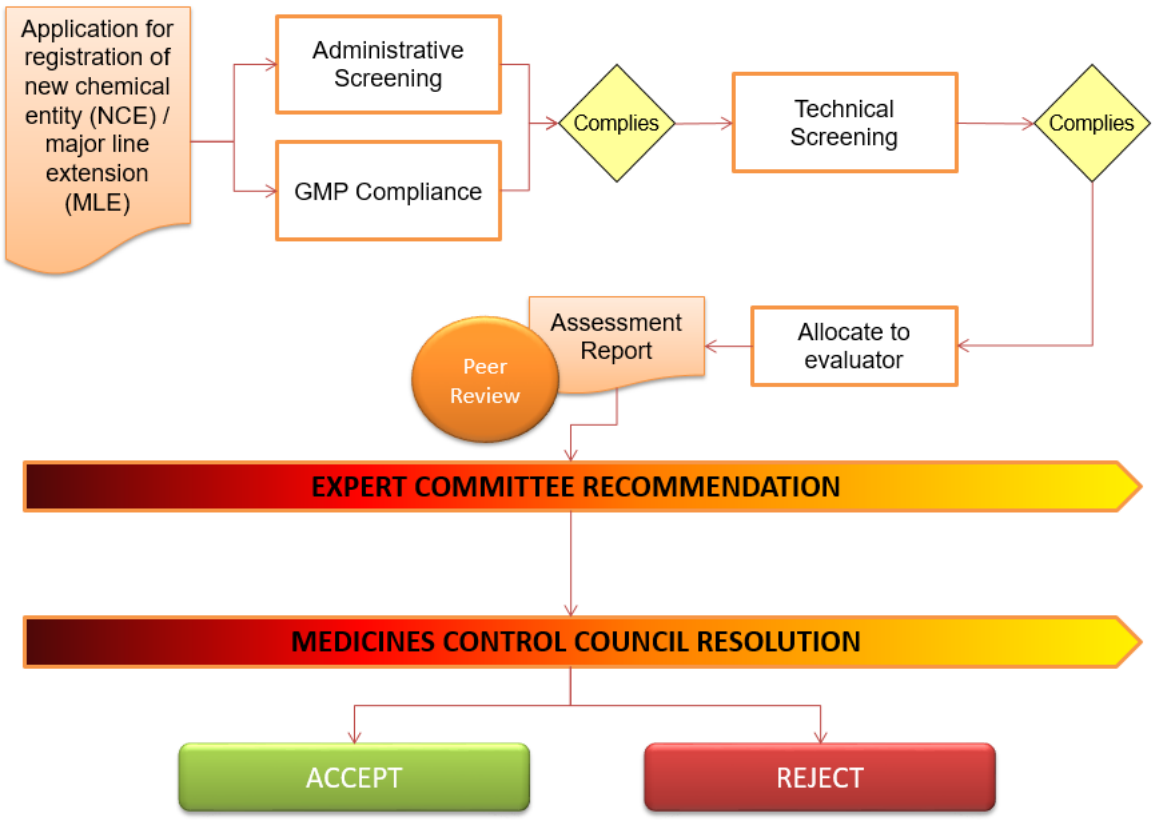
**Figure 3.1 Organisational structure of the Medicines Control Council (MCC)**




## Regulatory review process

The registration of medicines in South Africa is governed by the provisions and requirements of the Medicines Act including the regulations and the published guidelines. Legislative frameworks require that medicines including NCEs, multisource/generic medicines, biological medicines, complementary medicines and veterinary medicines are evaluated by the NRA prior to marketing of the product. Applicants are required to submit technical dossiers to demonstrate the quality, safety, and efficacy of such medicines intended for sale in South Africa. The confidentiality of information submitted to the NRA is governed by Section 34 of the Medicines Act regarding the preservation of secrecy. The regulatory review process of the MCC is presented in Figure 3.2 and provides a simple representation of the review and authorisation of applications that are approved in the regulatory review cycle.

**Figure 3.2 Regulatory review process of the Medicines Control Council (MCC)**




The NRA made use of both internal and external expertise to evaluate applications for the registration of medicines. A full review of the safety, quality, and efficacy data, together with the assessment reports prepared by reviewers were considered by the various expert committees to make recommendations on the approval of the proprietary name of the product, the allocation of a scheduling status for the active pharmaceutical ingredient and the evaluation of the good manufacturing practice (GMP) status of the applicant, the manufacturer of the active pharmaceutical ingredient, the manufacturer of the finished pharmaceutical product, the packer and the quality control laboratory. The final decision for authorisation or refusal was made by the MCC.

**History of enabling legislation**

The introduction of the regulation of medicines in South Africa was initiated in the 1960s when the National Department of Health appointed the Snyman Commission to investigate the high cost of medicines and medical services in South Africa (Snyman,

1965). The report of the Commission of Inquiry recommended that at the time the medicines should be controlled in terms of their purity, safety and therapeutic efficacy (Gouws, 2003, unpublished thesis). These recommendations resulted in the promulgation of the Drugs Control Act, 1965 (Act 101 of 1965) and the establishment of the Drugs Control Council responsible for the control of medicines for human use. The introduction of a registration procedure in 1968 meant that all medicines intended for sale in South Africa were evaluated and approved by the Drugs Control Council prior to entering the market. Medicines available on the market prior to 1968 were initially exempt from these requirements and were referred to as "old medicines". Over the next three decades the legislative framework and regulatory requirements were amended several times to reflect the intentions of the regulatory authority as it strived towards improved control of medicines in South Africa. Some of the important amendments made to the principal Act, the Medicines and Related Substances Act, 1965 (Act 101 of 1965) are listed in Table 3.1 and the historic projects and legislative changes are noted in Table 3.2 (Gouws, 2003, unpublished thesis).

The Amendment Act, 1997 (Act 90 of 1997) was the first legislative amendment to be made to the principal Act following the change of government in South Africa after the general elections held in 1994 (Gouws, 2003, unpublished thesis). With this change came the adoption of a programme for health reform and the launch of the National Drug Policy. This Amendment Act, 1997 was promulgated in 1997 and Section 15C specifically was the subject of a legal challenge by the Pharmaceutical Manufacturers Association (PMA) which prevented the implementation of this Amendment Act, 1997 until 2003 *PMA* v. *President of the Republic of South Africa* (1998). The then Minister of Health, Nkosazana Dlamini-Zuma appointed an advisory panel to review the medicine regulatory environment in South Africa (Dukes et al., 1998). In December 1998 a report titled "Operational and Financial Review - Discussion Draft" prepared by KPMG also endorsed the restructuring of the MCC with the aim of improving operational efficiencies. On the recommendation of the ministerial advisory panel a new Amendment Act (South African Medicines and Medical Devices Regulatory Authority Act 1998*)* establishing the (SAMMDRA) to replace the MCC was passed by Parliament. The SAMMDRA Act was promulgated prematurely without the necessary Regulations and was subsequently set aside *PMA and Another* v. *In re Ex Parte President of the Republic of South Africa and Others* (2000).

In late 2007, yet another decision was taken to restructure the MCC by establishing a new authority as a public entity outside of the National Department of Health. A report on the restructuring of the MCC was presented by a Ministerial Task Team led by Professor Green-Thompson who was appointed as a Special Advisor to the Minister of Health, Manto Tshabalala-Msimang (SAHPRA, 2016). The Green-Thompson Report recommended the establishment of a new NRA to replace the MCC referred to as SAHPRA and emphasised the need for international and regional harmonisation to support reliance and recognition frameworks with other regulatory authorities (Green-Thompson, 2008). This report amongst others recommended extending the regulatory mandate of the authority to include medical devices and highlighted the need to effect BR assessment of medicines and QDMPs to support transparent regulatory decision-making. Regulatory models of other NRAs were benchmarked and a key recommendation from this report informed the need for collection of metrics to facilitate the measurement and monitoring of regulatory performance and the impact of the proposed changes to the regulatory review process (Green-Thompson, 2008). The recommendations of the Green-Thompson report resulted in a further amendment of the principal Act and the Medicines Amendment Act, 2008 (Act 72 of 2008) was signed into law by then President Kgalema Motlanthe in 2009 but not implemented (SAHPRA, 2016). The reason for this was multi-factorial and included the need for strengthened governance and certain transitional provisions.

A project team led by Dr Nicholas Crisp was appointed in 2009 by the Minister of Health, Barbara Hogan to revive legislative endeavours directed towards regulatory reform and the establishment of an improved NRA (SAHPRA, 2016). The remit of this project team was to develop the business case for SAHPRA as well as the transitional mechanisms and the identification of further legislative amendments.

## Table 3.1 Amendments to Drug Control Act 1965

| Amendment Number | Change |
|---|---|
| Amendment Act No 29 of 1968 | ▪ Drugs that were subjected to registration were defined<br>▪ Categories for the classification of these drugs were defined |
| Amendment Act No 88 of 1970<br>Amendment Act No 95 of 1971 | ▪ Made provision for the control of advertising of drugs |
| Amendment Act No 65 of 1974 | ▪ The term “drug” was replaced with “medicine”<br>▪ The Drugs Control Council was changed to the Medicines Control Council<br>▪ The constitution of the Medicines Control Council, remuneration of the Council members and the appointment of the Committees of Council and a Medicines Control Appeal Board was defined |
| Amendment Act No 17 of 1979 | ▪ The mandate of the Act was extended to include the regulatory oversight of veterinary medicines, including the registration, labelling and advertising thereof |
| Amendment Act No 94 of 1991 | ▪ The powers, functions and constitution of the Council were defined<br>▪ The establishment of the Medicines Control Appeal Board was repealed<br>▪ Provisions for an alternative appeal procedure against the decision of the Council were defined |
| Amendment Act No 90 of 1997 | ▪ The Medicines Control Council was established as a juristic person<br>▪ Members of the Council or the Committees were required to declare commercial interests related to the pharmaceutical or health care industry<br>▪ The members of the Executive Committee of the Council, were to be appointed subject to the approval by the Minister of Health<br>▪ Conditions prohibiting the sale of any medicine, which were subject to registration, and which were not registered, were defined |

| | |
|---|---|
| | ▪ Provision for expedited registration of essential medicines<br>▪ Re-registration of medicines every 5 years<br>▪ Provisions for compulsory licensing and parallel importation<br>▪ Provisions to enable generic substitution were defined<br>▪ A Pricing Committee for medicines was established<br>▪ The process of appeal against a decision of the Director-General of Health was defined<br>▪ Provision was made for acquiring of additional funds by the Council<br>▪ The powers of the Minister of Health to make regulations pertaining to the Medicines Act were further defined |
| Amendment Act 59 of 2002 | ▪ Provision was made for the appointment of Deputy Registrars<br>▪ The term of office of the Pricing Committee members was defined<br>▪ Regulations relating to the marketing of medicines was defined<br>▪ The South African Medicines and Medical Devices Regulatory Authority Act 1998 was repealed |

## Table 3.2 Historic projects and legislative changes

| Timeline | Initiated by | Project Team | Objective | Recommendation | Result |
|---|---|---|---|---|---|
| 1960 | South African National Department of Health | Snyman Commission | ▪ Investigate the high cost of medicines and medical services in South Africa | ▪ Medicines should be controlled in terms of their "purity, safety and therapeutic efficacy" | ▪ Promulgation of the Drugs Control Act, 1965 (Act 101 of 1965)<br>▪ Establishment of the Drugs Control Council |
| 1998 | Minister of Health, Nkosazana Dlamini-Zuma | Advisory Panel | ▪ Review the medicine regulatory environment in South Africa | ▪ Endorsed the restructuring of the MCC with the aim of improving operational efficiencies | ▪ The new Amendment Act establishing the SAMMDRA to replace the MCC was passed by Parliament |
| 2007 | Minister of Health, Manto Tshabalala-Msimang. | Ministerial Task Team led by Professor Green-Thompson | ▪ Report on the restructuring of the MCC | ▪ The establishment of a new NRA to replace the MCC referred to as SAHPRA<br>▪ The need for international and regional harmonisation<br>▪ The need for collection of metrics to facilitate the measurement and monitoring of regulatory performance | ▪ Further amendment of the principal Act<br>▪ The Medicines Amendment Act, 2008 was signed into law by then President Kgalema Motlanthe in 2009 but not implemented |
| 2009 | Minister of Health, Barbara Hogan | Project team led by Dr Nicholas Crisp | ▪ Revive legislative endeavours directed towards regulatory reform | ▪ Develop the business case for SAHPRA<br>▪ Identification of further legislative amendments | ▪ Further amendment to the Medicines Amendment Act, 2008<br>▪ The Medicines and Related Substances Amendment Bill, 2012 |

| | | | | | |
|---|---|---|---|---|---|
| | | | ▪ Establishment of an improved NRA | | was published for comment in March 2012 |
| 2012 | Director General of Health, Malebona Precious Matsoso | Health Products Technical Task Team (HPTTT) | ▪ Advise on the key legislative, programmatic, infrastructural, structural and operational elements required for the transition to SAHPRA | ▪ Benchmark regulatory procedures in identified technical and operational areas<br>▪ Explore mechanisms for information sharing and systems to establish mutual recognition for registration requirements and product approval | ▪ Finalisation of the Medicines and Related Substances Amendment Bill, 2012<br>▪ The new Medicines Amendment Act, 2015 was approved (January 2016)<br>▪ The draft SAHPRA business case prepared by Dr Nicolas Crisp was amended to reflect current developments and the key elements required for the transition of the MCC to SAHPRA |

Abbreviations: HPTTT=Health Products Technical Task Team; MCC=Medicines Control Council; NRA=National Regulatory Authority; SAHPRA=South African Health Products Regulatory Authority; SAMMDRA=South African Medicines and Medical Devices Regulatory Authority

Through the work of the project team further amendments were made to the Medicines Amendment Act, 2008 (Act 72 of 2008) and the Medicines and Related Substances Amendment Bill, 2012 was published for comment in March 2012 (SAHPRA, 2016). In July 2012 the project team presented a draft business case for the establishment of SAHPRA (SAHPRA, 2012). The business case put forward a motion to establish SAHPRA as a Schedule 3A Public Entity to reinforce the political will to establish an NRA with operational autonomy and accountability. As a Schedule 3A Public Entity SAHPRA would be a separate juristic person outside of the National Department of Health accountable for sound corporate governance practices and adherence to compliance codes in terms of relevant legislation, financial regulations, directives, policies and procedures (National Treasury, 2015). The business case defined an extended mandate for SAHPRA including the regulatory oversight of food, complementary medicines, medical devices and radiation control. The report demonstrated historical under-funding of the NRA linked with recommendations for levying increased fees and motivated for proactive remuneration strategies to attract and retain the expertise required to execute the mandate of SAHPRA. It also expanded on the over-reliance on paper-driven systems and the necessity for an EDMS (SAHPRA, 2012).

The Director General of Health, Malebona Precious Matsoso, also appointed a Health Products Technical Task Team (HPTTT) in 2012 to consider the project team's recommendations and to advise further on the key legislative, programmatic, infrastructural, structural and operational elements required for the transition to SAHPRA (HPTTT, 2014; Pharasi & Banoo, 2015). The HPTTT as part of its mandate engaged several NRAs (the EMA, USFDA, Swissmedic, the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) and the Australian TGA to examine and benchmark regulatory procedures in identified technical and operational areas as well as to explore mechanisms for information sharing and systems to establish mutual recognition for registration requirements and product approval. These activities were also aimed at maximising regulatory capacity and operations under SAHPRA through understanding the structure and functioning of these agencies in line with international best practice standards. One of the outcomes of the HPTTT work was the finalisation of the Medicines and Related Substances Amendment Bill, 2012 and its introduction to Parliament for consideration. The new

Medicines Amendment Act, 2015 (Act 14 of 2015) was approved by the Parliament, assented to by the President in December 2015 and published in the *Government Gazette* in January 2016 (SAHPRA, 2016). The draft SAHPRA business case prepared by Dr Nicolas Crisp was further amended by the HPTTT to reflect current developments and the key elements required for the transition of the MCC to SAHPRA (SAHPRA, 2016). The amended business case defined the preparation and operationalisation of the transition, directed the development of a new fee schedule published in September 2015 to support the viability of the new NRA, informed the development and publication of the regulations for medical devices in December 2016 and confirmed the withdrawal of food control from the regulatory ambit of SAHPRA (SAHPRA, 2016). With the focus on financial and operational considerations these transitional arrangements overlooked the critical need for the review and improvement of the regulatory review process of the NRA as recommended in the Green-Thompson report. On the 1st June 2017 the amendments to the principal Act were enacted via proclamation of the Medicines and Related Substances Amendment Act, 2008 (Act 72 of 2008) read together with the Medicines and Related Substances Amendment Act, 2015 (Act 14 of 2015).

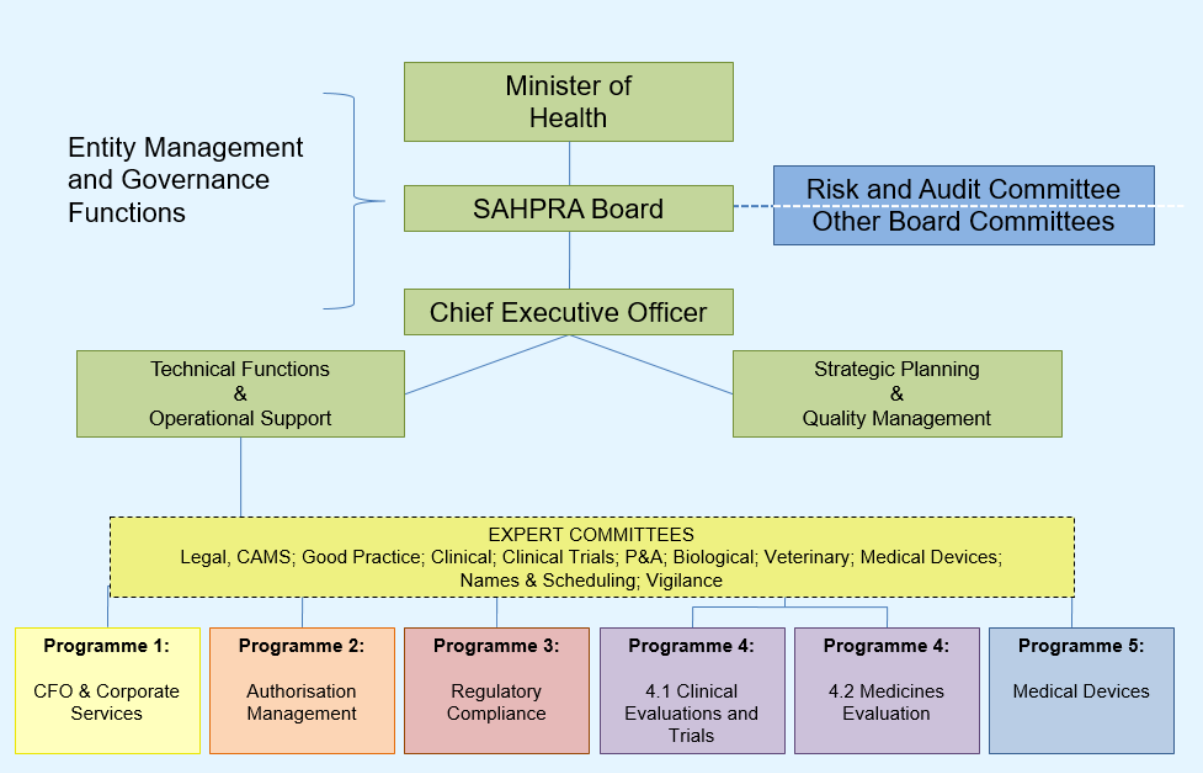
**THE SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY**

In February 2017 SAHPRA was legally established as a Schedule 3A Public Entity in terms of the Public Finance Management Act (PFMA), 1999 (Act 1 of 1999) to fulfil specific responsibilities on behalf of national government (National Treasury, 2015).

In October 2017 the Minister of Health, Aaron Motsoaledi, announced the appointment of 15 SAHPRA Board members. The Board members were appointed to serve for a period of three years under the leadership of Professor Helen Rees, the outgoing Chairperson of the MCC and the first Chairperson of the SAHPRA Board. In contrast to the MCC the SAHPRA Board has full operational autonomy and accountability. Through the Board the Authority is accountable to the Minister of Health (Medicines and Related Substances Act 2017). The SAHPRA Board after consultation with the Minister of Health must appoint a suitably qualified person as the CEO of the Authority (Medicines and Related Substances Act 2017). The CEO is accountable to and reports to the SAHPRA Board and is responsible for the general administration of the Authority and for the carrying out of any functions assigned to the Authority (Medicines

and Related Substances Act 2017). To this effect, Dr Boitumelo Semete-Makokotlela was appointed as the first CEO of SAHPRA. The organisational structure of SAHPRA is displayed in Figure 3.3.

**Figure 3.3 Transitional organisational structure of the South African Health Products Regulatory Authority (SAHPRA)**




Abbreviations: CFO=Chief Financial Officer; SAHPRA=South African Health Products Regulatory Authority

The four Directorates depicted will be replaced by five programmes responsible for performing the regulatory activities of the Authority. In order to ensure continuity transitional arrangements have been put in place for the expert committees to continue providing scientific expertise and support. A Regulatory Advisory/Oversight Committee for medicines and medical devices has been appointed by the CEO in consultation with the SAHPRA Board to investigate and report to the Authority on any matter within its purview in terms of Medicines and Related Substances Act, 1965 (Act 101 of 1965). The SAHPRA Board may appoint one or more committees from among its members to assist it with the performance of its functions and has appointed a

Technical Operations and Regulatory Strategy (TORS) Committee with investigation into the backlog in application for registrations as part of its remit. The SAHPRA Business Case (SAHPRA, 2016) stated that the legislative mandate of SAHPRA is derived from the Constitution of the Republic of South Africa, 1996 which places obligations on the state to progressively realise socio-economic rights including access to health care as well as the National Health Act, 2003 (Act 61) and the Medicines and Related Substances Act, 1965 (Act 101 of 1965) (pp. 23-24).

According to the Medicines and Related Substances Act, 1965 (Act 101 of 1965), SAHPRA's obligations include ensuring public protection, ensuring transparency and accountability in its operations and being responsive to the regulatory environment (SAHPRA, 2016, p. 26).

The functions of the Authority are defined in Section 2B of the Medicines and Related Substances Act, 1965 (Act 101 of 1965). The Authority must, in order to achieve its objectives, ensure that the:

- Evaluation or assessment and registration of medicines and medical devices, are efficient, effective and ethical and that registered medical products meet the defined standards of quality, safety, efficacy and performance;
- Process of evaluating or assessing and registering medicines and medical devices is transparent, fair, objective and concluded in a timely manner;
- Medicines and medical devices are re-evaluated or reassessed and monitored periodically;
- Existing and new adverse events, interactions and information with regard to post-marketing surveillance and vigilance are monitored, analysed and acted upon;
- Compliance with existing legislation is being promoted and controlled through a process of active inspection and investigation; and

- Clinical trial protocols are assessed according to prescribed ethical and professional criteria and defined standards.

The political will and leadership have seen the efforts for an improved regulatory landscape in South Africa come to fruition as the evolving NRA strives towards an effective and efficient regulatory authority. The key operational differences between the MCC and SAHPRA are highlighted in Table 3.3. The mandate of SAHPRA has been extended to include medical devices and complementary medicines and the legislative framework for reliance and recognition has been finalised. It is anticipated that improvements to the other operational elements listed in Table 3.3 will be realised with the establishment of SAHPRA.

**Extended mandate**

In the past the MCC was mandated to ensure regulatory oversight of human and veterinary medicines. With the promulgation of the amendments to the principal Act the mandate of the Authority has been extended to include medical devices, ionising and non-ionising radiation emitting devices, radioactive nuclides and complementary medicines.

**Challenges and changes**

Historically the MCC faced resource constraints as workloads placed on the regulator steadily increased. As a result, the MCC became dependent on over-committed external expertise. Evaluation structures which relied on external evaluators lacked effective performance management contracts and did not provide a sustainable mechanism for timely submission of evaluation reports. The regulatory functions mandated to SAHPRA are people-dependent (SAHPRA, 2016). Adequate, competent and motivated human capital plays a vital role in ensuring organisational success (SAHPRA, 2016). “It is the intended goal of SAHPRA to have an adequate number of staff with the right skills mix, at the right level, available and employed in appropriate positions within the organisation” (SAHPRA, 2016, p. 152). Efforts to reform organisational structures within SAHPRA should be prioritised to build and retain in-house scientific skills in order to decrease over-reliance on external expertise.

**Table 3.3 Key operational differences between the Medicines Control Council (MCC) and the South African Health Products Regulatory Authority (SAHPRA)**

| Operational element | MCC | SAHPRA |
|---|---|---|
| Mandate | Human and veterinary medicines | Medical devices and complementary medicines included |
| Organisational structure | Under-resourced:<br>Outsourced expertise | Fully-resourced:<br>In-house capacity |
| Harmonisation initiatives | Limited scope for reliance mechanisms | Legal framework for reliance mechanisms |
| Quality management system | Informal implementation of QMS | Formal implementation of the quality management system |
| Document management system | Paper-driven | Electronic document management systems-driven |
| Fee structure | Collection of fees by National Treasury | Retention of user-fees |
| Service delivery | History of backlogs | Improved timeliness |
| Stakeholder relationships | Stretched industry relationships | Transparency and accountability |

Abbreviations: MCC=Medicines Control Council; SAHPRA=South African Health Products Regulatory Authority; QMS=Quality Management System

### Harmonisation initiatives

As an Authority mindful of limited resources and capacity constraints the MCC had always recognised the value of harmonisation initiatives and had explored the possibility of implementing reliance mechanisms. In the past the MCC participated in regional collaboration initiatives such as the Zazibona collaborative work-sharing process which aimed to harmonise regulatory efforts between regional NRAs. Harmonisation efforts may now be actively enforced as the inclusion of Section 2B(2)(a) and 2B(2)(b) in the Medicines Act provides a mandate for the Authority to liaise with and enter into agreements with any other regulatory authorities or institutions (Medicines and Related Substances Act 2017).

The advantages of such regulatory relationships are offset by a number of prerequisites including the assumption that SAHPRA adopts internationally harmonised guidelines and standards (SAHPRA, 2016), relevant memoranda of understanding and confidentiality agreements are in place with reliable regulatory authorities recognised by SAHPRA (Green-Thompson, 2008), that SAHPRA remains accountable for the health and safety of the citizens of South Africa (SAHPRA, 2016), that some regulatory decisions may be made based on the regulatory activities and/or decisions made by other reliable authorities and recognised by SAHPRA (SAHPRA, 2016) and that enhancing regulatory convergence and participating in collaboration and work-sharing initiatives will contribute towards a decreased regulatory burden and a decreased workload on SAHPRA. SAHPRA will also have the opportunity to make better use of the limited resources available to improve post-marketing surveillance activities and will contribute towards efforts to minimise duplication of regulatory efforts (WHO, 2003).

**Quality management system**

The MCC has recognised the importance of formally implementing quality measures throughout the agency in order to ensure consistency, increase transparency and improve efficiencies. In the past the MCC did not have a dedicated Quality Management Unit however contingencies have been put in place to establish such a unit. This unit will be responsible for formalising the implementation of the QMS for the authority and for performing internal quality audits and for implementing strategies geared for continuous improvement. The implementation of a formalised QMS will ensure that GRevPs are codified into policies and guidelines, regularly monitored and subject to continuous improvement (WHO, 2016). Through the application of a robust QMS underpinned by the drive to cultivate an integral quality culture the regulatory performance and responsiveness of SAHPRA will be enhanced.

**Document management system**

"A regulatory authority must have an effective system of tracking application assessment processes and decision-making; these systems require an appropriate use of information technology" (Hill & Johnson, 2004, p.27). The development of an integrated information system, improvement of the current information and communication technology (ICT) infrastructure and the use of an EDMS will be essential for SAHPRA. Given the large volume of complex applications submitted to the Authority and the need for optimal document management it is critical that the Authority moves away from the historically paper-driven processes of the MCC. It is the intention of SAHPRA to implement an EDMS that can replace the legacy systems currently in use. SIAMED, a software programme adopted from the WHO, is one such system that was used by the MCC and inherited by SAHPRA to track and manage applications for the registration of medicines. This system has become outdated and will be phased out as electronic systems capable of facilitating the electronic submission of applications and robust document management functionalities are introduced.

**Fee structure**

The historical integration of the MCC into the operations of the South African National Department of Health has not served the MCC well as it worked towards ambitious goals of improved regulatory performance without the financial support required to establish a new regulatory authority that would be a viable regulator of medical products, trusted and respected by the pharmaceutical industry, civil society and patients of the Republic (SAHPRA, 2016). The Act makes provision for the Authority to levy fees for services rendered for example, a fee may be charged for the evaluation and registration of medical products. Fee structures vary significantly between different regulatory authorities. Fees may be set arbitrarily, they may be related to the cost of providing a service or they may be scaled, commensurate with the amount of data submitted and the time required for evaluation of the data.

The establishment of SAHPRA as a 3A Public Entity allows for change in that the finances generated by the Authority will be retained. This revenue structure is different to the past model that existed within the MCC whereby incoming fees were collected by the National Treasury and channeled to central government revenue. Although the

Authority will be partially funded from the national government funds a key deliverable for SAHPRA will be to raise the required revenue to make the Authority sustainable (SAHPRA, 2016). Suggestions to increase the fees for services levied by the Authority may be a solution but this will require significant improvements in regulatory efficiencies in order to appease the demands and expectations of stakeholders. Furthermore, an opportunity exists to generate more fees as the mandate of the Authority is extended to include the regulation of medical devices, complementary medicines and radiation control (SAHPRA, 2016).

**Service delivery and stakeholder relationships**

"SAHPRA has an obligation to effectively implement a regulatory framework that supports regulatory functions, enables the objectives of the National Drug Policy and promotes the priority goals of the National Department of Health" (SAHPRA, 2016, p.152). In order to do so it is necessary to improve structures within the Authority and advance the functions of the Authority to develop an accessible regulatory service footprint (SAHPRA, 2016).

Recognition of SAHPRA as a sustainable-well functioning regulatory system is a key feature of the strategic outcome orientated goals for the Authority (SAHPRA, 2016). The effectiveness of the regulatory systems developed, implemented and maintained by SAHPRA must be periodically measured against GRevP and pre-defined performance-based indicators (WHO, 2014b; SAHPRA, 2016). Global benchmarking of the Authority against the indicators of the GBT developed by the WHO to evaluate and grade the maturity level of the regulatory systems of NRAs will also provide a measurement of the Authority's performance in assuring independent and competent oversight of medical products in South Africa (WHO, 2020). Delivering on such regulatory performance objectives will also provide a platform for building strong and sustainable relationships with stakeholders with an emphasis on customer satisfaction.

## THE REGULATORY REVIEW PROCESS IN SOUTH AFRICA: MODALITIES FOR CHANGE

Through the amendment of the Medicines Act and the establishment of SAHPRA a new era has dawned bringing about new opportunities for regulatory reform and the possibility to re-engineer outdated processes. Priority should be given to addressing the inefficiencies of the current regulatory review process through consideration of different types of product review assessments used by NRAs worldwide in the review of applications for registration of medicines namely the verification review (type 1), an abridged review (type II) and a full review (type III) (McAuslane et al., 2009). SAHPRA may decide to continue with the current approach used historically by the MCC whereby a type III full independent assessment of quality, efficacy and safety data is performed in the review of all applications for registration however, it may be prudent to consider applying a risk-based assessment for those applications already reviewed by reference agencies in order to ensure timely access of medicines and medical devices.

### Risk-based approach to the evaluation of medicines

The management of limited resources may be improved through the application of a risk-based approach to medicinal product regulation. This approach allows regulators to direct the appropriate resources required to those medical products that pose a greater risk to patients. The amount of resources applied by the regulator should be commensurate with the level of risk of a medical product and should be applied only to the extent necessary to ensure patient safety (TGA, 2018). Many NRAs including resourced and mature regulatory authorities make use of FRPs for the assessment of applications for registration of medicines (Liberti, 2018). Primary FRPs are used to decrease review times of medicines that have not been reviewed by another NRA and that are not dependent on the review/decision made by another NRA for example products for unmet needs and oncology (Liberti, 2018). Secondary FRPs are used by NRAs to decrease review times of medicines that have been reviewed by another recognised NRA (Liberti, 2018). The regulatory decision can be expedited through reliance on or recognition of a prior review/decision by another NRA (Liberti, 2018). FRPs inform risk-stratification approaches to the assessment of applications for registration of medicines.

If SAHPRA wishes to apply such risk-based approaches the following types of review should be considered (Green-Thompson, 2008): The first is a full review of the complete quality, pre-clinical and clinical data applicable to medicines that have not been reviewed/approved by an NRA recognised by SAHPRA (Green-Thompson, 2008). The second is an abridged review applicable to a medicine that has been reviewed/approved by one recognised NRA (Liberti, 2018). Similar to the Mutual Recognition Procedure used in the EU the abridged review makes use of the evaluation report and the regulatory decision of a recognised NRA to guide the evaluation of the medicine by SAHPRA (Green-Thompson, 2008; Liberti, 2018). The third is the verification review that may be used to evaluate a medicine that has been approved by at least two recognised NRAs (Liberti, 2018). Through this review the product is validated for conformance to the authorised product specification (Pharasi & Banoo, 2015). The fourth is the evaluation of a dossier for a generic medicine (Green-Thompson, 2008). The generic medicine should be approved by at least one recognised NRA and should correspond to the reference product (with the same dosage form and strength) registered by SAHPRA (Green-Thompson, 2008).

Despite the type of review chosen for any given submission SAHPRA may insist that a full dossier consisting of complete quality, pre-clinical and clinical data is submitted upon application for medicine registration. Although a full assessment of the complete data may not be performed having the full dossier available on file will be advantageous for purposes of future reference or for post-market surveillance activities. A letter of intent for submitting an application for registration of medicine would be required to allow the regulator to adequately plan and allocate the necessary resources required to evaluate upcoming submissions. Through this process, the regulator may also anticipate whether specific expertise would be required in the assessment of the application and may be afforded the advantage of recruiting such expertise in advance thus circumventing unnecessary delays in the review process. This risk-based approach could be successfully applied provided that agreements are in place between SAHPRA and recognised NRAs to ensure that information pertaining to medicine assessment reports, post-marketing surveillance and post-marketing variations and/or amendments is easily shared and disclosed. As this system develops SAHPRA may consider introducing improved processes based on similar risk-stratification processes to address the submission of applications for variations and amendments to registered dossiers (Green-Thompson, 2008). In re-designing

the regulatory review process it would be prudent to consider the application of an appropriate framework for BR assessment to facilitate the evaluation of the BR balance of medicines prior to registration (Green-Thompson, 2008; Leong et al., 2015b). The implementation of GRP and GRevP (SAHPRA, 2016) and QDMPs are also recommended with a view to reinforce transparent decision-making processes. Therefore, the application of risk-stratification approaches and FRPs would be an advantage when considered in line with the recommendations of the WHO (WHO, 2014a; Ward, 2014).

**Monitoring and measuring**

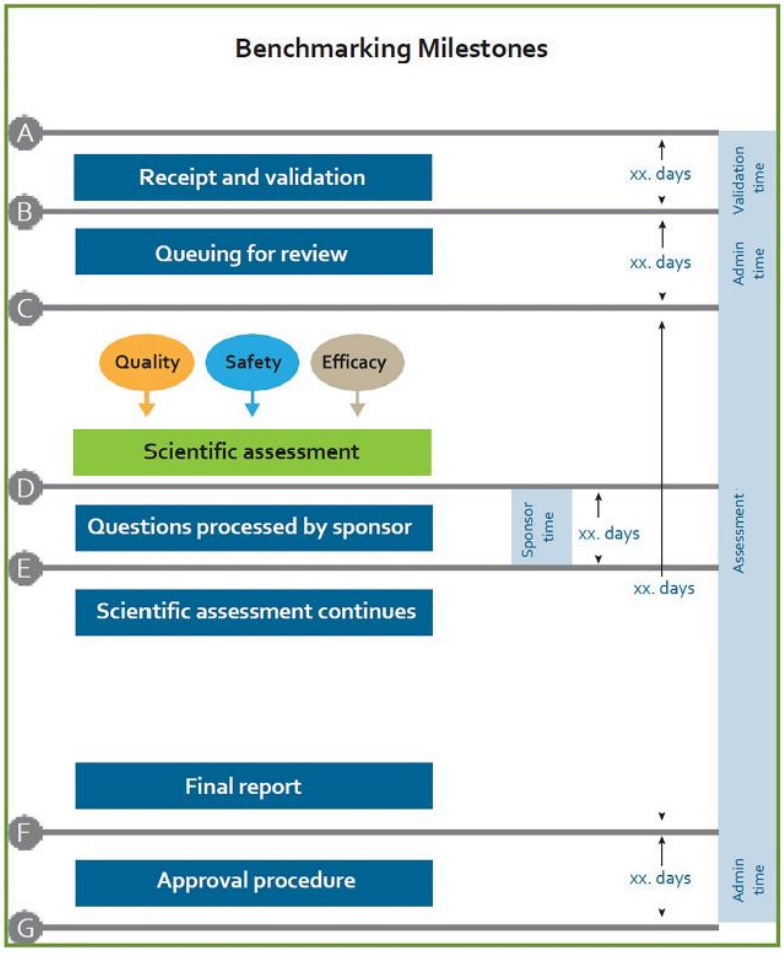
In the current model there is no target for overall approval time of applications for registration and no targets for the key review milestones. The targets for overall approval time and key review milestones need to be identified, codified into policy and guidelines, recorded, measured and monitored. Figure 3.4 provides a generic figure of individual milestones that have been used by other regulatory authorities and that may be considered for use within SAHPRA.

Appropriate systems and resources need to be put in place to support the accurate tracking of the overall approval times and key milestones in the regulatory review process. Administrative and technical screening time, queuing time prior to review and clock stops, measuring the time with applicants must be recorded and monitored. The metrics collection process must be strengthened in order to allow measurement and improvement of SAHPRA regulatory performance.

With accountability and transparency being the focus within the medicine regulatory landscape in South Africa, SAHPRA has to be cognisant of the past administrative injustices and take ownership of its performance. SAHPRA targets for regulatory review must be communicated to all stakeholders and it must be held responsible for meeting its obligations in terms of such targets and demonstrate accountability to parliament, to the public, to the industry and to all relevant stakeholders (Green-Thompson, 2008). Furthermore, SAHPRA should undertake to employ the basic principles of administrative justice within the routine practices and activities of the Authority (Green-Thompson, 2008). Providing written reasons to support regulatory

decisions made by the Authority could be one such practice that may support legal certainty and contribute to enhanced regulatory efficiencies and transparency (Green-Thompson, 2008). *Quid pro quo* provisions to relieve applicants of consequences of regulatory under-performance may also need to be considered (Green-Thompson, 2008).

**Figure 3.4 Benchmarking milestones currently utilised by national regulatory authorities (NRAs)**




*Adopted from CIRS, 2016*

## KEY RECOMMENDATIONS FOR A NEW REGULATORY ENVIRONMENT

In order to ensure the full potential of the new regulatory environment in South Africa the following recommendations are considered to be fundamental in underpinning the success of SAHPRA:

**Quality management system**

Establishment of such a system would help to safeguard accountability, consistency and transparency of SAHPRA and streamline the implementation of GRP and GRevP including QDMPs and BR assessment.

**Measuring and monitoring**

This will ensure the measurement and improvement of regulatory performance, targets for overall approval time and key review milestones. Consequently, this will lead to the implementation of appropriate systems for and a culture of accurate metrics collection and measurement of key performance indicators and their continuous improvement.

**Risk-based approach to the evaluation of medical products**

This will help to implement the appropriate allocation of resources, codify the use of FRPs in policy and culture, apply a risk-based approach commensurate with the product's risk to patients and apply increased resources for pharmacovigilance activities to support the reliance and recognition of reference agencies.

The purpose of this review was to provide insight into the history of the enabling legislation and expert reviews and recommendations for regulatory reform that have given rise to a new regulatory regime in South Africa. Many key opportunities and modalities for change have been identified and it is evident that re-enforcement of strategies to address inadequate financial and human resources, stakeholder relationships, paper-driven document management systems, service delivery and regulatory review processes, need to be considered in order to strengthen the regulatory systems in South Africa. With time and active leadership from the SAHPRA Board together with the SAHPRA CEO and the management team it is hoped that the re-engineered strategies and processes, planned for implementation will serve to enhance the regulatory landscape in South Africa.

**SUMMARY**

- The drive for improved regulatory systems and the establishment of a more effective regulatory framework in South Africa has been evident for the past two decades

- A significant backlog has developed and has resulted in extended timelines for medicine registration in South Africa

- The promulgation of the recently amended Medicines and Related Substance Act of 1965 triggered the establishment of the South African Health Products Regulatory Authority (SAHPRA) to replace the former medicine regulatory authority the Medicines Control Council (MCC).

- The aim of this review is to provide the historical context supporting the new regulatory environment in South Africa and the transition from the MCC to SAHPRA.

- Key recommendations to SAHPRA include:
    - The formal development and implementation of a QMS
    - The measurement and monitoring of regulatory performance
    - Setting targets for overall approval time and key review milestones to instil a culture of accurate metrics collection and measurement of key performance indicators and their continuous improvement
    - Codifying the use of facilitated regulatory pathways in policy and culture
    - The application of a risk-based approach to regulatory review commensurate with a medicine's risk
    - The implementation of reliance frameworks and the recognition of the regulatory decisions of reference agencies

# CHAPTER 4

## Evaluation of the Regulatory Review Process in South Africa

## INTRODUCTION

As part of a multi-country study on effective drug regulation, the WHO described four dimensions of medicine regulation, namely, administrative elements, regulatory functions, level of regulation, and technical elements (Ratanawijitrasin & Wondemagegnehu, 2002). Further studies by Hill and Johnson (2004) recognised that regulators often operated in an environment with insufficient political support resulting in inadequate legislative frameworks and financial resources, inconsistent application processes and an inappropriate regulatory culture (Hill & Johnson, 2004). During the past decade, regulatory authorities have acknowledged the need to develop efficient and effective regulatory review processes (Cone & Walker, 2005; Cone & McAuslane, 2006). Regulatory authorities are encouraged to facilitate the expedited approval of new medicines within mandated prerequisites of ensuring patients' access to safe, effective and quality medicines. Regulators face scientific, administrative and legislative capacity constraints yielding sometimes inoperable regulatory directives, limited solutions for timely evaluations and a drive for maintaining sovereignty. Many regulators have dedicated resources to improve the review processes and to develop indicators that go beyond the measurement of time and speed (Cone & Walker, 2005; Cone & McAuslane, 2006). The implementation of GRevP plays a pivotal role in ensuring consistency, predictability, clarity and efficiency in the product review process (Al-essa et al., 2012; WHO, 2015) and contributes toward the evaluation of the performance of the regulatory authority. This review was the first to be carried out to evaluate the current South African regulatory review process as it is had been applied by the Medicines Control Council (MCC), prior to the establishment of the SAHPRA.

### Medicines Control Council of South Africa

The pharmaceutical market in South Africa was valued at approximately 45 billion Rand (US$3.2 billion) in 2015 (Soomaroo, 2017). The domestic manufacturing pharmaceutical industry almost exclusively produces generic products and the South African pharmaceutical sector is import dependent (Soomaroo, 2017). In 2013 generic medicines accounted for 63% of the private pharmaceutical market and 80% market share in the South African government's pharmaceutical use (Soomaroo, 2017). Over the last 50 years South Africa has developed a medicines regulatory authority with internationally recognised standing (MCC, 2017). Through the Medicines and Related

Substances Act, 1965 (Act 101 of 1965) the MCC was responsible for the monitoring, evaluation, regulation, investigation, inspection, registration and control of medicines, scheduled substances, clinical trials, medical devices and related matters in the public interest (MCC, 2006). The MCC operated through external experts who were members of Council committee structures and a staff component that included doctors, pharmacists, veterinarians, other scientists, project managers and administrative staff (MCC, 2017). This study aimed to appraise the regulatory review process within the MCC, identify key milestones and evaluate the review times for NASs and major line extensions (MLEs) from 2015 to 2017. The findings of this study provided a baseline for assessing the changes and improvements to be made as the MCC transitioned into the newly established SAHPRA. This was the first study to evaluate the status quo of the regulatory review process of the MCC since the promulgation of the Medicines and Related Substances Act, 1965, as amended on June 1, 2017 (Republic of South Africa, 2017).

The aim of this study was to:

- Assess the current regulatory review process in South Africa;
- Identify the key milestones, timelines and stages of the review process;
- Evaluate the effectiveness of the measures used to ensure consistency, transparency, timeliness and predictability in the review process; and
- Review the challenges and opportunities for enhanced regulatory practices in South Africa with a view to improving patients' access to innovative medicines.

## METHODS

### Data collection process

A questionnaire (see Appendix 1) was used to map the key milestones and activities associated with the review processes and practices within NRAs (CIRS, 2019c). Through the use of the questionnaire, NRAs are able to identify the models of review that are being used within the authority, identify target times and the main activities between milestones for registration, identify the organisation structure and the capacity of the authority. The questionnaire, on the regulatory review process in South Africa, was completed by the Registrar of Medicines for the MCC. The questionnaire was completed with a view of analysing the quality measures that were in place, to

identify areas of capacity constraints and to provide a baseline for the MCC review process, in the light of the transition to the newly established SAHPRA. The questionnaire (see Appendix 1) consisted of four parts:

***Part I - Organisation of the authority***

Part I documented an introduction to the authority; its current structure and size, the resources available and the review model(s) currently in place (CIRS, 2019c).

***Part II - Key milestones in the registration of medicines within the review process***

Part II of the questionnaire was based on a standard process map that was previously developed by CIRS, through the study of established and emerging NRAs (McAuslane et al., 2009). This process map provided a detailed description of the pathway of a dossier, through administrative and technical screening steps, scientific evaluation and Committee and Council processes. The completed process map enabled the collection of information in a standardised format that was used to simplify the comparison of the MCC and its review process with the regulatory pathways used by other NRAs.

***Part III - Good review practice***

Part III of the questionnaire pertaining to building quality into the assessment and registration processes provided an account of the activities and practices, implemented by the MCC, that contributed towards improved consistency, transparency, timeliness and predictability in the regulatory review and to the quality of the decision-making process. This questionnaire had been developed for use in the analysis of the regulatory environment in several emerging pharmaceutical markets (CIRS, 2019c).

***Part IV – Identification of the enablers and barriers***

Part IV of the questionnaire aimed to identify the NRA's own perception of its unique positive qualities (enablers) and the major impediments (barriers) it faced in carrying out the timely review of NASs.

## RESULTS

### Part I - Organisation of the authority

The MCC was first established in 1965 and historically operated within the National Department of Health. Since then, the authority had undergone many changes including its establishment as a 3A Public Entity (National Treasury, 2015) known as SAHPRA. Provision was made for the restructuring of the authority through the amendment of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), which was published on the 1 June 2017 (Republic of South Africa, 2017).

The scope of responsibility of the MCC included medicinal products for human and veterinary use and medical devices. The MCC was mandated through the Medicines and Related Substances Act, 1965 (Act 101 of 1965) to ensure the efficient, effective and ethical evaluation or assessment and registration of medicines and medical devices that met the defined standards of quality, safety, efficacy and performance (MCC, 2017). The MCC also performed licensing activities, inspectorate and law enforcement functions, laboratory analysis of biological products, post-market surveillance and pharmacovigilance activities and controlled the advertising of medicines and medical devices.

The MCC had a staff component of approximately 200 full-time personnel including management and technical and administrative personnel and approximately 100 external consultants. At the time of this study, approximately 100 internal and external technical personnel were responsible for the technical evaluation of applications which included NASs, generics, biologicals, veterinary and complementary medicines. The majority of the staff responsible for the regulatory review process were qualified as pharmacists and many of the assessors had post-graduate qualifications.

#### *Model of assessment in South Africa*

Three types of product review assessments are used by NRAs: the verification review (type I), an abridged review (type II) and a full review (type III) (McAuslane et al., 2009). The MCC conducted a type III full assessment in the review of all applications including NASs and generics for orthodox, biological, complementary and veterinary medicines. A full independent assessment of quality, efficacy and safety data was performed. The authority had access to assessors who had the relevant qualification and technical

experience to perform a full assessment of the data provided. The majority of the assessors were external consultants who were not bound by contractual performance agreements. Over the last few years the MCC had made major changes in building in-house capacity through assistance from the external experts.

***Data requirements and assessment***

The Certificate of Pharmaceutical Products (CPP) was not essential for registration but a copy of the authorisation letter had to be provided if the product had been registered in a reference country (e.g., for fast track/priority products). Evidence of GMP status of the manufacturer and copies of labelling for products authorised in reference countries were also required. Full quality data (Module 3), full non-clinical data (Module 4) and full clinical data (Module 5) were required. A detailed assessment of the data was carried out by the MCC and the relevant assessment reports were prepared.

The MCC performed BR assessments and the clinical opinion of the authority took account of differences in medical culture/practice, ethnic factors, national disease patterns and unmet medical needs. Where relevant, the authority would obtain internal assessment reports from other authorities and publicly available reports such as European Public Assessment Reports (EPARs). The MCC referred to pharmacovigilance reports and confirmed the GMP status and product compliance during the review process. Although registration elsewhere was not a pre-requisite for making an application, information on existing registrations had to be provided, where available.

**Part II - South African regulatory review process**

The South African regulatory review process is presented in Figure 4.1. The review process map illustrates the main steps in the review process and identifies the key milestone dates for monitoring and analysing timelines for review. The map provides a simple representation of the review and authorisation of applications for NASs and MLEs that are approved on the first review cycle. The map does not describe the process in the event that the application was refused. The appeal process that may be initiated, following refusal of an application, has also not been included in the review process map.

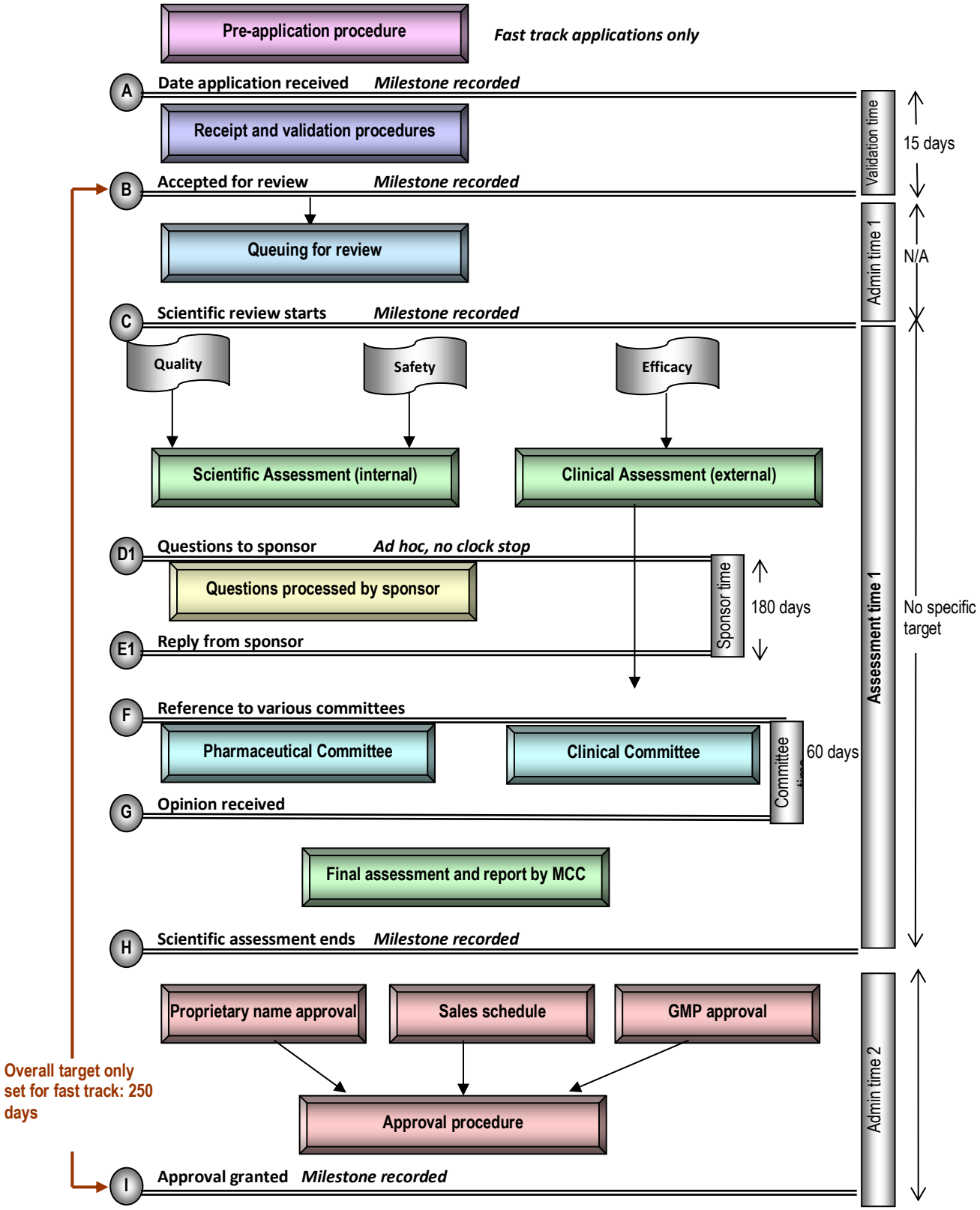
***Queue time***

Applications for NASs were received by the Operations and Administration Unit and administrative screening of applications was performed within 15 calendar days from the time of receipt. Applications were routed to the relevant unit where they were allocated to an assessor to start the review process. There was no target set for the overall review time of an NAS application and there were no targets set for the key milestones identified in the review process. There was a mechanism in place whereby priority applications may be fast tracked. Products that were considered for expedited review were medicines on the essential drug list (EDL) and NASs that were considered essential for national health but did not appear on the EDL (MCC, 2012). The scientific data requirements did not differ between fast track and other products and the level of scientific assessment was the same. Once submitted however, such products were always given priority in the queuing system and an overall target of 250 calendar days was set for fast track products. At the time of this study, there was a substantial backlog due to the large number of applications received for the registration of generic medicines, however, applications for NASs were not placed in the same queue as generic medicine applications and were routed for allocation to assessors upon completion of administrative screening.

***Scientific assessment***

Scientific data, presented in applications, were assessed in parallel for quality, safety and efficacy by the different units within the MCC. The assessments were performed by internal as well as external assessors. While internal assessors were subject to annual performance appraisals, the external assessors were not contractually bound by service-level agreements and this limitation had an impact on review times.

## Figure 4.1 Regulatory review process map for South Africa




*Days reflected are calendar days*

Abbreviations: GMP=Good Manufacturing Practice; MCC=Medicines Control Council; NAS=New Active Substance

Detailed assessment reports and recommendations were prepared by the assessors and these were peer reviewed and tabled at the relevant Scientific Committee meetings for discussion which then made a recommendation to the MCC for ratification. Although there was no set timeline for the scientific assessment of applications, a request was sent to assessors to support completion of the assessment within 90 calendar days.

***Questions to sponsor***

Recommendations pertaining to quality data were sent to sponsors following ratification by the MCC and those who had submitted an application for an NAS were requested to provide a response to the recommendations within 180 calendar days. The response from the sponsor would be reviewed by an assessor and tabled at the next Scientific Committee meeting and subsequent Council meeting.

Questions pertaining to safety and efficacy data could be provided to the sponsor at any time during the assessment. Recommendations from the Scientific Committee were sent to the sponsor prior to ratification by the Council. Sponsors were required to respond to the recommendations within 180 calendar days. In the event that major deficiencies were identified in the data submitted, the response from the sponsor would be subjected to the full procedure of evaluation, discussion at the Scientific Committee meeting and ratification at the Council meeting. The MCC had accepted responses that exceed the time limit.

***Expert committees***

Applications for an NAS were referred to a number of Scientific Committees for discussion prior to the medicine's consideration for registration by the MCC. These included the Pharmaceutical & Analytical Committee, the Clinical Committee, Good Practice (e.g. GMP) Committee and the Names & Scheduling Committee. There was no target time limit for the Committee procedure, however, routine Committee meetings were held every 60 calendar days. Committee processes were conducted in parallel to support efficiencies in the review process. Council meeting dates were scheduled to accommodate the work of the Committees and prevent delays between the outcome of Committee meetings and Council ratification. The recommendations

made by the Committees were tabled at the Council meeting and the Council was responsible for the decision on whether or not to grant authorisation for medicine registration. This decision was based on the scientific assessment of the quality, safety and efficacy data submitted by the sponsor. The Council would also base the decision for authorisation or refusal on the approval of the proprietary name of the product, the allocation of a scheduling status to the active pharmaceutical ingredient (API) and the evaluation of the GMP status of the sponsor, the manufacturer, the assembler, the quality control laboratory and the final product release responsibility. The decision for authorisation or refusal was neither dependent on sample analysis nor on a pricing agreement. Based on the timing of the Council meetings, the authorisation process could take up to 60 calendar days from receiving a positive recommendation from the Scientific Committees. Sponsors were informed of the decision of the Council within seven calendar days after the Council meeting and the target timelines for the MCC review process can be seen in Table 4.1.

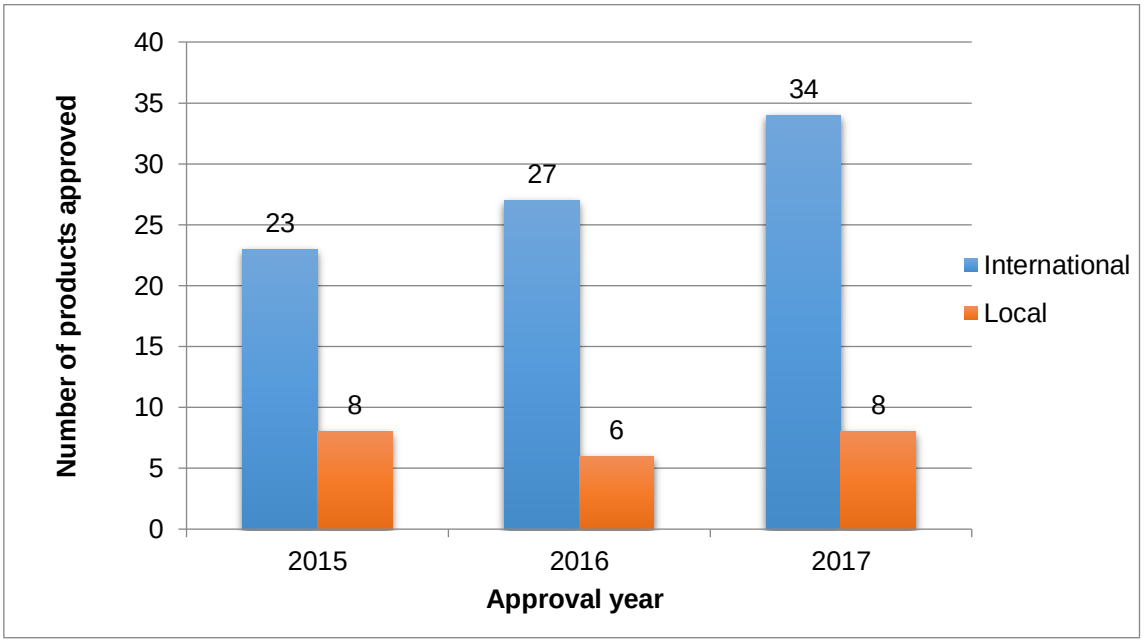
**Table 4.1 Target timelines for the Medicines Control Council (MCC) review procedures**

| Process | Target |
|---|---|
| Validation | 15 calendar days |
| Scientific assessment | 90 calendar days |
| Sponsor response time (Quality data) | 180 calendar days |
| Sponsor response time (Safety and efficacy data) | 180 calendar days |
| Expert Committee(s) | 60 calendar days |
| Authorisation procedure | 60 calendar days |
| Notification of decision | 7 calendar days |
| Overall review time (Fast track) | NAS: 250 calendar days |
| Overall review time | NAS: No target |

Abbreviation: NAS=New Active Substance

The majority of NASs approved over the period 2015-2017 were submitted by international companies, while local companies were responsible for 21% of such approvals. The number of approved NASs from international and local companies, during the period 2015-2017 is shown in Figure 4.2.

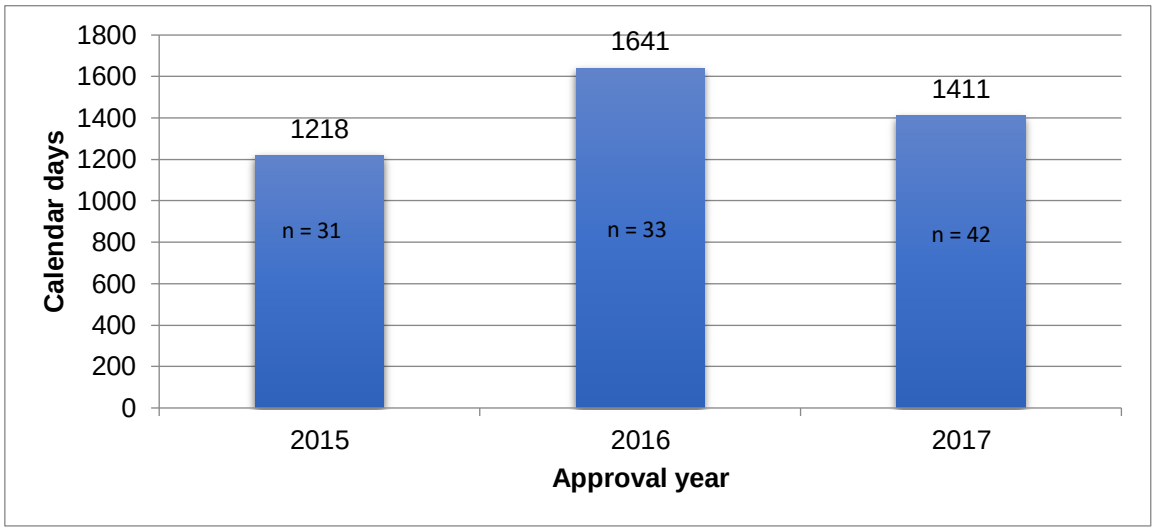
**Figure 4.2 Number of approved new active substances (NASs) from local and international companies (2015-2017)**




The highest number of approved NASs for international companies was 34 in 2017 while the highest number of approved NASs for local companies was eight in both 2015 and 2017. The highest number of NASs was approved in 2017 (n = 42) with a median approval time of 1411 calendar days. In 2016, 33 NASs were approved with a median approval time of 1641 calendar days, which is comparable to the median approval time in 2017. The fastest median approval time of 1218 calendar days was achieved in 2015 for 31 NASs (Figure 4.3).

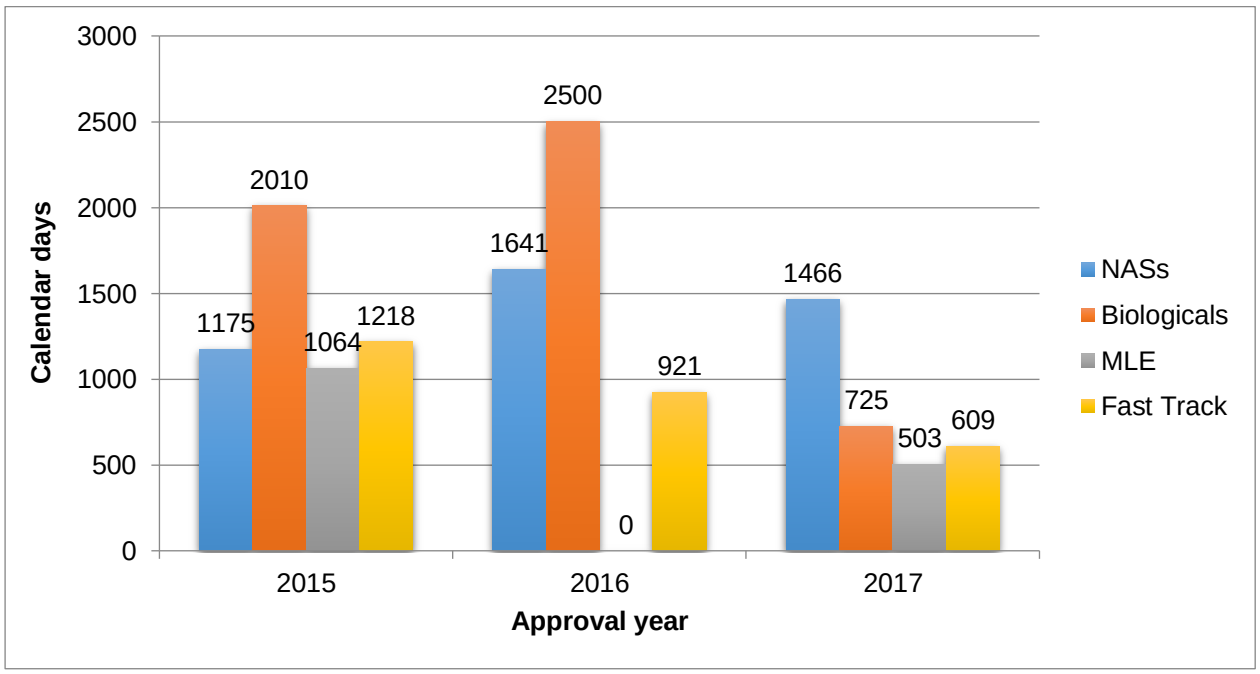
In 2015 and 2016, the approval times for biological products were longer than for NASs (Figure 4.4). However, in 2017 the median approval time for biological products (n=5) was less than NASs (n=31). In 2016 and 2017, fast track products had shorter approval times in comparison to NASs.

**Figure 4.3 Median approval timelines for new active substances (NASs) (2015-2017)**




Fast track products also had shorter approval times in 2015-2017 when compared to biologicals. In 2015 and 2017, MLEs had the shortest approval times when compared with NASs, biologicals and fast track products.

**Figure 4.4 Median approval times for new active substances (NASs) compared with biologicals, major line extensions (MLEs) and fast track products (2015-2017)**



The most commonly approved NASs, by therapeutic class, during the period 2015-2017 included: cytostatic agents (14 products), analgesics (eight products), anticonvulsants, including anti-epileptics (six products) and non-steroidal anti-inflammatory drugs (six products). The lowest number of NASs approved, by therapeutic class, during the period were: local anaesthetics (one product), vasoconstrictors (one product), ophthalmic preparations (one product), medicines against protozoa (one product) and macrolides and lincosamides (one product).

**Part III - Good review practices: Building quality into the registration and review processes**

*General measures used to achieve quality*

The MCC had developed an internal quality policy that described the overall intentions and direction of the authority related to the quality of the review process. The MCC intended to formally implement the quality policy and prescribe the measures that would be used to achieve and continuously improve on quality within the next two years. GRevPs are defined as a framework applied to the process and documentation related to regulatory review procedures.

GRevP measures aim to standardise and improve overall documentation and to ensure timeliness, predictability, consistency and high quality in reviews and assessment reports. The MCC had initiated the development and implementation of a GRevP framework however it was acknowledged that the system was still evolving. Table 4.2 provides an overview of the status of the implementation of GRevP by the MCC and demonstrates that there were a number of elements of the framework that needed to be formalised and improved.

The MCC recognised that the currently implemented elements of the GRevP framework had been underutilised by staff. Additional training to learn and understand GRevP would be valuable so that the benefits of formally implementing a comprehensive GRevP framework, within the authority, may be fully realised.

**Table 4.2 Status of implementation of good review practices (GRevPs) by the Medicines Control Council (MCC)**

| INDICATOR | IMPLEMENTED | | COMMENTS |
|---|---|---|---|
| **Quality measures** | | | |
| Internal quality policy | ✓ | | Planned to formally implement |
| Good review practice system | ✓ | | Planned to formally implement |
| Standard operating procedures for guidance of assessors | ✓ | | Planned to formally implement |
| Assessment templates | ✓ | | Planned to formalise the use of a single, common template |
| Dedicated quality department | x | | Establishment of a dedicated quality department is planned |
| Scientific committee | ✓ | | |
| Shared and joint reviews | ✓ | | |
| **Transparency and communication parameters** | | | |
| Feedback to industry on submitted dossiers | ✓ | | |
| Details of technical staff to contact | ✓ | | Contact details are made available on an ad-hoc basis |
| Pre-submission scientific advice to industry | ✓ | | Meetings are held with industry on an ad-hoc basis |
| Official guidelines to assist industry | ✓ | | |
| Industry can track progress of applications | x | | Implementation of electronic document management system is planned |
| Summary of grounds on which approval was granted | ✓ | | Summary is available but is currently not published |
| Approval times | ✓ | | Approval times are not made available to the public |

| INDICATOR | IMPLEMENTED | | COMMENTS |
|---|---|---|---|
| Advisory committee meeting dates | ✓ | | |
| Approval of products | ✓ | | |
| **Continuous improvement initiatives** | | | |
| External quality audits | ✓ | | External quality audits are not performed routinely |
| Internal quality audits | × | | Planned |
| Internal tracking systems | ✓ | | Implementation of electronic document management system is planned |
| Review of assessors' feedback | ✓ | | |
| Reviews of stakeholders' feedback | ✓ | | Planned to be formally and routinely reviewed |
| **Training and education** | | | |
| International workshops/conferences | ✓ | | |
| External courses | ✓ | | |
| In-house courses | ✓ | | Training programme to be formalised |
| On-the-job training | ✓ | | Training programme to be formalised |
| External speakers invited to the authority | ✓ | | |
| Induction training | ✓ | | Training programme to be formalised |
| Sponsorship of post-graduate degrees | ✓ | | |
| Placements and secondment in other regulatory authorities | ✓ | | |

Legend: Formally implemented | Informally implemented | Not implemented

Furthermore, the MCC intended to formally codify the critical elements of GRevP so that they may be written into the internal organisational policy. The authority also aimed to develop a QMS to support the successful application of GRevP. Standard operating procedures (SOPs) were available to describe the routine procedure for the regulatory review process and these provided guidance for the scientific assessors and the advisory committee who were consulted during the review process. The SOPs needed to be revitalised to provide a detailed description of processes that had been enhanced since the inception of the review process and there were plans to update these SOPs within the next two years.

Assessment templates that set out the content and format of written reports on scientific reviews were available and both external and internal peer reviews were carried out when an NAS was assessed. Elements included in this assessment template were a listing of the drug substance, the name of the drug product, comments on the product label, non-clinical data, clinical pharmacology, safety and efficacy, good clinical practice (GCP) aspects and a list of recommendations to the sponsor.

The Scientific Committees involved in the regulatory review process met approximately every 60 calendar days to review NAS applications. The assessment reports discussed at these meetings were prepared by both internal and external assessors but these were not published on the MCC website. The recommendations made by the Scientific Committees were tabled at the MCC meeting where the decision for acceptance or refusal of the application was made.

***Quality management***

The MCC recognised the importance of implementing quality measures throughout in order to ensure consistency, increase transparency, improve efficiencies and enhance allocation of regulatory resources. The MCC held regular meetings with external stakeholders, in the form of Industry Task Group (ITG) forums, which provided a forum for candid discussion between the industry and the regulator. The MCC maintained an open-door policy whereby meetings with the regulator were routinely facilitated. Furthermore, the industry and interested parties were invited to participate in workshops hosted by the regulator through which opinions, feedback and complaints could be received and channeled into corrective and preventative actions.

The MCC did not have a dedicated unit for assessing quality in the review process for new medicines however, contingencies had been put in place to establish such a unit. This unit would be responsible for developing a QMS for the authority, for performing internal quality audits and for implementing strategies geared for continuous improvement through retrospective evaluation of the assessment and authorisation process. Provision had been made to employ the use of an EDMS. The tracking functionality of the EDMS would allow for internal monitoring of the process, thus contributing to efficiency and accuracy in the review process. The quality unit would also be responsible for ensuring that the requirements of the QMS of the authority were fulfilled in order to be certified to the quality standards of the International Standardization Organization (ISO). The quality unit would also be responsible for ensuring that the requirements, for the relevant sub-indicators of the WHO GBT relating to the development, implementation and maintenance of an appropriate QMS, are met.

***Quality in the review and assessment process***

The MCC has implemented a number of mechanisms in an effort to improve the quality of applications received from sponsors and the scientific review of such applications. Guidelines for industry have been developed and have been published on the MCC website and in official publications. These guidelines were also available on request from the regulator and through industry associations. There was no policy for providing pre-application scientific advice to a sponsor and such advice was not routinely monitored. Pre-application scientific advice could be provided following a request from the sponsor who was also given the contact details of technical staff that could be contacted to discuss an application during the review. Formal contact, such as scheduled meetings with the regulator, was possible during product development and assessment and in this time there was also an extensive amount of informal contact between the sponsor and the regulator via telephone or email.

***Shared and joint reviews***

The MCC took part in joint reviews through the Zazibona collaborative process which aimed to harmonise regulatory efforts across Africa. The collaborative process started as a partnership between the NRAs in Zambia, Zimbabwe, Botswana and Namibia

and participation by interested South African Development Community (SADC) Member States is encouraged (Regulatory Resources for Africa, 2015). In order to be eligible to participate in the Zazibona collaborative process the sponsor was required to submit the application for registration to two of the participating NRAs (MCC, 2012). Products that had been registered by recognised regulatory authorities were eligible for an abridged review process provided that the assessment report from the authorising authority was available. The collaborative process aimed to complete product authorisation or refusal within 11 months. Products could be considered for two review cycles and sponsors were required to respond to the consolidated list of regulatory assessment questions within a period of 60 days. The overall review target for the collaborative process was 210 days (Regulatory Resources for Africa, 2015). Participating NRAs maintained the right to make a final determination on any application and the final regulatory decisions were the responsibility of individual participating NRAs (Regulatory Resources for Africa, 2015).

***Training***

Training and professional development of internal and external assessors continued to contribute to the element of quality within the MCC review process. Although the training programme had not been formalised, assessors were required to take part in induction training and on-the-job training. Mentorship programmes between experienced assessors/inspectors and those less experienced were developed to support reviews. The National Department of Health provided financial support to assessors enrolled in post-graduate studies and external courses. Assessors had the opportunity to be seconded to other NRAs for further training and regularly attended international workshops and conferences to enrich their learning. Participation in training provided by the WHO on topics such as the pre-qualification process and QMSs as well as training provided by the European Directorate for the Quality of Medicine formed an integral part in the training of assessors.

***Transparency of the review process***

The MCC assigned a high priority to being open and transparent in relationships with the public, health professionals and industry. Along with political will, the MCC had recognised the need to increase confidence in the regulatory system and to provide

assurances on safety safeguards as the main drivers for assigning resources to activities that enhanced the transparency of the regulatory system. Table 4.2 provides an overview of the measures that had been put into place by the MCC in an effort to promote transparency and improve communication with stakeholders. The MCC had a manual system in place which was used to trace applications that were under review and identify the stage at which the application was in the process. Sponsors were able to track the status of their applications via telephone and email contact. The MCC was progressing towards the use of an EDMS that was capable of signaling any target review dates that may have been exceeded, recording the terms of the authorisation once granted and providing searchable archiving of information on applications. The MCC published the list of licensed manufacturers, wholesalers and quality control laboratories, Committee meeting dates and a list of registered products on the MCC website. Where relevant such information was published in the *Government Gazette.*

**Part IV – Identification of the enablers and barriers**

This study identified aspects that the MCC considered to be pivotal enablers in the effectiveness and efficiency of the MCC review process and decision-making procedures for NAS applications. These included the eagerness of the NRA in South Africa to build confidence in the regulatory system, the minimal staff turnover at the MCC that contributed toward the retention of institutional knowledge and the support from scientific committees in the regulatory review of applications for market authorisation. The lack of an electronic document management system (EDMS) and outdated review processes, coupled with fixed committee structures and decision-making processes, were deemed to be barriers in effecting the regulatory mandate of the MCC in a timely manner.

## DISCUSSION

The NRA in South Africa strived to be an authority of international standing and was one of the most developed authorities in the African region. The authority had taken into account international best practices in the development of its legislation, guidelines and SOPs. The MCC was not sufficiently resourced to provide an efficient and effective service. As a result, review times for NASs were in excess of four years whereas for mature agencies this was of the order of 10 to 16 months (CIRS, 2019a).

This subsequent delay with respect to patients' access to new medicines was the rationale for the establishment of SAHPRA and the re-engineering of the current regulatory processes in South Africa. The success of the new system was imperative as the South African authority strived to be considered alongside other comparable agencies.

This study evaluated the overall regulatory approval times for NASs, biologicals, MLEs and fast track applications in South Africa from 2015-2017. The number of products approved by the MCC had been increasing each year and during 2015-2017, 79% were sponsored by international companies. While local companies did submit applications for NASs, these companies often did not have the resources and dedicated research facilities to develop such products in-house, but rather enter into contractual agreements with international companies to develop the products abroad or to sell the product under licence.

The MCC recognised the importance of building confidence into the regulatory system and the support from expert review committees as factors that could contribute to the effectiveness and efficiency of the review and decision-making processes for NAS applications. While outdated mechanisms for review could be improved through the re-engineering of the operational process and decision model, consideration of an appropriate benefit-risk model was recommended. The amendment of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) supports reliance and harmonisation strategies. The MCC considered the use of an alternative risk stratification model incorporating reliance on reference NRAs. It was also evident that firm target times for the review process needed to be written into the organisational policy and had to be tracked through the use of an EDMS in order to realise effective regulatory mandates.

This study has evaluated the MCC regulatory review process as it had been applied prior to the establishment of SAHPRA. Key milestones and timelines within the regulatory review process have been identified and the measures used for GRevP have been considered. The value added in codifying the guidelines for GRevP and formalising the quality policy and QMS were recognised. The findings from the study suggested that the MCC had identified the opportunities for enhanced regulatory

review and could consider an abridged assessment model which encompassed elements of risk stratification and reliance. As the MCC transitioned to the newly established SAHPRA it was hoped that the resource constraints could be alleviated and capacity developed to meet target timelines.

**SUMMARY**

- Regulatory authorities have acknowledged the need to develop efficient and effective regulatory review processes

- The MCC review times for NASs were in excess of four years and a significant backlog had developed

- Efforts to address the increasing volume of applications that were received had failed as resources were stretched to capacity

- The aims of this study were to assess the regulatory review process in South Africa from 2015 to 2017, identify the key milestones and timelines and evaluate the effectiveness of measures to ensure consistency, transparency, timeliness and predictability in the review process

- A questionnaire (see Appendix 1) was completed by the MCC to describe the organisation of the authority, record key milestones and timelines in the review process and to identify GRevPs

- The overall regulatory median approval time decreased by 14% in 2017 (1411 calendar days) compared with that of 2016, despite the 27% increase in the number of applications

- The MCC had no target for overall approval time of NAS applications and no targets for key review milestones

- The findings from the study suggested that the MCC had identified the opportunities for enhanced regulatory review and could consider an abridged assessment model

- As the MCC transitioned to the newly established SAHPRA it would be crucial for the authority to recognise the opportunities for an enhanced regulatory review that encompassed elements of risk stratification and reliance

# CHAPTER 5

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# Evaluation of Regulatory Review timelines for submissions and approvals of Medicines in South Africa

## INTRODUCTION

National regulatory authorities (NRAs) are responsible for the registration of NASs and patients' timely access to medicines (Ndomondo-Sigonda et al., 2017; Rago & Santoso, 2008; WHO, 2018a). However, the WHO has reported that one-third of the world's population does not have access to such products (Hogerzeil & Mirza, 2011). Roth et al. (2018) have suggested that the lack of timely access to new medicines may be addressed through the strengthening of registration efficiencies and timelines by establishing and refining value-added registration processes, resources and systems. An evaluated the South African regulatory review process, as it had been applied by the MCC, prior to the establishment of SAHPRA has been carried out (see Chapter 4). While this study provided an indication of the overall timelines of NASs approved and registered by the MCC during 2015-2017, the study focused on the organisation and the regulatory review process of the MCC and the status of good review practices that had been implemented.

This study aimed to identify the key milestones of the review process and to evaluate review times in South Africa for NASs approved during 2015-2018. This review was the first to be carried out of the specific milestones and timelines embedded within the South African regulatory review of NASs, as it had been applied by the MCC between 2015-2017 as well as through the transition period of the MCC to SAHPRA during 2018.

### Study objectives

The main objectives of this study were to:

- Identify the key milestones and measure the timelines of the South African review process for the period 2015-2018;
- Evaluate the overall timelines for the different new medicines approved in South Africa during this period;
- Review the challenges and opportunities for expediting the overall review timelines to enhance the regulatory performance in South Africa with a view to improving patients' access to new medicines.

## METHODS

### Data collection process

Data were collected reflecting the timelines between the various milestones including dossier validation and queue time, scientific assessment as well as the overall approval times for NASs, including NCEs, biologicals and MLEs registered by the South African NRA during the period 2015-2018. The data was sourced directly from the directorate within the Authority responsible for recording the timelines required to complete the regulatory review process. The number of NASs registered during this period was validated against the notifications of registration of medicines published by the Authority in the *Government Gazette* and available in the public domain. The definitions of the application types included in the study are shown in Table 5.1.

**Table 5.1 Definitions of the application types included in the study**

| APPLICATION TYPE | DEFINITION |
|---|---|
| **New active substances (NASs**) | Applications including new chemical entities (NCEs), biologicals and major line extensions (MLEs). |
| **New chemical entity (NCEs)** | Applications for medicines that have not previously been approved by the MCC or SAHPRA. These included chemical and radiopharmaceutical substances that had not been previously available in South Africa for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans and animals. |
| **Biological medicines (Biologicals)** | Applications for medicines where the active ingredient and/or key excipients had been derived from living organisms or tissues, or manufactured using a biological process. Biological medicines can be defined largely by reference to their method of manufacture (the biological process) and include applications that require additional scientific assessment by the Biological Medicines Committee of the MCC or SAHPRA (MCC, 2012) |

| | |
|---|---|
| **Major line extension (MLEs)** | Applications for medicines, already registered by the MCC or SAHPRA, where a change to the registered medicines, was sufficiently great that it could not be considered to be a simple variation to the original product, but required a new product authorisation. Such changes included major new therapeutic indications or new disease states, extension to new patient populations (e.g., paediatric patients), a new route of administration, or a novel drug delivery system. |
| **Fast track** | Applications that were eligible to be assigned to a "fast track" status in order to expedite the registration of essential medicines. While the review process was the same for "fast track" applications, these applications would be prioritised over existing applications, queued for allocation to reviewers. |

Abbreviations: MCC=Medicines Control Council; MLE=Major Line Extension; NAS=New Active Substance; NCE=New Chemical Entity; SAHPRA=South African Health Products Regulatory Authority

**Data analysis**

Data collected during the period 2015-2018 were analysed and the characteristics of the medicinal products submitted to the Authority for registration were described. The review type (fast-track/standard) applied to each application was identified (Table 5.1) as well as the origin (multinational company/local company) of the submission and the definition of the milestones within the review process (Table 5.2). The median timelines for each of the milestones within the review process as well as the median overall approval times were calculated and analysed. Median approval times by product type and therapeutic area were determined and all data was analysed as calendar days.

**Table 5.2 Definition of the milestones within the review process**

| MILESTONES | DEFINITION |
|---|---|
| **Overall approval time** | The time between the date stamped on **receipt of dossier** when received by the Authority and the **date that marketing authorisation** was granted. |
| **Dossier validation and queue time** | The time between the date stamped on **receipt of dossier** and the **"date of allocation"** of the dossier to a reviewer. |
| **Scientific assessment time** | Amount of time spent actively reviewing the dossier or additional information provided from the **"start of scientific assessment"** to **"completion of scientific assessment".** |
| **Applicant time* (clock stop-start time)** | Time during which the clock was stopped during the review whilst the authority awaited responses or additional data from the company. |
| **Other regulatory authority time** | Time taken up by the authority during the review for administration from the **"Completion of Scientific Assessment"** to the date of **"Marketing Authorisation Granted".** |

*Data pertaining to applicant time was not available

***Time series analysis***

Time series analysis was used to identify trends, indicating increases or decreases in the number of NASs registered by the MCC between 2015-2017; whether such increases or decreases in registrations were observed to be seasonally repetitive and related to specific seasons, quarters or months and whether there were any data points that did not lie close to the regression line and could be identified as outliers (PennState Eberly College of Science, 2019). As the scope of this study was exploratory in nature and not designed to support hypothesis testing, no further statistical analysis of the generated data was performed. The forecasted number of NASs registrations for 2018 was compared to the actual number of NASs registered by SAHPRA in 2018.

**RESULTS**

The characteristics and number of the NASs approved (NCEs, biologicals and MLEs) are shown in Table 5.3. While the data reflected for the period 2015-2017 represent the performance of the MCC, the results described for 2018 reflected the performance of SAHPRA during the initial stages of its establishment and transition. However, the results for 2018 do not reflect the re-engineered, streamlined processes developed by SAHPRA that were still in the process of being piloted prior to their final implementation. The NRA registered a total number of 121 NASs during 2015-2018. The applications for NASs registered during this time were submitted by 22 multinational companies and six local companies. The results of this study will be valuable in providing a baseline to quantitatively reflect the improvements that are envisaged through the implementation of the finalised, enhanced SAHPRA regulatory review process.

**Table 5.3 Categories of new active substances (NASs) approved (2015-2018)**

| | | Year of Submission | | | | (2015 – 2018) |
|---|---|---|---|---|---|---|
| **Submissions** | | **2015** | **2016** | **2017** | **2018** | **Total** |
| **Number approved (NASs)** | | 31 | 33 | 42 | 15 | 121 |
| **Number of approved NASs submitted by multinational companies** | | 23 | 27 | 33 | 10 | 93 |
| **Number of approved NASs submitted by local companies** | | 8 | 6 | 9 | 5 | 28 |
| **Type of NASs approved** * | | | | | | |
| **NCEs** | Regular Review | 16 (15;1) | 24 (19;5) | 31 (25;6) | 12 (7;5) | 83 |
| | Fast Track Review | 8 (2;6) | 3 (2;1) | 5 (4;1) | 0 | 16 |
| **Biologicals** | Regular Review | 3 (3;0) | 6 (6;0) | 5 (3;2) | 3 (3;0) | 17 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Fast Track Review | 0 | 0 | 0 | 0 | 0 |
| **MLEs** | Regular Review | 4 (3;1) | 0 | 1 (1;0) | 0 | 5 |
| | Fast Track Review | 0 | 0 | 0 | 0 | 0 |

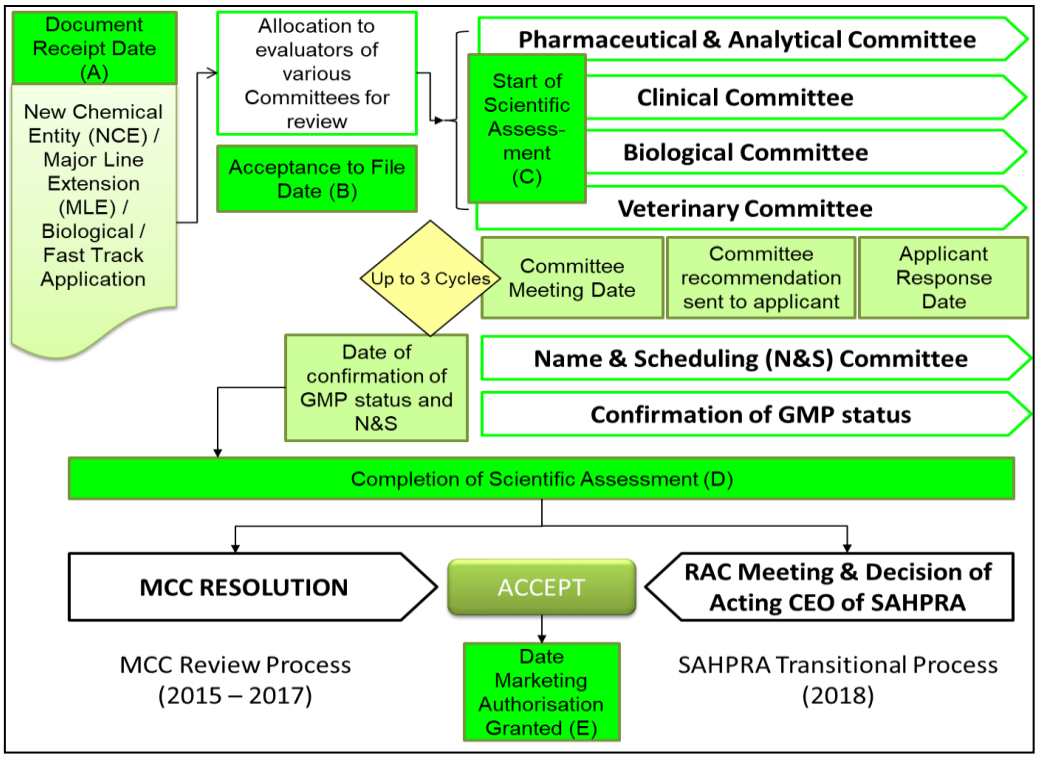
Abbreviations: MLE=Major Line Extension; NAS=New Active Substance; NCE=New Chemical Entity

*Number of applications submitted by multinational company; Number of applications submitted by local company

**Milestones and timelines in the regulatory review process**

The milestones in the MCC review process (2015-2017) were similar to those identified by other NRAs and are reflected in Figure 5.1 (A – E).

**Figure 5.1 Regulatory review process of the Medicines Control Council (MCC) and South African Health Products Regulatory Authority's (SAHPRA) transitional process**



Abbreviations: CEO=Chief Executive Officer; GMP=Good Manufacturing Practice; MCC=Medicines Control Council; MLE=Major line extension; N&S=Names & Scheduling; NAS=New Active Substance; NCE=New Chemical Entity; RAC=Regulatory Advisory Committee; SAHPRA=South African Health Products Regulatory Authority

Applications for registration were received and the dossier receipt date (A) recorded. Each application underwent administrative and technical screening against the evaluation criteria published in the various guidelines prepared by the Authority and were made available in the public domain. Following the validation of the application, the acceptance to file date (B) was recorded and the application would be allocated to a reviewer for evaluation. The date of allocation of the application to either an internal or external reviewer was recorded and considered to be the start date of the scientific assessment (C). Following the initial assessment of the application the reviewer prepares an assessment report which was tabled for discussion at the relevant scientific committee meeting and a recommendation was made. Scientific committee meetings were typically planned in 6-8 weeks cycles and there was no limit to the number of committee cycles for an application. The committee either prepared a recommendation to the company requesting further information to support the registration of the product or a final recommendation supporting its approval or rejection. Companies were required to provide a response to the committee's request for additional information within 180 calendar days. Once all the relevant scientific committees had made a final recommendation the date for the completion of the scientific assessment (D) was recorded.

Up until this point, the review process applied previously by the MCC and the transitional review process applied by SAHPRA in 2018 were the same. Under the MCC review process (2015-2017) the final recommendation of the various committees would be tabled for ratification at a Council meeting. A Council resolution would then be prepared and if this was supported, the registration of the product, a marketing authorisation would be granted. The date of the Council meeting at which the Council resolved to register the product was recorded as the date when marketing authorisation (E) was granted.

Under the transitional SAHPRA review process (2018), recommendations of the various scientific committees were considered by a regulatory advisory committee (RAC) that advised the CEO of the Authority on the approval or rejection of an application, in line with the amended provisions of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) (Medicines and Related Substances Act 2017). As such, the SAHPRA CEO was responsible for carrying out the functions of the Authority, including regulatory decisions to approve or reject an application for the registration of a medicine, as described in Section 3 (4)(e) of Act 101 of 1965 (Medicines and Related Substances Act 2017). Section 39 of Act 101 of 1965 allowed the CEO to appoint relevant committees to advise on all registration and regulatory matters.

**Overall approval times**

The NASs approved by the MCC (2015-2017) and SAHPRA (2018) covered 16 common therapeutic areas of which oncology products (n=25; 14 NCEs – 4 fast track; 6 biologicals; 1 MLE) were the highest followed by analgesics and anti-infectives (Figure 5.2). The results showed that the largest number of NAS approvals (n=42) were recorded in 2017 and that the majority (n=36) approved were NCEs (Table 5.3). All the NAS applications (n=121) that were registered during 2015-2018 were reviewed by the Authority using the full review process. Sixteen NCEs were assigned priority status and were reviewed through the fast track review process, while no applications for biologicals or MLEs were processed through this route.

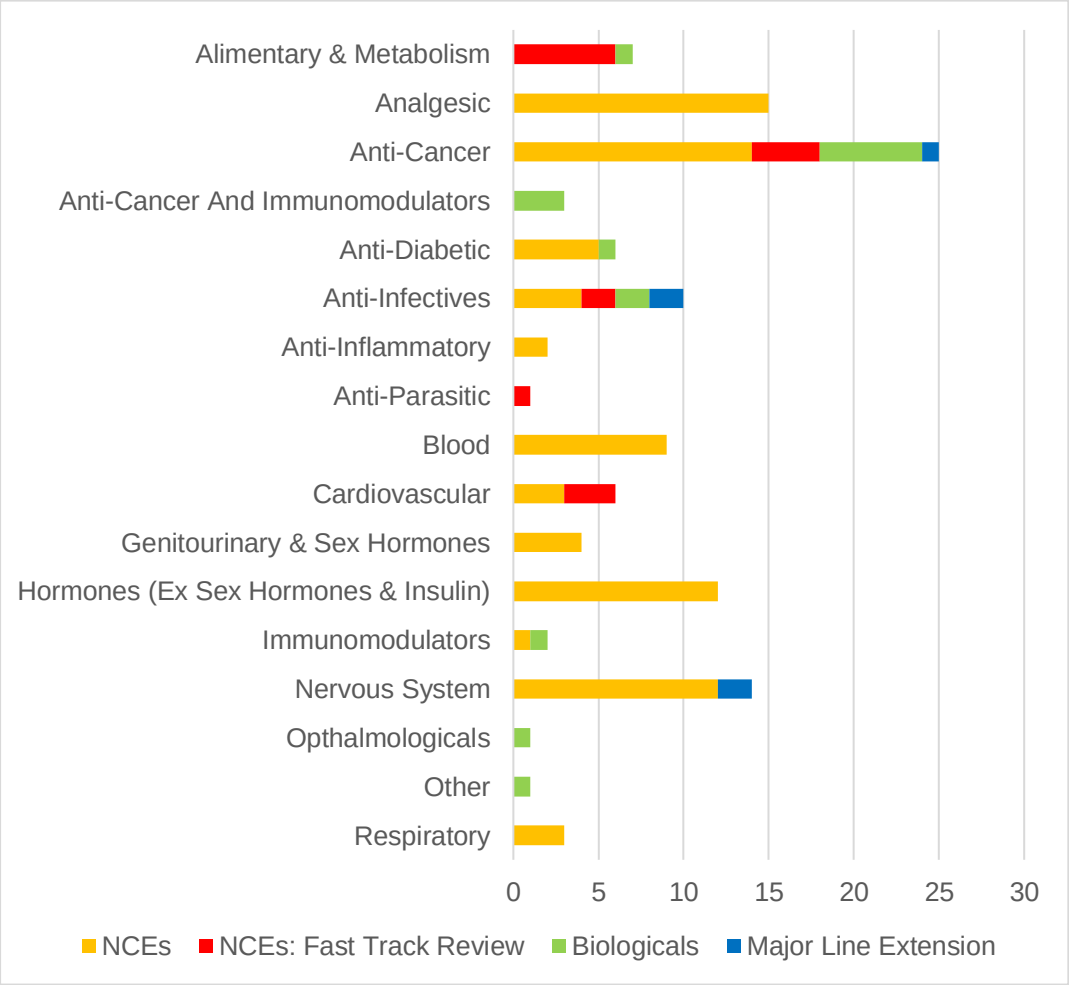
The overall median approval time for NASs was 1466 calendar days and this included NCEs evaluated through the standard and fast track review process as well as biologicals and MLEs approved between 2015-2018 (Figure 5.3). Furthermore, the shortest median approval time of 1218 calendar days was achieved in 2015 and the longest median approval time of 2124 calendar days was recorded in 2018. Most NASs (n=42) were approved in 2017 and the least number of NASs (n=15) were approved in 2018.

**Approval times for new chemical entities (NCEs) and biologicals**

During 2015 and 2016 the median overall approval timelines were less for NCEs (1175 and 1726 calendar days respectively) when compared with biologicals (2010 and 2027

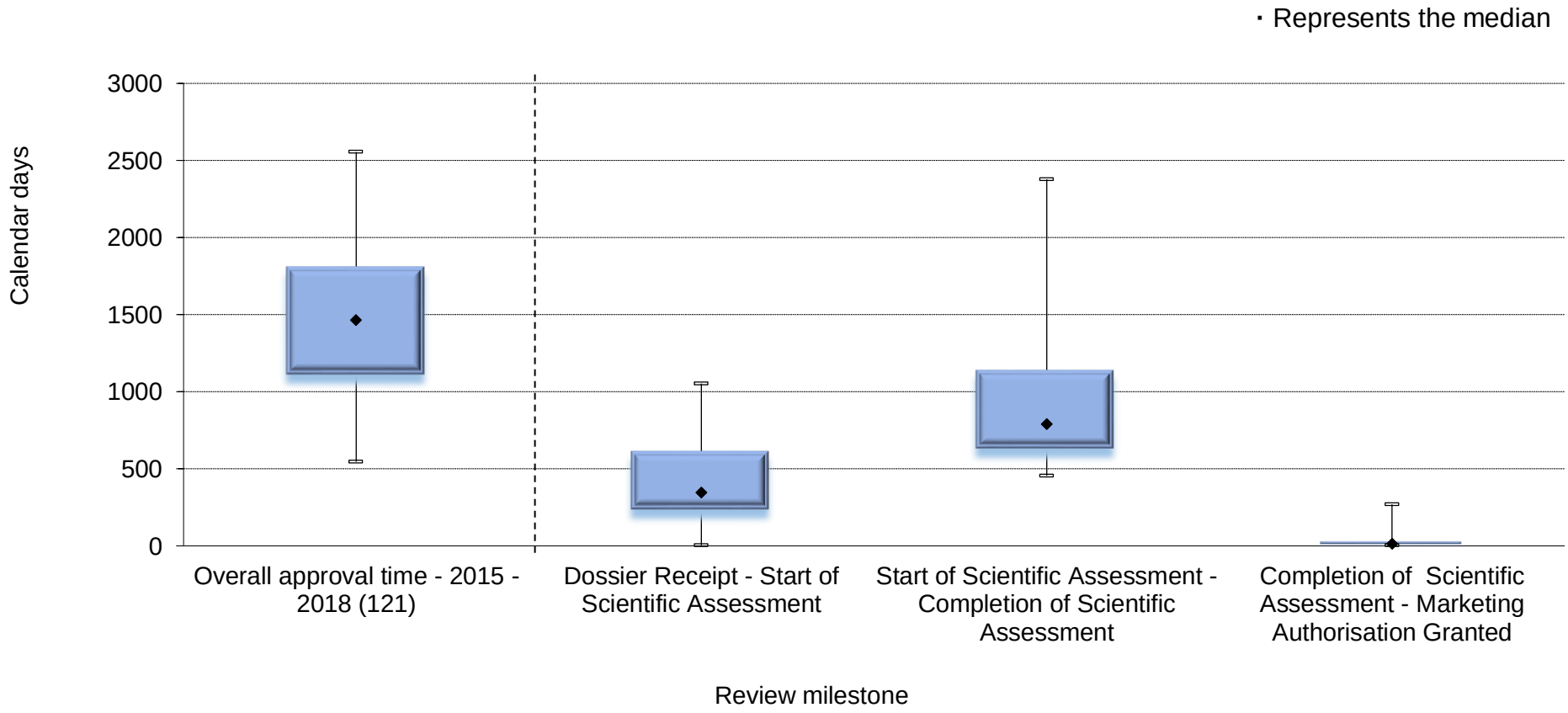
calendar days respectively) (Figure 5.4). In 2017 and 2018, the median overall approval timelines for biologicals decreased (725 and 1476 respectively) and was less than that observed for NCEs (1466 and 2124 respectively). The shortest median overall approval time achieved during this period was for 6 biologicals approved in 2017 (725 calendar days). The longest median overall approval time (2124 calendar days) was observed for 12 NCEs approved in 2018.

**Figure 5.2 Categories of new active substances (NASs) approved by therapeutic area (2015-2018)**



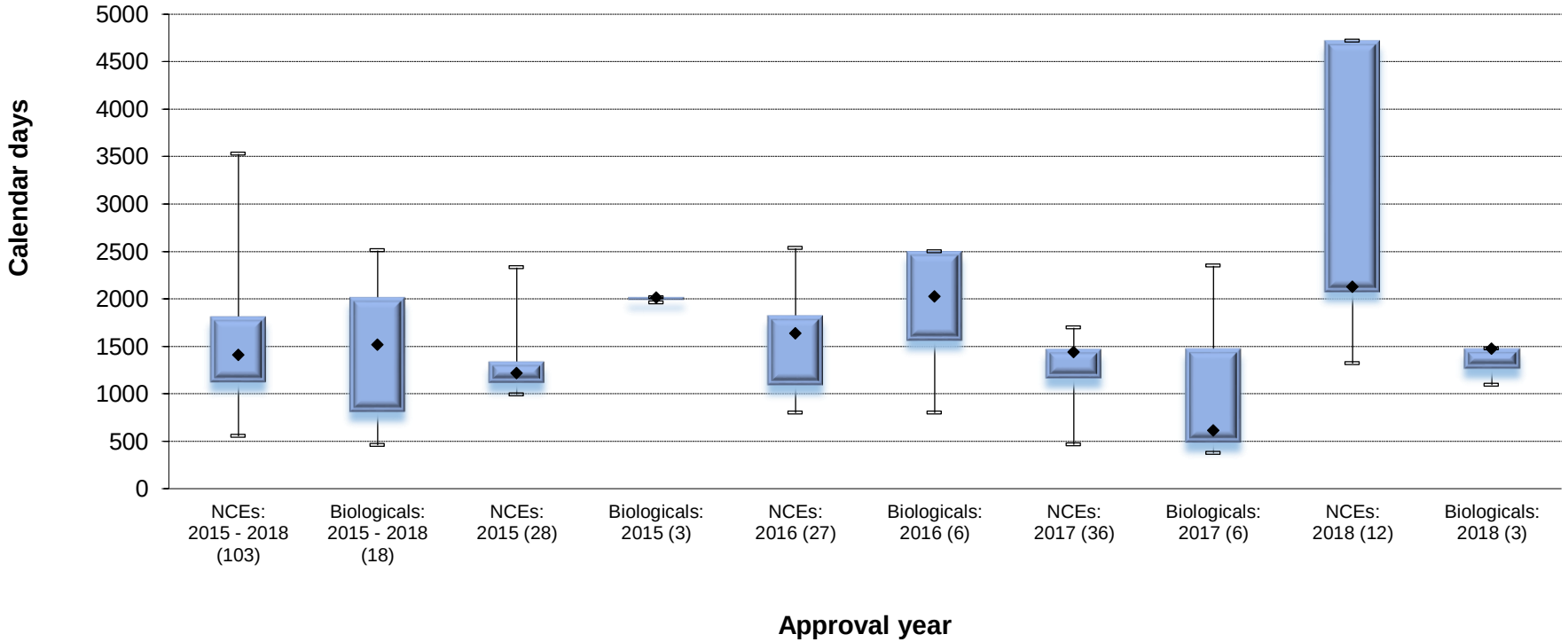

Abbreviations: NCE=New Chemical Entity

**Figure 5.3 Median overall approval times* for new active substances (NASs) (2015-2018)**



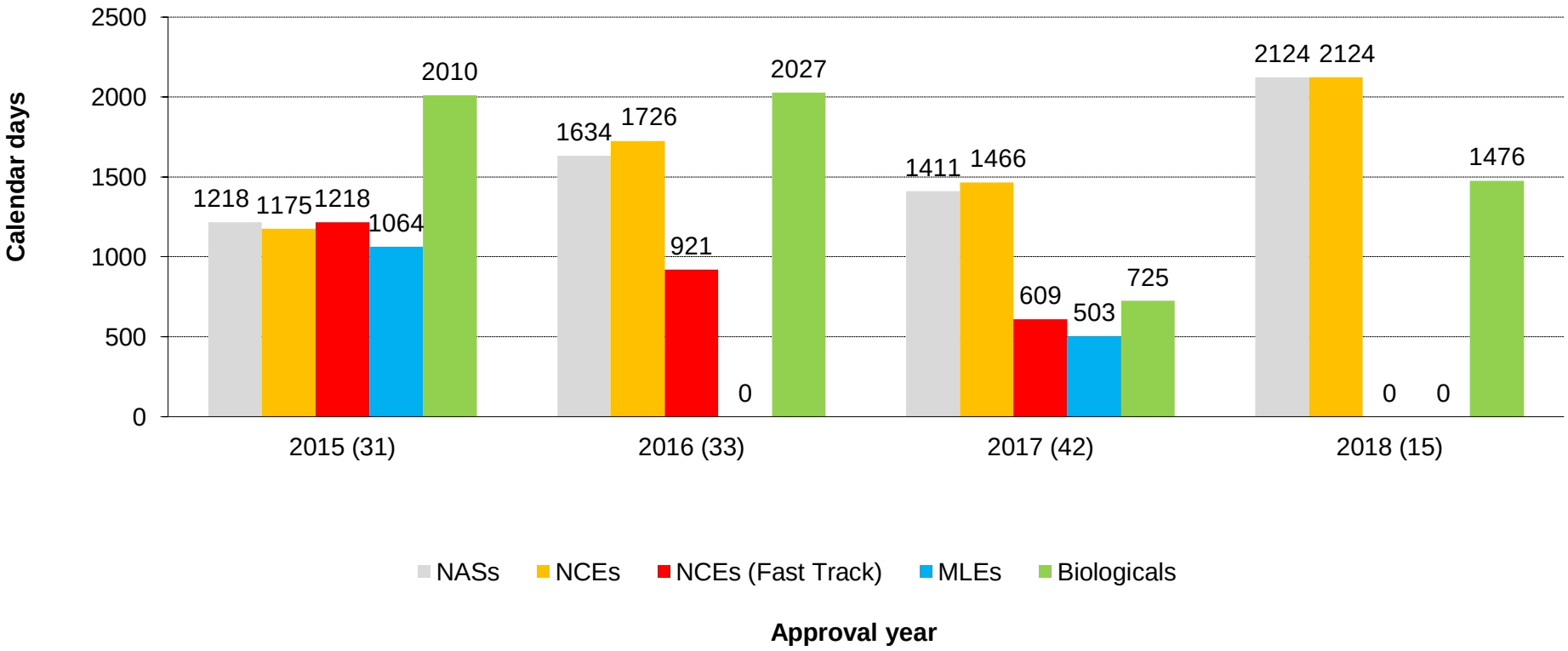

*Number of NASs approved

**Figure 5.4 Median overall approval times for new chemical entities (NCEs) and biologicals (2015-2018)**




Abbreviations: NCE=New Chemical Entity

**Figure 5.5 Median overall approval time for new actives substances (NASs) by categories (2015-2018)**




Abbreviations: MLE=Major Line Extension; NAS=New Active Substance; NCE=New Chemical Entity

Three biologicals and 16 NCEs were approved in 2015, eight NCEs were approved through the fast track review process and the four MLEs approved were also for NCEs (Figure 5.5). There were no MLEs approved in 2016 or 2018. Only one MLE, which was a biological, was approved in 2017. During the SAHPRA transitional period of 2018, no applications for registration were assigned fast track status. The fast track review process was applied to three NCEs approved in 2016 and five NCEs approved in 2017. Overall this study demonstrated that over the period 2015-2018 the review times for NCEs significantly increased from 1175 (2015) to 2124 (2018) while for biologicals this decreased from 2010 in 2015 to 1476 in 2018.

***Time series analysis***

Time series analysis was used to analyse the data collected during this study, which consisted of the number of NASs registered by the MCC, per quarter, in the period 2015-2017 (Table 5.4).

**Table 5.4 Number of new active substances (NASs) registered by the Medicines Control Council (MCC) per quarter (2015-2017)**

| | **Quarter 1** | **Quarter 2** | **Quarter 3** | **Quarter 4** | TOTAL |
|---|---|---|---|---|---|
| **2015** | 8 | 5 | 4 | 14 | 31 |
| **2016** | 7 | 8 | 18 | 0 | 33 |
| **2017** | 8 | 21 | 13 | 0 | 42 |

The ratio-to-moving-average method was used to calculate seasonally adjusted indices for each quarter in the period 2015-2017. This method was selected because it is widely used to measure seasonal variation and integrate trends into forecasting. The four-quarter moving average was calculated by dividing the sum of four values for “y” by 4 on a rolling basis from quarter 1: 2015 to quarter 4: 2017 (Table 5.5). The centred average was calculated by determining the average of two “four-quarter moving averages” on a rolling basis (Table 5.5). The percentage of average was calculated by multiplying “y” by the corresponding centred average (Table 5.5).

**Table 5.5 Calculation of the four-quarter moving average, the centred average and the percentage of average for new active substances (NASs) registered by the Medicines Control Council (MCC) per quarter (2015-2017)**

| Time Period | Quarter | x Code | y (number of NAS registered per Quarter) | Four-Quarter Moving Average | Centred Average | % of average |
|---|---|---|---|---|---|---|
| 2015 | Q1 | 1 | 8 | | | |
| 2015 | Q2 | 2 | 5 | | | |
| | | | | 7,75 | | |
| 2015 | Q3 | 3 | 4 | | 7,625 | 52,459 |
| | | | | 7,5 | | |
| 2015 | Q4 | 4 | 14 | | 7,875 | 177,777 |
| | | | | 8,25 | | |
| 2016 | Q1 | 5 | 7 | | 10 | 70 |
| | | | | 11,75 | | |
| 2016 | Q2 | 6 | 8 | | 10 | 80 |
| | | | | 8,25 | | |
| 2016 | Q3 | 7 | 18 | | 8,375 | 214,925 |
| | | | | 8,5 | | |
| 2016 | Q4 | 8 | 0 | | 10,125 | 0 |
| | | | | 11,75 | | |
| 2017 | Q1 | 9 | 8 | | 11,125 | 71,91 |
| | | | | 10,5 | | |
| 2017 | Q2 | 10 | 21 | | 10,5 | 200 |
| | | | | 10,5 | | |
| 2017 | Q3 | 11 | 13 | | | |
| 2017 | Q4 | 12 | 0 | | | |

Abbreviation: NAS=New Active Substance

**Table 5.6 Calculation of the mean, adjustment factor and seasonal index for new active substances (NASs) registered by the Medicines Control Council (MCC) per quarter (2015-2017)**

| YEAR | Q1 | Q2 | Q3 | Q4 | TOTAL |
|---|---|---|---|---|---|
| 2015 | | | 52,459 | 177,777 | |
| 2016 | 70 | 80 | 214,925 | 0 | |
| 2017 | 71,91 | 200 | | | |
| MEAN | 70,955 | 140 | 133,692 | 88,885 | 433,532 % |
| MULTIPLY BY ADJUSTMENT FACTOR | 0,922654 | 0,922654 | 0,922654 | 0,922654 | |
| SEASONAL INDEX | 65,46691 | 129,1715 | 123,3514 | 82,01009 | 400 % |

The mean for each quarter was determined by calculating the mean of the percentage of average for each quarter (Table 5.6). The adjustment factor was calculated by dividing the sum of 100% for each quarter (4 x 100 %) by the sum of the means for each quarter (Table 5.6):

$$Adjustment\ Factor = \frac{400}{433{,}532}$$

$$Adjsutment\ Factor = 0{,}922654$$

The seasonal index for each quarter was calculated by multiplying the mean for each quarter with the adjustment factor (Table 5.6):

$$Seasonal\ Index\ Q1 = 70{,}955\ X\ 0{,}922654$$

$$Seasonal\ Index\ Q1 = 65{,}46691$$

$$Seasonal\ Index\ Q2 = 140\ X\ 0{,}922654$$

$$Seasonal\ Index\ Q2 = 129{,}1715$$

$$Seasonal\ Index\ Q3 = 133{,}692\ X\ 0{,}922654$$

$$Seasonal\ Index\ Q3 = 123{,}3514$$

$$Seasonal\ Index\ Q4 = 88{,}885\ X\ 0{,}922654$$

$$Seasonal\ Index\ Q4 = 82{,}01009$$

A regression analysis was performed in order to get the line of best fit for the data collected.

Regression line equation:

$y = a + bx$

$$y = 7{,}42445 + 0{,}2167\,x$$

Using this equation, values of y were predicted for quarter 1 to 4 for 2018 and 2019 and xy and $x^2$ were calculated (Table 5.7).

**Table 5.7 Calculation of xy and $x^2$**

| | $x$ code | $y$ | $xy$ | $x^2$ |
|---|---|---|---|---|
| | 1 | 8 | 8 | 1 |
| | 2 | 5 | 10 | 4 |
| | 3 | 4 | 12 | 9 |
| | 4 | 14 | 56 | 16 |
| | 5 | 7 | 35 | 25 |
| | 6 | 8 | 48 | 36 |
| | 7 | 18 | 126 | 49 |
| | 8 | 0 | 0 | 64 |
| | 9 | 8 | 72 | 81 |
| | 10 | 21 | 210 | 100 |
| | 11 | 13 | 143 | 121 |
| | 12 | 0 | 0 | 144 |
| $\sum$ | 78 | 106 | 720 | 650 |

$a = \frac{\sum y}{n} - b\frac{\sum x}{n}$ $\quad n = 12$

$a = \bar{y} - b\bar{x}$

$a = 8{,}833 - b\,(6{,}5)$

$a = 8{,}833 - (0{,}2167)\,(6{,}5)$

$a = 7{,}42445$

$\mathrm{b} = \frac{n\sum xy}{n\sum x^2} - \frac{\sum x \sum y}{(\sum x)^2}$

$\mathrm{b} = \frac{12(720)}{12(650)} - \frac{(78)(106)}{(78)^2}$

$b = \frac{372}{1716}$

$b = 0{,}2167$

$\bar{x} = \frac{\sum x}{n}$

$\bar{x} = \frac{78}{12}$

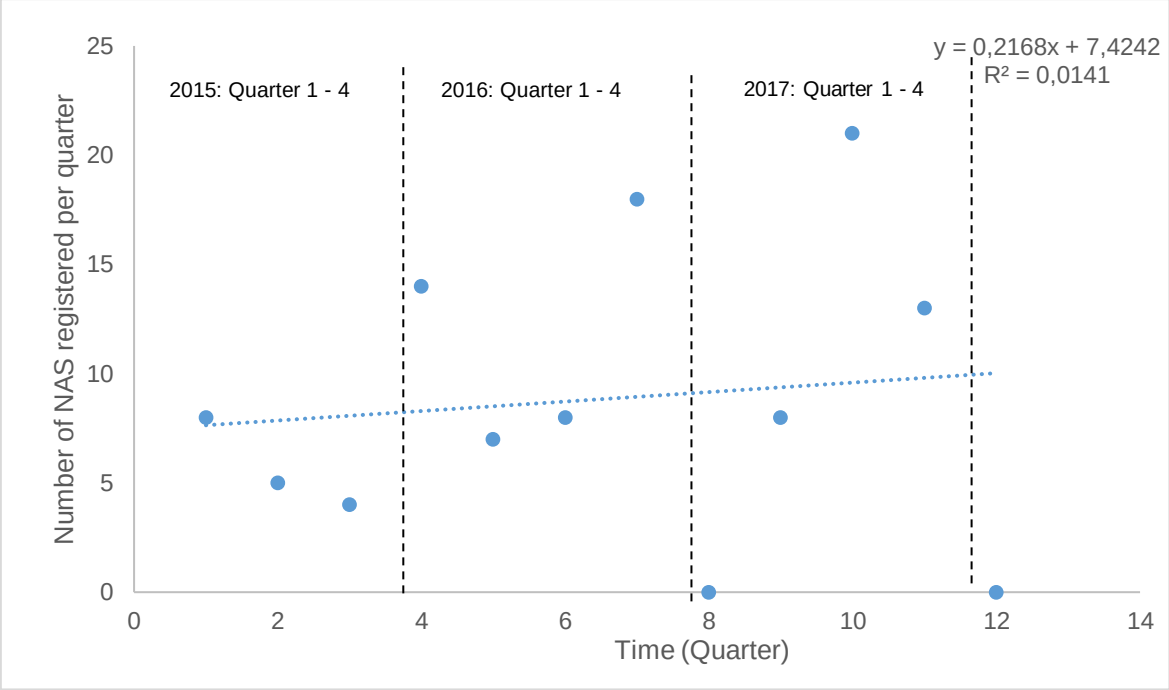
$\bar{x} = 6{,}5$

$\bar{y} = \frac{\sum y}{n}$

$\bar{y} = \frac{106}{12}$

$\bar{y} = 8{,}833$

**Figure 5.6 Scatter plot representing the number of new active substances (NASs) registered by the Medicines Control Council (MCC) per quarter (2015-2017)**




Abbreviation: NAS=New Active Substance

$a = 7{,}42445$ indicated the point at which the trend line intercepts the y-axis

$b = 0{,}2167$ indicated the slope of the trend line which was increasing slightly

$R^2 = 0{,}0141$

The standard error ($R^2$ = 0.0141) represented the residual standard deviation and indicated the typical deviation between the actual data (actual number of NASs registered in 2018) and the predicted value (predicted number of NASs registered in 2018) which was represented by the trend line. While the trend line was observed to be increasing slightly, the typical fluctuation around the regression line was 6,84 ~ 7 (Figure 5.6). The regression statistics were calculated and analysed (Table 5.8) and the seasonally adjusted trend estimates used to forecast the number of registrations expected for quarter 1 – quarter 4 (2018-2019) were determined (Table 5.9). The results of actual vs. the predicted number of new active substances (NASs) registered in 2018 were determined (Table 5.10).

## Table 5.8 Regression statistics

| *Regression Statistics* | |
|---|---|
| Multiple R | 0,1188618 |
| R Square | 0,01412813 |
| Adjusted R Square | 0,08445906 |
| Standard Error | 6,84796603 |
| Observations | 12 |

ANOVA

| | *df* | *SS* | *MS* | *F* | *Significance F* |
|---|---|---|---|---|---|
| Regression | 1 | 6,72027972 | 6,72027972 | 0,143305928 | 0,712929123 |
| Residual | 10 | 468,9463869 | 46,89463869 | | |
| Total | 11 | 475,6666667 | | | |

| | *Coefficients* | *Standard Error* | *t Stat* | *P-value* | *Lower 95%* | *Upper 95%* | *Lower 95,0%* | *Upper 95,0%* |
|---|---|---|---|---|---|---|---|---|
| Intercept | 7,4244 | 4,2146 | 1,7615 | 0,1086 | -1,9665 | 16,8150 | -1,9665 | 16,8150 |
| X Code | 0,2167 | 0,5726 | 0,3785 | 0,7129 | -1,0591 | 1,4927 | -1,0591 | 1,4927 |

Abbreviation: ANOVA=Analysis of Variance.

**Table 5.9 Seasonally adjusted trend estimates used to forecast the number of registrations expected for quarter 1 – quarter 4 (2018-2019)**

| Quarter/Year | $x$ code | $y = a + bx$ | $y$ | Multiplied by the seasonal index for each quarter | Expected number of NAS to be registered in each Quarter * |
|---|---|---|---|---|---|
| QUARTER 1 - 2018 | 13 | $y = 7{,}42445 + 0{,}2167(13)$ | 10,24155 | $y = 10{,}24155\ x\ \frac{65{,}46691}{100}$ | 6,70 = 7 |
| QUARTER 2 - 2018 | 14 | $y = 7{,}42445 + 0{,}2167(14)$ | 10,45825 | $y = 10{,}45825\ x\ \frac{129{,}1715}{100}$ | 13,51 = 14 |
| QUARTER 3 - 2018 | 15 | $y = 7{,}42445 + 0{,}2167(15)$ | 10,67495 | $y = 10{,}67495\ x\ \frac{123{,}3514}{100}$ | 13,17 = 13 |
| QUARTER 4 - 2018 | 16 | $y = 7{,}42445 + 0{,}2167(16)$ | 10,89165 | $y = 10{,}89165\ x\ \frac{82{,}01009}{100}$ | 8,93 = 9 |
| QUARTER 1 - 2019 | 17 | $y = 7{,}42445 + 0{,}2167(17)$ | 11,10835 | $y = 11{,}10835\ x\ \frac{65{,}46691}{100}$ | 7,27 = 7 |
| QUARTER 2 - 2019 | 18 | $y = 7{,}42445 + 0{,}2167(18)$ | 11,32505 | $y = 11{,}32505\ x\ \frac{129{,}1715}{100}$ | 14,63 = 15 |
| QUARTER 3 - 2019 | 19 | $y = 7{,}42445 + 0{,}2167(19)$ | 11,54175 | $y = 11{,}54175\ x\ \frac{123{,}3514}{100}$ | 14,24 = 14 * |
| QUARTER 4 - 2019 | 20 | $y = 7{,}42445 + 0{,}2167(20)$ | 11,75845 | $y = 11{,}75845\ x\ \frac{82{,}01009}{100}$ | 9,64 = 10 |

Abbreviation: NAS=New Active Substance

Values rounded off to the nearest whole number

**Table 5.10 Results of actual vs. predicted number of new active substances (NASs) registered in 2018**

| | 2018 | | | | |
|---|---|---|---|---|---|
| | **Quarter 1** | **Quarter 2** | **Quarter 3** | **Quarter 4** | **TOTAL** |
| **Actual number of NAS registered per Quarter** | 6 | 5 | 2 | 2 | 15 |
| **Predicted number of NAS registered per Quarter** | 7 | 14 | 13 | 9 | 43 |

## DISCUSSION

National regulatory authorities (NRAs) globally measure overall approval timelines for the registration of medicines to demonstrate their performance as regulators. While this metric is not the only indicator of regulatory performance, it does contribute significantly to achieving the mandate of the NRAs in ensuring timely access of safe, quality and effective medicines to patients. As such, it is critical to any improvement to ensure the routine and accurate measurement and monitoring of performance metrics of the regulatory review process. Benchmarking milestones currently used by NRAs typically include the times for receipt and validation, scientific assessment, applicants' response, market authorisation to be granted as well as the time taken to complete all administrative activities. The data collected from the MCC and SAHPRA for the period 2015-2018 demonstrated that several of these milestones were recorded, but not measured and monitored.

The Authority conducted a full assessment for each of the applications registered during the period 2015-2018. This type of review required the scientific assessment of the quality, safety and efficacy data submitted by the company to support the approval of the medicines on the South African market. While the dossier receipt date and date of allocation of the dossier to a reviewer were recorded it was not possible to confirm the time taken to validate the document through administrative and technical screening. Consequently, it could not be determined how long each application spent in the queue prior to being allocated to a reviewer. While there was no set target for the completion of the scientific assessment, reviewers were requested to complete

assessments within 90 calendar days, however this timeline was not systematically monitored and the data collected demonstrated that this timeline was not always met. Each application was evaluated in parallel by the various scientific committees and the dates of the scientific committee meetings, at which the reviewer's assessment reports were discussed, were available. There was no limit to the number of times an application went through a scientific committee cycle. The data collected during the period 2015-2018 reflected that on average there was a maximum of three cycles for an application within any given scientific committee. While applicants were encouraged to respond to the request of the scientific committees for additional information within 180 calendar days, this requirement was neither monitored nor enforced. Unfortunately, the data provided did not allow for the accurate calculation of the clock stop so it was not possible to determine the amount of time the applications spent with the scientific committee nor the time it took for the applicant to respond. Based on the data collected and reflecting on the correspondence from companies, the consequent assessment report dates and the committee meeting dates, it was apparent that the Authority routinely accepted responses from companies that considerably exceeded the recommended response timeline of 180 calendar days. Nevertheless, if the company response time was to be reduced and implemented, this could reduce the time that an application would spend in the system.

The review process of the former MCC as well as that during the transitional period for SAHPRA did not set targets for milestones within the review process and no target was set for the overall approval time of applications. It is critical for NRAs to develop, maintain and strengthen a culture of performance measurement so that the results can be used to optimise regulatory outcomes.

**Regulatory review approval timelines**

The overall approval timelines for the regulatory review achieved by the MCC (2015-2017) and by SAHPRA (2018) were extensive and did not contribute to ensuring timely access to medicines for patients in South Africa. The forecasted number of NASs registrations for 2018 was compared to the actual number of NASs registered by SAHPRA in 2018. The actual data for quarter 1 of 2018 was comparable with the predicted value for number of NASs registered in quarter 1 2018. The predictions for the number of NASs registered in quarter 2 to quarter 4 of 2018 did not correspond

with the actual number of NASs registered for Quarter 2 to 4 in 2018. The results of the time series analysis indicated that there was inconsistency in the data, there was no trend, no indication of seasonal fluctuations and no repetition in any particular pattern.

As previously described in Chapter 3, both the historical and the operational factors contributed to these extended timelines. There were no comparative studies available to reflect the regulatory performance of South Africa relative to other African countries, however it was noted that a target overall approval timeline of 330 calendar days had been set by the Zazibona collaborative process (Makamure-Sithole, 2019); a harmonisation and joint-review initiative in the SADC region, in which South Africa has participated since 2016. This target was almost five times less than the median approval timeline for NASs reported in this study. The scope of Zazibona included NASs and was not limited to the assessment of generic medicines although this was predominantly the group of products being reviewed. It also raised the question as to whether applicants wishing to register medicines in South Africa preferred to opt for a registration through the Zazibona pathway in order to circumvent the longer review timelines for NASs demonstrated in this study.

Median approval times for NASs approved during 2014-2018 in developing markets have already been studied and demonstrated that the timelines achieved by South Africa were the longest when compared to those in other developing markets (CIRS, 2019b). The timelines reported for South Africa were nearly double when compared to Indonesia and Algeria (for whom the second and third longest timelines were reported respectively); and approximately seven times longer when compared to Mexico (for whom the shortest timeline was reported) (CIRS, 2019b). It is, however, important to note that while these results demonstrated vast differences in the overall approval time achieved by South Africa in comparison to other developing markets, many of these countries have implemented FRPs. The FRPs allow NRAs to reduce duplication of regulatory effort, recognise the decisions made by other NRAs and apply abridged review or verification processes in their assessment of applications for registration of NASs. All the applications for NASs registration approved by South Africa during this period underwent a full review. All of the NASs registered by SAHPRA during 2018 had been previously assessed and approved by at least one or

more of the following countries: Australia, Canada, Europe, Japan, Switzerland and USA. Considering that SAHPRA intends to rely on or recognise the regulatory decisions of many of these listed countries, FRPs could have been utilised in the registration of the NASs approved by SAHPRA in 2018. The formalised implementation of FRPs in the assessment of these NASs could have resulted in a considerably reduced time line for registration and accelerated patients' access to these NASs. To this effect, SAHPRA is considering the use of FRPs in the future.

**Challenges and opportunities for improvement**

Historically the MCC did not identify key milestones within the review process and did not set or enforce target timelines for these milestones. The median overall approval time for the registration of NASs was neither measured nor monitored and, together with a growing number of applications, consequently resulted in a large backlog in medicine registration. At its inception, SAHPRA's inherited backlog of work comprised of approximately 16 000 applications, including 8300 registration applications and 7200 variation applications (Mahlatji, 2019, unpublished industry update). Over 90% of these applications were for generic medicines and included duplicate applications as well as applications for products with multiple strengths. Of these, approximately 545 were applications for the registration of NASs. An application survey was concluded in January 2019 and an analysis of the information provided through this survey resulted in the agreed withdrawal of approximately 3 000 registration applications from the backlog. A validation exercise was completed in consultation with the industry stakeholders to facilitate the planning of the backlog work schedule and to define the process and timelines for resubmission of updated applications for registration. The work plan was devised to support the prioritisation of applications for medicines serving the therapeutic areas that addressed the highest public health need within South Africa, as agreed upon in consultation with the South African National Department of Health. A dedicated team was appointed by SAHPRA to address the backlog, in an effort to avoid resource constraints or delays in its routine workload. The backlog clearance program was planned for implementation in the third quarter of 2019 and it was the intention of SAHPRA to clear the backlog within two years (Mahlatji, 2019, unpublished industry update). Median overall approval times recorded for 2015-2018 demonstrated a noteworthy departure from the approval times achieved by other NRAs of a similar size and with a similar regulatory mandate. All of the NASs

approved during this period were evaluated using a full review. The regulatory effort applied in the assessment of applications for registration should be commensurate with the level of risk of the product and should not impose an unwarranted regulatory burden. In view of the fact that the NASs, registered during this period, had been previously reviewed by one or more reference agency, the review time for these NASs could have been considerably reduced if a reliance mechanism had been in place.

Section 2B (2b) of the Medicines and Related Substance Act, 1965 (Act 101 of 1965) supported the use of FRPs (Medicines and Related Substances Act 2017). The implementation of FRPs should be considered in order to ensure the effective allocation of limited resources (Liberti et al., 2016). Participation in joint and shared review initiatives will continue to support the effort to decrease the overall approval time for medicine registration (Azatyan, 2019). While the former MCC had set a target review time of 250 calendar days for products reviewed using the fast track review process, this target was not achieved during the period 2015-2017. SAHPRA should define the eligibility criteria for fast track designation and should consider the possibility of stratifying the pathways and target timelines within the fast track process (USFDA, 2018). SAHPRA should implement systems to accommodate the accelerated approval of NASs that address unmet needs, NASs required in response to emergency situations and breakthrough NASs that demonstrate substantial improvement over available medicines (USFDA, 2018). This stratified approach may also require SAHPRA to consider regulatory trade-offs involving acceptance of surrogate end-points supported by strengthened post-marketing commitments such as the reallocation of regulatory resources from pre-marketing to post-marketing functions (Roth et al., 2018; USFDA, 2018).

As SAHPRA moves forward with the implementation of the newly restructured review process it is critical to ensure that the quality management system (QMS) is formalised to support the consistent application of GRPs, GRevPs and GRelPs within the review process. Furthermore, in an effort to prove itself as an effective, responsive, transparent and accountable regulatory authority, SAHPRA should consider the use of the UMBRA framework for the BR assessment of NASs and progressive QDMPs (Walker et al., 2014; Bujar et al., 2016).

This study has evaluated the regulatory review process of the former MCC as well as that applied by SAHPRA during the initial stages of its establishment and transition. The key milestones and timelines of the South African review process for the period 2015–2018 have been identified and measured and the challenges and opportunities for decreasing the overall approval timelines together with an improved review process have been considered. While the extensive delays in NAS approvals could be attributed to deficient operational processes, resource constraints and increased volume of applications for registration, there is now an opportunity for improvement. The SAHPRA have developed a re-engineered, streamlined regulatory review process that has been piloted for final implementation.

The following key recommendations may be considered to support the restructuring and enhancement of the SAHPRA regulatory review process:

**Measuring & Monitoring:** Identify, record, monitor and measure milestones in the review process**,** codify and enforce benchmarked targets for each milestone.

**Facilitated Regulatory Pathways (FRPs):** Define and codify the type of product review assessments that will be used by SAHPRA, including a full review, abridged review and verification review as well as continuing to enhance regional, continental and international collaborations for joint and shared reviews.

**Regulatory trade-offs:** Consideration of surrogate endpoints to inform expedited market authorisation for NASs supported by strengthened post-market surveillance commitment.

**Robust Information and Communication Technology (ICT) System:** The development, implementation and maintenance of enhanced ICT solutions, supported by dedicated resources, should be considered in order to facilitate the adequate and accurate tracking of applications and decision-making as well as improved document management, transparency and stakeholder communication.

**Quality Management System (QMS):** Formalise GRPs, GRevPs and GRelPs within the review process**,** implement the UMBRA framework for BR assessment and ensure transparent and consistent QDMPs.

**SUMMARY**

- The aim of this study was to evaluate the timelines of the milestones of the South African review process and the overall approval process for NASs for the period 2015-2018

- Data identifying the milestones and overall approval times for NASs, including NCEs, biologicals and MLEs registered by the South African Agency during the period 2015-2018 were collected and analysed

- The results showed that the largest number of NAS approvals were recorded in 2017 (n=42) and that the least (n=15) were in 2018

- The shortest median approval time for NASs, of 1218 calendar days, was achieved in 2015 and the longest median approval time of 2124 calendar days, was recorded in 2018

- All the applications that were registered during 2015-2018 were reviewed by the Authority using the full review process

- Sixteen out of a total of 99 NCEs (16%) were assigned priority status and were reviewed and approved through the fast track review process, whereas no applications for biologicals and MLEs were processed by this route

- While the extensive delays in NASs approvals may be attributed to inefficient operational processes, resource constraints as well as an increased number of applications for registration, there is still an opportunity for improvement

- SAHPRA has re-engineered and streamlined its regulatory review process which has been piloted and will be ameliorated prior to final implementation

# CHAPTER 6

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# Comparison of the Medicine Control Council's Regulatory Review Processes with Australia, Canada, Singapore and Switzerland

## INTRODUCTION

Efforts toward regulatory harmonisation and convergence have been evident over the last 20 years and have been supported through the initiation of both NRAs and the pharmaceutical industry. The impact of these efforts has translated into globally standardised technical regulations and requirements for the quality, efficacy, and safety of medicines and their improved access by patients (WHO, 2000). While each country has autonomy in the manner in which it effects its regulatory mandate in line with national requirements, it is recognised that there is value in benchmarking regulatory models and sharing best practices (Mashaki Ceyhan et al., 2018). Comparisons between NRAs of similar size, regulatory mandates, structures, resource characteristics and regulatory challenges would be more beneficial than comparisons between authorities with vastly different characteristics and competencies (Mashaki Ceyhan et al., 2018). National regulatory authorities (NRAs) in jurisdictions within the emerging pharmaceutical markets would benefit from comparisons with other mature NRAs of similar size such as Health Canada and the Australian TGA (Hashan et al., 2016).

The NRA of South Africa was mandated through the Medicines and Related Substances Act, 1965 (Act 101 of 1965) to ensure the efficient, effective and ethical assessment and registration of medicines and medical devices that met defined standards of quality, safety, efficacy and performance (Medicines and Related Substances Act 2017). The South African NRA was also responsible for ensuring that the process of assessing and registering medicines and medical devices was transparent, fair, objective and concluded within an appropriate time frame (Medicines and Related Substances Act 2017). In June 2017, the Medicine and Related Substances Act, 1965 (Act 101 of 1965), was amended to allow for the transition of the MCC to SAHPRA. This transition provided an opportunity to study the regulatory processes applied by the MCC with a view to enhancing the regulatory review process and the responsiveness of the NRA as it moved toward effecting its improved regulatory landscape as SAHPRA. As SAHPRA moved forward with its objective for regulatory reform, it was important that the authority had the relevant capabilities and decision-making frameworks in place to ensure the efficient application of resources with a view to improving overall approval times and patients' access to new medicines. The former regulatory performance of the MCC served as a baseline from which

SAHPRA could monitor progress and achievements whilst benchmarking planned reform against that of other NRAs in order to identify the strengths and areas for improvement. A comparative study of the regulatory performance of the MCC registration process with that of other NRAs in the developed and emerging markets had not been previously performed. Therefore, there was a need for such a study as the South African NRA strived to become a reference NRA in the African region. Similar studies have been performed to compare the Turkish Medicines and Medical Devices Agency (Mashaki Ceyhan et al., 2018), the Saudi Food and Drug Authority (Hashan et al., 2016) and the Jordan Food and Drug Administration (Haqaish et al., 2017) with the NRAs of Australia, Canada and Singapore. This study aimed to compare the registration process of the MCC in South Africa with the processes of Australia, Canada, Singapore and Switzerland. It allowed for the identification of the strengths, challenges and areas of improvement within the regulatory review processes applied by the MCC. This study also aimed to assess the level of implementation of quality measures, GRevPs, QDMPs and continuous improvement initiatives within the MCC operations.

## METHODS

### Study participants

This study provided a comparison of the registration process historically administered by the MCC against that of four other NRAs, including TGA, Health Canada, the HSA and Swissmedic. These NRAs were selected as comparators as the size of the agencies, the patient population they served, the year established and the nature of the review model (full assessment) applied were comparable to those of the MCC. The data for the comparator agencies was collected in 2014 and subsequently updated in 2017. It was recognised that it would not be appropriate to compare the MCC against an agency such as the USFDA, whose financial resources and number of reviewers were not comparable, or an agency such as the EMA, whose review process engaged rapporteur and co-rapporteur in the review and constituted a totally different review model to that of South Africa. NRAs in the region, such as Kenya and Nigeria were not considered as the population they serve was much larger than that of South Africa. Many NRAs in the emerging economies did not conduct a full review of NASs and as such were deemed to be inappropriate as comparator NRAs.

### Study tool and data collection process

The questionnaire (McAuslane et al., 2009; CIRS, 2019c) (see Appendix 1) used in the study was completed and validated by the then Registrar of the MCC in 2017. The completed questionnaire described the regulatory review system for market authorisation of NASs as applied by the MCC and the overall review times of NASs from the date of application to the date of approval during the period 2015-2017. The questionnaire (McAuslane et al., 2009; CIRS, 2019a) used in this study was initially developed to facilitate the collection of data pertaining to regulatory systems in emerging market jurisdictions with respect to their implementation of GRevP. Data were collected using a standardised format to allow for appropriate comparison and analyses of information collected from multiple NRAs. The questionnaire (see Appendix 1) consisted of four parts: part 1 – structure of the NRA, the resources available and the review models applied by the authority; part 2 – regulatory review process using a standardised process map format to allow for ease of comparison; part 3 – indicators and description of the measures that have been implemented to build quality into the regulatory review process and decision-making practices and the implementation of GRevP to ensure transparent, consistency and timely regulatory review outcomes; and part 4 – identification of the enablers and barriers to quality decision making. The completion of the questionnaire and preparation of the report by the researcher were validated by the Registrar of the MCC. Similar questionnaires were completed by the Head of the licensing (registration) division of the TGA, Health Canada, the HSA and Swissmedic. The validated country reports that were prepared to describe the regulatory systems applied in each of these countries were used to inform the results of this study. The questionnaire (see Appendix 1) used in this study was designed to allow for simple comparative analyses of the structure, processes, and practices of international NRAs (McAuslane et al., 2009; Mashaki Ceyhan et al., 2018).

### Models of regulatory review

National regulatory authorities (NRAs) may apply different regulatory pathways requiring stratified levels of data assessment depending on the type of medicine under review and the regulatory status of the medicine in other reference or benchmark jurisdictions. There are three types of product review assessments used by regulatory

authorities: the verification review (type I); abridged (type II); and full review (type III) (McAuslane et al., 2009).

## RESULTS

### Comparative assessment of regulatory review processes and milestones

The five NRAs compared in this study had similar mandates for regulating medicines for human use. They were responsible for ensuring that harmonised standards for market authorisation of such products were applied whilst ensuring timely access to medicines that were safe, effective and of good quality. National regulatory authorities (NRAs) have demonstrated autonomy in the manner in which they executed their mandates, however, differences were observed within their regulatory review processes, timelines and the application of GRevPs. The regulatory review processes applied by the MCC were shown in the standardised process map (Figure 4.1). The map provided a simple representation of the review and authorisation of applications for NASs and MLEs that were approved on the first cycle, but did not include generic medicines, biosimilars, complementary medicines, veterinary medicines or medical devices. The map did not describe the process, in the event that the application was refused. The MCC conducted a type III full assessment in the review of all applications, including NASs, MLEs and generics for orthodox, biological, complementary and veterinary medicines. A full independent assessment of quality, efficacy and safety data was performed and an application for market authorisation for NASs and MLEs could be submitted to the MCC prior to approval by any other NRA worldwide. The MCC did not place any reliance on or consider the review performed by any other NRAs. The TGA, Health Canada, the HSA and Swissmedic also performed type III full assessments and a CPP was not required at the time of submission (Table 6.1).

The type II (abridged) review was employed by the TGA if requested by the sponsor and if the medicine had been approved by one or more reference authority. Swissmedic used a type II abridged review for selected applications and mainly for generic medicine applications and the HSA used the type II abridged review only if the medicine had been approved by one or more authority. The HSA also conducted a type I verification review but only if the medicine had been approved by two or more

authorities. While Health Canada were planning to implement this reliance pathway (Health Canada, 2018), Swissmedic intended to roll this out by 2019.

**Data requirements**

The MCC and the HSA did not have a formal pre-application procedure in place, however, Swissmedic offered this in cases of a priority review. For type III full reviews, the HSA required the sponsor to submit a notification of intent to apply for market authorisation. The TGA and Health Canada had formalised this process and considered it as an opportunity to familiarise reviewers with the medicine, potentially uncover any major areas of concern early in the registration process, identify the potential for priority review and provide a platform for the sponsor to discuss their submission and obtain scientific advice. The MCC required the full chemistry, manufacturing and control (CMC) data, nonclinical data and clinical data to be submitted in the CTD format to support the application for market authorisation. The other four comparative NRAs also requested full CMC, nonclinical and clinical datasets and also conducted an extensive assessment of these datasets for a type III full review. All five of the NRAs performed a review of quality, safety and efficacy data in parallel and pricing negotiations were separate from the technical review of the data submitted. The primary scientific review of the data was performed by internal technical staff of the four comparative NRAs, with the possibility of seeking advice from contracted external experts on an ad hoc basis. The quality assessment of NASs and MLEs conducted by the MCC was performed by both internal technical staff and external reviewers while the assessment of clinical data for NASs and MLEs was reviewed by external reviewers only. Committee structures within the four comparative NRAs were similar in that the NRAs engaged with various expert committees on an ad hoc basis to support the scientific review process and to provide scientific advice and expert opinion on selected dossiers.

**Table 6.1 Models of assessment of the five agencies and extent of the scientific review**

| TYPE OF REVIEW MODEL | South Africa (MCC) | Australia | Canada | Switzerland | Singapore |
|---|---|---|---|---|---|
| Verification review (type I) | × | × | × | × | ✓[a] |
| Abridged review (type II) | × | ✓[b] | × | ✓[c] | ✓[d] |
| Full review (type III) | ✓ | ✓ | ✓ | ✓[e] | ✓ |
| EXTENT OF SCIENTIFIC REVIEW | | | | | |
| 1. Chemistry, manufacturing, and control (CMC) data | | | | | |
| Extensive assessment | ✓ | ✓ | ✓ | ✓ | ✓ |
| 2. Nonclinical data | | | | | |
| Extensive assessment | ✓ | ✓ | ✓ | ✓ | ✓[f] |
| 3. Clinical data | | | | | |
| Extensive assessment | ✓ | ✓ | ✓ | ✓ | ✓ |
| ADDITIONAL INFORMATION OBTAINED (WHERE APPROPRIATE) | | | | | |
| Other agencies' internal review reports | ✓ | ✓ | ✓ | ✓ *(Occasionally)* | × |
| Reports on the internet | ✓ | ✓ | ✓ | ✓ *(Occasionally)* | ✓ |
| General internet search | ✓ | ✓ | ✓ | ✓ *(Occasionally)* | ✓ |

Abbreviations: CMC=Chemistry, Manufacturing and Control; MCC=Medicines Control Council

[a] Only if the product had been approved by two or more reference agencies

[b] Only if requested by the sponsor and if the product had been approved by two or more reference agencies

[c] Used for selected applications, mainly generic applications

[d] Only if the product had been approved by one or more reference agencies

[e] Used mainly for applications for innovative medicines

[f] Only for biological and biosimilar products

The committee structure within the MCC was different in that all assessment reports would be channelled to various scientific committees for expert opinion and the final regulatory decision would be taken by the Council. All five NRAs were members of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) (PIC/S, 2018) and had implemented processes to ensure that evidence of the GMP status of the manufacturer was provided during the review process. Sponsors could submit a copy of the GMP certificate issued by a reference agency as evidence of a manufacturers GMP status, however, if the GMP status of the manufacturer could not be confirmed at the time of application for market authorisation, the regulatory authority could conduct a GMP inspection at the manufacturing site in parallel to the review process.

**Target and approval times**

The MCC review process consisted of application receipt and validation procedures, queue time for allocation of applications to reviewers, a scientific review of CMC, nonclinical and clinical data conducted in parallel, company response and final authorisation through the regulatory decision taken by the Council. The milestone timelines for the MCC review procedures were displayed in Figure 4.1. A “fast track” status was assigned to eligible applications in order to expedite the registration of essential medicines. While the review process was the same for “fast track” applications, these applications would be prioritised over existing applications, queued for allocation to reviewers. The target set for the overall review time of fast track applications was 250 calendar days. The median approval times for fast track NAS applications approved in 2015, 2016, and 2017 were 1218, 921, and 609 calendar days, respectively. There was no target time set for the overall review time of NASs, but the median approval times for NAS marketing authorisation applications approved in 2015, 2016, and 2017 were 1175, 1641, and 1466 calendar days, respectively.

These data demonstrated that the MCC was neither able to achieve the target timelines set for fast track applications nor meet the targets in 2015, 2016, and 2017 for the key milestones within the regulatory review process (Figure 4.1). The data represented the overall approval time based on the date of application and the date of registration; data that were routinely monitored and measured for the period 2015–2018. The median overall approval time did not include or account for sponsor response time and the time taken to reach the other milestones identified within the regulatory review process.

In comparison the TGA, Health Canada, the HSA and Swissmedic had set overall target review times, for standard full approvals, at 305 calendar days, 355 calendar days, 270 working days (i.e. 378 calendar days) and 330 calendar days, respectively. The overall target review times set by these four NRAs did include sponsor response time, unlike those for MCC. During the period 2013-2017, the TGA, Health Canada and Swissmedic achieved median approval times of 364, 350, and 487 days, respectively (Bujar et al., 2018). In 2017, Health Canada, Swissmedic and the TGA approved 30, 29, and 24 NASs, respectively. Despite these numbers varying on an annual basis, the number of NAS approvals between 2008 and 2012 increased by 56% for the TGA, 46% for Health Canada and 41% for Swissmedic when compared to the number of NASs approved between 2013 and 2017 (Bujar et al., 2018).

**Comparative assessment of good review practices**

This study identified the quality measures that had been established and implemented by the five NRAs with a view to comparing the aptitude and culture of the authorities in the application of these measures in order to ensure quality, transparency, consistency and continuous improvement in the regulatory review process.

**Quality measures**

Swissmedic was the only NRA in this comparative study that had a dedicated quality department and that had implemented all the listed quality measures (Table 6.2). The MCC and the TGA implemented six of the seven measures and Heath Canada and the HSA had implemented five quality measures. Only Health Canada and Swissmedic had formally implemented GRevPs while the other three authorities had

informally implemented GRevPs. All of the five NRAs occasionally participated in shared and joint reviews.

**Transparency and communication**

Improved transparency and communication were common goals for NRAs worldwide. There were nine established transparency and communication parameters that could be implemented by NRAs to enhance stakeholder relationships (Table 6.3). The MCC implemented seven out of the nine parameters. At the time of this study, the industry was unable to track the progress of applications. Although the MCC documented and communicated the summary of grounds for regulatory approval with the sponsor, this summary was not published or made available in the public domain. The HSA also did not publish the summary basis of approval or provide feedback to the industry on submitted dossiers. The TGA implemented all of the nine transparency and communication parameters while Swissmedic and Health Canada implemented eight and the HSA six of the nine measures (Table 6.3).

**Continuous improvement initiatives**

A comparison was made of the continuous improvement initiatives that had been implemented by the five NRAs. Swissmedic implemented all five initiatives, the TGA and the HSA implemented four, Health Canada implemented three and the MCC implemented two of the five initiatives (Table 6.4). The MCC did not undergo routine external or internal quality audits. Furthermore, reviews of assessors' feedback were performed and the MCC carried out an informal review of feedback from stakeholders.

**Training and education**

Various types of training and education such as induction training, on-the-job training, attendance at internal and external courses, international workshops and secondments in other regulatory authorities can contribute to the development of personnel and the continuous improvement of the regulatory review process.

## Table 6.2 The quality measures implemented by the five agencies

| Measure | Regulatory authority | | | | |
|---|---|---|---|---|---|
| | South Africa (MCC) (6/7) | Australia (6/7) | Canada (5/7) | Switzerland (7/7) | Singapore (5/7) |
| Internal quality policy | ✓ *(Informally)* | ✓ | × | ✓ | × |
| Good review practice system | ✓ *(Informally)* | ✓ *(Informally)* | ✓ *(Formally)* | ✓ *(Formally)* | ✓ *(Informally)* |
| Standard operating procedures for guidance of assessors | ✓ *(Informally)* | ✓ | ✓ | ✓ | ✓ |
| Assessment templates | ✓ | ✓ | ✓ | ✓ | ✓ |
| Dedicated quality department | × | × | × | ✓ | × |
| Scientific committee | ✓ | ✓ | ✓ | ✓ | ✓ |
| Shared and joint reviews | ✓ *(Occasionally)* | ✓ *(Occasionally)* | ✓ *(Occasionally)* | ✓ *(Occasionally)* | ✓ *(Occasionally)* |

Abbreviation: MCC=Medicines Control Council

All five of the regulatory authorities in this comparative study implemented all eight of the measures for training and education (Table 6.5).

**Enablers and barriers to good quality decision-making**

The MCC identified its willingness to improve its regulatory performance as an enabler to good quality decision-making and the lack of an EDMS as a major barrier. The other four NRAs in the comparative study listed a variety of enablers that contributed to good decision-making, with common themes of regulatory convergence, harmonisation and the implementation of GRevPs emerging as top enablers on the list. The barriers identified by these authorities included frustrations with incomplete submissions for market authorisation, the need for appropriate electronic systems to support the review process and a full integration of electronic tracking systems. The comparison of the key features of the regulatory review process of the MCC, the TGA, Health Canada, the HSA and Swissmedic were summarised in (Table 6.6).

## DISCUSSION

National regulatory authorities (NRAs) around the world strive to enhance their regulatory performance and in doing so ensure timely patients' access to safe, good quality, effective medicines. A comparison of the regulatory systems and review processes implemented by NRAs globally contribute to the understanding of these challenges and inform solutions through sharing of best practices and lessons learned. The MCC recognised the importance of harmonisation and regulatory convergence and was striving to align itself with the systems and processes implemented by mature NRAs in an effort to improve regulatory performance and ensure timely patients' access to medicines. This study aimed to identify the similarities and differences between the registration processes applied by similar-sized mature NRAs and those applied by the MCC. The results demonstrated the strengths in the regulatory review process of the MCC and the areas that required improvement, evaluated the regulatory performance of the MCC review model and reflected on the progress by the MCC in applying GRevPs. The TGA, Health Canada, the HSA and Swissmedic were selected for this study as authorities with similar regulatory characteristics and review models to allow for an appropriate comparison.

## Table 6.3 Transparency and communication parameters in the five agencies

| Measure | Regulatory authority | | | | |
|---|---|---|---|---|---|
| | South Africa (MCC) (7/9) | Australia (9/9) | Canada (8/9) | Switzerland (8/9) | Singapore (6/9) |
| Feedback to industry on submitted dossiers | ✓ | ✓ | ✓ | ✓ | × |
| Details of technical staff to contact | ✓[a] | ✓ | ✓ | ✓ | ✓ |
| Pre-submission scientific advice to industry | ✓[b] | ✓ | ✓ | ✓ | ✓ |
| Official guidelines to assist industry | ✓ | ✓ | ✓ | ✓ | ✓ |
| Industry could track progress of applications | ×[c] | ✓ | ✓ | ✓ | ✓ |
| Publication of summary of grounds on which approval was granted | ×[d] | ✓ | ✓ | × | × |
| Approval times | ✓[e] | ✓ | ✓ | ✓ | ✓ |
| Advisory committee meeting dates | ✓ | ✓ | × | ✓ | × |
| Approval of products | ✓ | ✓ | ✓ | ✓ | ✓ |

Abbreviation: MCC=Medicines Control Council

[a] Contact details were made available on an ad hoc basis

[b] Meetings were held with industry on an ad hoc basis

[c] Implementation of an EDMS was planned

[d] Summary was available but was not published

[e] Approval times were not made available to the public

In particular, these four agencies have a work-sharing approach, which provided the rationale for their comparison. Over the past decade a number of NRAs from the emerging economies have been evaluated using this questionnaire. Therefore, the four NRAs selected as comparators for this study were based on the size of the agencies, the patient population they serve, the year since established and the nature of the review model (full review) applied.

Furthermore, NRAs from the emerging economies, such as Tanzania and Kenya, were not considered comparable to MCC because of the size of these NRAs and the size of the population they serve. In addition, the MCC carried out a full review which was different to that of the other NRAs in the region. It was also recognised that the USFDA and the EMA were not appropriate NRAs to which benchmark the MCC. The reasons include both the size of the NRA, the population they serve and in particular the resources available; both in financial terms and the number of reviewers (which in the case of the USFDA included 1200 reviewers of whom 220 are statisticians). As regards EMA, being a consortium of 32 countries, engaging rapporteur and co-rapporteur in the review process would constitute a totally different review model to that of South Africa.

**Review type and process**

The MCC conducted a type III full assessment for all NAS applications for market authorisation and such applications could be submitted to the MCC prior to approval by another NRA. In line with the other four comparative NRAs, the GMP status of the manufacturer was confirmed concurrently with the review process and a CPP was not required at the time of submission. The MCC participated in regional alignment initiatives and conducted shared or joint reviews with other NRAs such as Zambia, Zimbabwe, Namibia and Botswana (Regulatory Resources for Africa, 2015).

## Table 6.4 Continuous improvement initiatives in the five agencies

| Measure | Regulatory authority | | | | |
|---|---|---|---|---|---|
| | South Africa (MCC) (4/5) | Australia (4/5) | Canada (3/5) | Switzerland (5/5) | Singapore (4/5) |
| External quality audits | ✓[a] | × | × | ✓ | × |
| Internal quality audits | ×[b] | ✓ | ✓ | ✓ | ✓ |
| Internal tracking systems | ✓[c] | ✓ | ✓ | ✓ | ✓ |
| Reviews of assessors' feedback | ✓ | ✓ | × | ✓ | ✓ |
| Reviews of stakeholders' feedback | ✓[d] | ✓ | ✓ | ✓ | ✓ |

Abbreviation: MCC=Medicines Control Council

[a] External quality audits were not performed routinely

[b] Planned to formally implement

[c] Implementation of EDMS was planned by SAHPRA

[d] Planned to be formally and routinely reviewed

## Table 6.5 Training and education in the five agencies

| Measure | Regulatory authority | | | | |
|---|---|---|---|---|---|
| | South Africa (MCC) (8/8) | Australia (8/8) | Canada (8/8) | Switzerland (8/8) | Singapore (8/8) |
| International workshops/conferences | ✓ | ✓ | ✓ | ✓ | ✓ |
| External courses | ✓ | ✓ | ✓ | ✓ | ✓ |
| In-house courses | ✓ | ✓ | ✓ | ✓ | ✓ |
| On-the-job training | ✓ | ✓ | ✓ | ✓ | ✓ |
| External speakers invited to the authority | ✓ | ✓ | ✓ | ✓ | ✓ |
| Induction training | ✓ | ✓ | ✓ | ✓ | ✓ |
| Sponsorship of post-graduate degrees | ✓ | ✓ | ✓ | ✓ | ✓ |
| Placements and secondments in other regulatory authorities | ✓ | ✓ | ✓ | ✓ | ✓ |

Abbreviation: MCC=Medicines Control Council

## Table 6.6 Key features of the five agencies' review processes

| Measure | Regulatory authority | | | | |
|---|---|---|---|---|---|
| | South Africa (MCC) | Australia | Canada | Switzerland | Singapore |
| Certificate of Pharmaceutical Product was required at time of submission | × | × | × | × | × |
| More than 20% of review staff were medically qualified | ✓ | ✓ | × | ✓ | × |
| The authority set target time for scientific assessment | ✓ | ✓ | ✓ | ✓ | ✓ |
| The authority set overall review and approval target time | ✓ | ✓ | ✓ | ✓ | ✓ |
| Questions to sponsors were batched at fixed points in the review | × | ✓ | × | ✓ | ✓ |
| Recording procedures allowed company response time to be measured and differentiated in the overall processing time | × | ✓ | × | ✓ | ✓ |
| The authority recognised medical urgency as a criterion for accelerating the review and approval process for qualifying products | ✓ | × | ✓ | ✓ | ✓ |
| Quality, safety, and efficacy technical data sections were reviewed in parallel rather than sequentially | ✓ | ✓ | ✓ | ✓ | ✓ |
| Pricing discussions were separate from the technical review | ✓ | ✓ | ✓ | ✓ | ✓ |
| The focus was on checking quality in the market place and requirements for analytical work did not delay marketing authorisation | ✓ | ✓ | ✓ | ✓ | ✓ |

Abbreviation: MCC=Medicines Control Council

However, no formal measures were put in place to ensure consistent quality during shared or joint reviews and participation in this initiative did not influence the way in which the MCC conducted reviews in general. A work-sharing programme was a creative way to maximise resources even when NRAs were separated by time and distance. This was the rationale for the collaboration between the NRAs in Australia, Canada, Switzerland and Singapore that established efficient work-sharing experience (McAuslane et al., 2017).

Considering the resource constraints faced by the MCC and the large volumes of applications for market authorisation received; it was beneficial to consider the use of FRPs to expedite regulatory decisions and to enhance the re-engineered registration process envisaged by SAHPRA. Applying FRPs that provide a risk-based approach for the review of applications for market authorisation may help to conserve limited resources and reduce regulatory burden by avoiding duplication of regulatory efforts (Alsager et al., 2015). This would be an advantage when considered in line with the recommendations of the WHO (Ward, 2014; WHO, 2014a) by embracing regulatory harmonisation/convergence strategies; engaging in reliance and recognition activities that allowed NRAs in resource-limited settings to take into account or accept regulatory decisions made by other comparable NRAs (McAuslane et al., 2018). Furthermore, this would enable the application of an appropriate framework for BR assessment to enhance consistency in the clinical assessment of medicines (Leong et al., 2015a) as well as incorporating the principles of GRevPs in routine regulatory undertakings (WHO, 2014a).

**Approval times**

As stated by Leng et al. (2015), “The MCC had been under considerable pressure to increase the rate of medicines registration and was accused of delaying patients’ access to affordable and essential medicines” (p.1). The outcomes of an investigation into delayed timelines for registration of medicines, initiated in 2006 by the Minister of Health, noted a lack of skilled staff, poor infrastructure and inefficient regulatory processes as the major barriers affecting patients’ timely access to medicines (Green-Thompson, 2008). This demonstrated that the MCC neither achieved the target timelines set for the eligible applications of essential medicines, that were assigned

"fast track" status, nor met the targets between 2015 and 2017 for the key milestones within the regulatory review process (Leng et al., 2015). Furthermore, the MCC made use of a manual system to track applications for market authorisation, but it is hoped that the imminent implementation of an EDMS by SAHPRA would promote systematic and formal communication regarding timelines and milestones to both internal and external stakeholders. The MCC did not set a target for overall approval time of NAS applications. In order for SAHPRA to measure and improve its regulatory performance it was recommended that targets for overall approval time and key review milestones needed to be identified, codified into policy and guidelines, recorded, measured and monitored. Appropriate systems and resources, therefore, need to be put in place to ensure that regulatory performance metrics were analysed on a continuous basis through formal and routine monitoring.

The key milestones in the regulatory review process, including administrative and technical screening time, queuing time prior to review and clock stops measuring the time with sponsors need to be measured. There is now the potential to improve regulatory review time through ongoing analysis of the performance metrics that may inform continuous improvement initiatives, aimed at streamlining and prioritising the progression of the review process. Review times may be improved as a result of the more flexible approach to committee structures implemented by SAHPRA. The committee structures within SAHPRA have been revised to allow for more frequent ad hoc consultation with scientific committees, limited to applications for market authorisation requiring expert review and recommendation, as opposed to routinely channelling assessment reports through the committees for recommendation at 6-weekly intervals. Nevertheless, operationalisation of the system proposed by SAHPRA may not produce satisfactory outcomes and therefore a more fundamental review of the entire agency could still be proved to be of value.

**Good review practices**

The implementation of GRevPs provides a mechanism for NRAs to enhance regulatory performance (WHO, 2015) and previous studies have demonstrated that regulatory performance indicators such as overall approval timelines can be enhanced by instituting quality management systems and GRevPs into the regulatory review process (Cone & McAuslane, 2006). Good review practices (GRevPs) are a

fundamental part of overall GRP with a focus on medical product review (WHO, 2015, p193). These are defined by the WHO as “documented best practices for any aspect related to the process, format, content and management of a medical product review” (WHO, 2015, p194). The application of GRevP provides a platform for NRAs to “achieve timeliness, predictability, consistency, transparency, clarity, efficiency and high quality in both the content and management of reviews”; with a view to achieve successful review outcomes (WHO, 2015, p194). Many NRAs have implemented systems to ensure the consistent application of GRevPs and continue to work toward the evaluation and improvement of such systems.

The five NRAs in this study implemented the majority of the essential elements of GRevPs. The MCC did not have a dedicated quality department, however, there were plans to include dedicated quality personnel within the newly established SAHPRA. While key quality measures had been established and were evident in the work performed by the MCC, the need to formalise the quality management system, including the internal quality policy, GRevP systems, SOPs and harmonised assessment templates had to be prioritised in order to enhance SAHPRA operations. The establishment of a codified QMS within SAHPRA needs to be supported by formally introduced continuous improvement measures such as internal and external quality audits that would routinely and formally be implemented underpinned by initiation of an EDMS. The MCC had always recognised the importance of transparency and communication with stakeholders. As SAHPRA moves forward, it is hoped that many of the measures that contribute toward transparency and communication would be formally and routinely implemented in an effort to enhance the consistency, timeliness and predictability of the review process. The imminent application of an EDMS would allow for improved transparency as sponsors would be able to track the progress of applications. In addition, the overall approval times and the monitoring and measurement of key milestones in the review process would be readily available. However, whilst it is generally agreed that there are several aspects to review practices that are considered important, it is recognised that the summary basis of approval has a far greater impact with respect to the regulatory process transparency than other relevant aspects (Vawda & Gray, 2017).

The MCC implemented a guideline in 2007 for the evaluation of BR assessment of medicines and prepared a summary basis of approval for each medicine evaluated; both of which were key steps in the regulatory review process. The clinical assessment of NASs was conducted by external experts who prepared assessment reports that were peer reviewed within the clinical committee structure. Without a standardised template for the clinical assessment report, informing regulatory decisions concerning the registration of a NAS relied heavily on the experience and expertise of such reviewers. SAHPRA should consider improving the benefit-risk assessment framework by building quality into the process and standardising the template used for BR assessment. SAHPRA should also consider implementing the UMBRA framework which has been assessed and applied by several mature NRAs (Walker et al., 2013) as well as NRAs in the emerging markets (Mashaki Ceyhan et al., 2018). This structured approach would promote improved consistency and predictability in the BR assessment of medicines as the use of the UMBRA framework "assists decision makers with clearly defining the decision, agreeing the requisite properties of the treatments being considered, assessing the trade-offs among these properties and making defensible and transparent decisions regarding the registration of the medicine" (Levitan et al., 2014).

The publication of the summary basis of approval is a norm for many mature NRAs globally and is a tool that can be used by NRAs to build confidence in the review process in order to provide assurance regarding safety provisions (McAuslane et al., 2009). It is recommended that SAHPRA consider publishing the summary basis for approval that was not previously made available in the public domain by the MCC. However, it is recognised that in order to achieve this outcome a change in legislation will be required. The data collected for the purpose of this study has allowed for a valuable comparison of NRAs with similar regulatory mandates, size and resources characteristics. A number of recommendations are provided with a view to inform areas of improvement that may be prioritised to underpin the success of SAHPRA as it moves toward goals of regulatory reform and enhanced regulatory performance.

**Recommendations**

A comparison of the registration process applied by the MCC with those of similar medium-size NRAs such as the TGA, Health Canada, the HSA and Swissmedic has highlighted key areas for change and development. The following recommendations should be considered by SAHPRA in order to improve the MCC regulatory review process:

- Defining target timelines for the key milestones in the regulatory review process and overall approval time and ensuring the formal and routine monitoring and measurement of such metrics;
- Formally implementing and maintaining GRevPs in order to build quality into the review process, resulting in consistent, predictable, transparent and a timely regulatory review;
- Applying the Universal Methodology for Benefit-Risk Assessment (UMBRA) framework to enhance consistency in the clinical review of medicines and promote defensible and transparent decision-making;
- Implementing facilitated regulatory pathways (FRPs) and applying a risk-based approach to the regulatory review process in order to conserve limited resources and avoid duplication of regulatory efforts;
- Establishing committee structures within the South African NRA should allow for ad hoc consultation limited to applications for market authorisation requiring expert review and recommendation; and
- Enhancing transparency and communication through the development of summaries for the basis of approval that should be made available in the public domain.

**SUMMARY**

- The timely access to new medicines may be addressed through the strengthening of registration efficiencies and timelines by establishing and refining value-added registration processes, resources, and systems

- The aims of this study were to evaluate the timelines of the milestones of the South African review process and the overall approval process for NASs (2015-2018) and to provide recommendations for improved patients' access to new medicines through timely registration

- Data identifying the milestones and overall approval times for NASs registered by the South African NRA during 2015-2018 were collected and analysed

- The most NASs (42) were approved in 2017 and the least (15) in 2018. The shortest median approval time (1218 calendar days) was achieved in 2015 and the longest (2124 days), in 2018

- All applications were reviewed using the full review process, and 16/99 (16%) were assigned priority status and were reviewed and approved through the fast track process

- Extensive delays in NASs approvals in South Africa may be attributed to inefficient operational processes, resource constraints and an increased number of applications for registration

- SAHPRA has re-engineered and streamlined its regulatory review process which has been piloted and will be enhanced prior to final implementation

- Among recommendations for improvement, SAHPRA should consider the measurement and monitoring of milestones, facilitated regulatory pathway (FRPs) as well as implementing a reliance strategy and a quality management system (QMS).

# CHAPTER 7

# Evaluation of the Transparency of the Quality Decision Making Practices by SAHPRA

## INTRODUCTION

National regulatory authorities (NRAs) are responsible for making the decision to register a medicine based on an assessment of its overall benefits and risks. Often the BR balance, which ideally included an account of the uncertainties and risks and relevant stakeholder perspectives (McAuslane et al., 2017), is at the core of the regulatory decision to register a medicine (Pignatti et al., 2015). The NRAs, academics and the industry have recognised the need for a common, structured, systematic approach to the BR assessment of medicines that may be used during the review of an application for the registration of a medicine and for communicating the results of the review (Walker et al., 2011). A number of frameworks for BR assessment have been developed over the past few years (Walker et al., 2014). Many of these have incorporated mechanisms to support the systematic processing of data prior to making the regulatory decision (Walker et al., 2011) and featured structured, coherent, comprehensive approaches to BR assessment (Pignatti et al., 2015). While differences amongst these frameworks exist, the principles of "defining the decision, agreeing on the requisite properties of the treatments being considered, assessing the trade-offs among these properties and making defensible transparent decisions" are common (Levitan et al., 2014, 564).

A universal BR assessment framework that incorporates the existing frameworks has been developed (Walker et al., 2014) and validated (McAuslane et al., 2017). The Universal Methodology for Benefit Risk Assessment (UMBRA) is an overarching acceptable standard BR framework (Figure 1.8) (Leong et al., 2015b) that provides a template that may be used during the review and documents the elements considered to be essential in the assessment of benefits and risks (Leong et al., 2014). The BR Template is considered useful in collating the conclusions of the BR decisions (Leong et al., 2015b) and can be used to effectively communicate the basis for the regulatory decision to register a medicine.

In an effort to ensure transparency and accountability, some NRAs publish their assessment reports to communicate the regulatory decision in a clear and understandable manner for consideration by the public. Public assessment reports (PARs) provide information about how the NRA has assessed the benefits and risks of a medicine (Raynor & Bryant, 2013). The PARs usually include information

pertaining to the data submitted to the NRA for evaluation as well as the conclusions made by the NRA (Raynor & Bryant, 2013). The PARs are published in the public domain by the NRAs to document the basis of and justification for the regulatory decision and to promote transparency (Leong et al., 2014). The results from a previous study (Leong et al., 2014) have demonstrated that making use of a BR framework enforces a structured, documented discussion and contributes to the improved quality of communication in terms of transparency and consistency (Leong et al., 2014).

Ensuring transparency in decision-making and documenting regulatory decisions in a structured systematic manner promotes an enhanced understanding of the basis for a regulatory decision and the rationale for the inclusion or exclusion of benefits and risks and the determinants of the consequent BR balance (Leong et al., 2014). Many NRAs in the emerging economies place reliance on the PARs of reference agencies to inform their own regulatory decisions (Ward, 2019). Users of PARs often criticise the redacted nature of the PARs and have experienced challenges in identifying the key benefits and risks that underlie the decisions made by reference agencies as well as the value judgments and the trade-offs between the benefits and risks (Raynor & Bryant, 2013). This study aims to review the PARs available in the public domain against the UMBRA BR Summary Template using a case study approach. This study is the first review carried out to evaluate the approach initiated by SAHPRA to document and communicate the BR decision.

**Study objectives**

The main objectives of this study were to:

- Assess the transparency of the SAHPRA's regulatory review decision making process
- Determine whether the SAHPRA's review process incorporates an appropriate evaluation of benefit and risk of medicines
- Evaluate the Public Assessment Report of four reference agencies (TGA, Health Canada, EMA and USFDA) to determine whether these provide sufficient information to identify their decision-making practices

- Develop recommendations for SAHPRA for the implementation of an effective approach for communicating BR decisions and developing a framework for a "public assessment report" based on best practice.

## METHODS

### Case study comparing the PARs from four reference agencies against the UMBRA BR Summary Template

The PARs, for three NASs, including Ertugliflozin l-pyroglutamic acid, Erenumab and Durvalumab, recently published by the TGA, EMA, Health Canada and USFDA were compared against the validated UMBRA BR Summary Template (Walker et al., 2014). The TGA, EMA, Health Canada and USFDA have a long history of established regulatory processes and global recognition of regulatory standards. At the time of this study, these NRAs were the only agencies that published a PAR in the public domain, namely the TGA: Australian Public Assessment Report (AusPAR), EMA: EPAR, Health Canada: Summary Basis of Decision (SBD) and the USFDA: Summary Review. The PARs for Ertugliflozin l-pyroglutamic acid, Erenumab and Durvalumab were selected because each of these NASs had been recently approved by the TGA, EMA, Health Canada and USFDA and the AusPAR, EPAR, SBD and USFDA Summary Review were available for each of these NASs.

**Table 7.1 Public assessment reports (PARs) of new active substances (NASs) selected for comparison against the Universal Methodology for Benefit-Risk Assessment (UMBRA) Benefit-Risk (BR) Summary Template**

| API | ATC Classification System | Indication | TGA Approval Date | EMA Approval Date | Health Canada Approval Date | USFDA Approval Date |
|---|---|---|---|---|---|---|
| Ertugliflozin l-pyroglutamic acid | A10 | Selective inhibitor of the sodium-dependent glucose cotransporters (SGLT) indicated for Type II Diabetes | 14/05/2018 | 21/03/2018 | 09/05/2018 | 19/12/2017 |
| Erenumab | N02 | Analgesic indicated for treatment of migraine | 28/06/2018 | 26/07/2018 | 01/08/2018 | 17/05/2018 |
| Durvalumab | L01 | Human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody indicated for locally advanced or metastatic urothelial carcinoma | 02/10/2018 | 21/09/2018 | 03/11/2017 | 01/05/2017 |

Abbreviations: API=Active Pharmaceutical Ingredient; ATC=Anatomical Therapeutic Classification; EMA=European Medicines Agency; TGA=Australian Therapeutic Goods Administration; USFDA=United States Food and Drug Administration.

The PARs were retrieved online for each of the NASs. The comparison of the PARs for the three NASs, prepared by the four reference agencies, was conducted by comparing the information documented within the PARs against the various section headings of the UMBRA BR Summary Template and the findings have been tabulated.

**Evaluation of the approach initiated by SAHPRA to communicate the BR decisions**

The approach initiated by SAHPRA to document and communicate the BR decisions was evaluated. Since SAHPRA does not currently produce PARs, the following guidelines and templates used by SAHPRA to support the review of the quality, safety and efficacy of NASs were compared against the section headings of the UMBRA BR Summary Template: Guideline 2.09 Clinical Guideline (SAHPRA, 2019a); Guideline 6.31 Summary of Critical Regulatory Elements (SCoRE) Document (SAHPRA, 2019b) and the SCoRE template (SAHPRA, 2018b); the Clinical Full Review Report Template (CRT) (SAHPRA, 2019c); and the SAHPRA Guideline for Clinical Reviewers (SAHPRA, 2019d). This study was designed to be exploratory in nature and the results of the study provided qualitative interpretations related to the study objectives.

**Focus group**

A focus group was conducted with representatives of NRAs, industry, HTA groups and patient groups from different jurisdictions. The focus group consisted of approximately 12 participants, a moderator responsible for facilitating the discussion and a rapporteur who consolidating the results and reported the outcomes. A brief guide was prepared for the focus group and this described the discussion topic, provided background information and outlined the objectives for the focus group. A list of questions and issues were developed and made available to the focus group. The focus group was held in Tysons Corner, Virginia, United States in June 2019. The topic was “PARs – Are these good knowledge management tools for stakeholders such as other regulatory authorities, HTA agencies, companies and patients in understanding an agency’s or company’s decision-making? If not, how can they be improved?”.

## RESULTS

For the purpose of clarity, the results are presented in three parts:

- Part I – Comparison of the four reference agencies' PARs against the validated UMBRA BR Summary Template
- Part II – Review of the approach initiated by SAHPRA to document and communicate the BR decision
- Part III – Outcomes of the focus group

### Part I – Comparison of the four reference agencies' PARs against the validated UMBRA BR Summary Template

The TGA, EMA, Health Canada and USFDA produce publically available assessment reports to document the agency's decisions for medicine registration. The formats of these reports have been previously studied (Leong et al., 2014) and found to be generally similar and comparable to the format of the UMBRA BR Summary Template (Walker et al., 2014). Three of the four agency's PARs made provision for a documented BR assessment of the medicine. These included the TGA AusPAR: Section VII. Overall conclusion and BR assessment, the EMA EPAR: Section 3. BR Balance and the USFDA Summary Review: Section 1. BR Assessment. The PARs produced by each of the four agencies followed a similar format and were comparable for each of the three medicines (Durvalumab, Erenumab and Ertugliflozin l-pyroglutamic acid) selected for the case study. The results of the three PARs, produced by each of the four agencies, was compared against the UMBRA BR Summary Template as well as the current approach by SAHPRA in their regulatory review (Table 7.2).

#### *TGA AusPAR*

The AusPAR for durvalumab was not available at the time of the study. The results reflected in Table 7.2 were based on the outcomes of the comparison of the AusPARs produced for Erenumab and Ertugliflozin l-pyroglutamic acid against the UMBRA BR Summary Template. The assessment of ethnic factors was not well documented within the AusPAR. The list of Phase I, pivotal, supportive and ongoing studies was provided but a record of the key benefits or risks identified in the studies was not included. A narrative describing the risks of the medicine was available however, the

summary of risks was not easily identified and a table of the pooled overall incidence of events was not provided. Section V of the AusPAR provided a documented clinical rationale for the use of the medicine but did not provide documented justification for the decision on the medicine fulfilling or not fulfilling an unmet medical need. The assessment of the benefits and the risks was documented in Section V (clinical findings). The reviewed benefits and risks selected for inclusion in the assessment were not explicitly listed or assessed in terms of relative importance and were not valued. The justification for the inclusion or exclusion of the benefits and risks was not documented. The reviewer's considerations in terms of the BR assessment were provided as a narrative discussion in Section VII, however a clear conclusion on the BR being positive or not for the proposed indication was not provided.

***EMA EPAR***

The regulatory history of the medicine with regard to its assessment by a reference agency was not documented. The list of clinical trials conducted was provided but a record of the key benefits or risks identified in the studies was not included. The EPAR documented the favourable and unfavourable effects of the medicine as well as the associated uncertainties and limitations of these effects. However, the EPAR did not provide a record of the benefits and risks that were reviewed or the reasons for their inclusion or exclusion in the BR assessment of the medicine. An effects table was provided in Section 3.6 of the EPAR and the importance of favourable and unfavourable effects was discussed in Section 3.7.1. The assignment of weighting (relative importance) on each of the benefits and risks identified and the valuing of the options of the effects was not explicitly recorded. The EPAR did not provide a record of the expected evolution of the BR balance over time.

***Health Canada Summary Basis of Decision (SBD)***

The SBD did not make provision for the explicit assessment and documenting of the BR balance. Ethnic considerations were not routinely documented. The clinical study summary and associated benefits and risks identified in each study were not documented. The overall summary of risks, the benefits and risks and the effects table were not available. The relative importance and values of the benefits and risks were not documented or the justification for their inclusion or exclusion and no comments were made regarding the strengths and uncertainties of the benefits and risks that

were included in the review. No information was available to describe the expected evolution of the BR balance over time. The SBD provided limited information to describe the outstanding issues and how these issues were to be addressed. For example, the requirements for additional follow up measures or specific obligations, the need for further medicine development as well as studies to improve the BR balance were not documented.

***US FDA Summary Review***

While the summary review did not document the justification for the decision on the medicine fulfilling or not fulfilling an unmet medical need, an analysis of the condition was provided and included related evidence and uncertainties as well as brief conclusions and reasons justifying the need for the treatment of the condition. The summary review did not specify any local clinical guideline or other issues which needed to be considered to contextualise the decision. The regulatory history of the medicine, with regard to any previous assessment by the agency or by another reference agency, was not documented. The consideration of ethnic factors was not recorded. The clinical/statistical efficacy and safety issues were documented in Section 7 and Section 8 respectively. A clinical study summary providing a highlight of the study designs, treatments and the conclusions, identifying the key benefits or risks, was not included. In line with the findings noted by Leong et al. (2014) the summary review had not been amended to make provision for a record indicating which benefits and risks were reviewed by the agency or the rationale as to which were subsequently included or excluded. The summary review did not include a record of the relative importance assigned to each benefit and risk and did not make provision for valuing the options or commenting on the strengths and uncertainties for each benefit and risk identified. The BR integrated assessment was available but did not necessarily describe how the BR balance was expected to evolve over time; for example, in the event that late side effects emerge or if long-term efficacy decreased.

**Table 7.2 Comparison of TGA, EMA, Health Canada and USFDA Public Assessment Reports (PARs) and South African Health Products Regulatory Authority's (SAHPRA) appraisal of Benefit-Risk (BR) with the Universal Methodology for Benefit-Risk Assessment (UMBRA) Summary Template**

| UMBRA BR Summary Template: Content | | TGA (AusPAR) | EMA (EPAR) | Health Canada (SBD) | USFDA (Summary Review) | SAHPRA's appraisal of BR |
|---|---|---|---|---|---|---|
| **1.1** | **Background (Decision context)** | | | | | |
| 1.1.1 | Specify proposed therapeutic indication | Section I. Introduction to product submission – Product background | Section 3.1.1 Disease or condition | Section 1 What was approved | Section 1: Benefit-risk integrated assessment | Not available |
| 1.1.2 | Treatment options evaluated | Section V. Clinical findings – Current treatment options | Section 3.1.2 Available therapies and unmet medical need | Section 2 Why was <product> approved? | Section 1: Benefit-Risk Dimensions – Current treatment options | CRT: Section 4.3.1 |
| 1.1.3 | Unmet medical need | Section V. Clinical findings – Clinical Rationale | Section 3.1.2 Available therapies and unmet medical need | Not available | Section 1: Benefit Risk Dimensions – Analysis of conditions | Not available |
| 1.1.4 | Local clinical, guideline or other issues | Not available | Section 3.1.2 Available therapies and unmet medical need | Not available | Not available | Not available |
| 1.1.5 | Previous review of active substance by the agency | Section I. Introduction to product submission – Regulatory status | Section 1.1 Submission of the dossier | Post-Authorization Activity Table | Not available | CRT: Section 3 |
| 1.1.6 | Reference agency regulatory history | Section I. Introduction to product submission – Regulatory status | Not available | Not available | Not available | CRT: Section 3<br>2.09: Section 4.2.6 |
| **2.1** | **Overall summaries** | | | | | |

| UMBRA BR Summary Template: Content | | TGA (AusPAR) | EMA (EPAR) | Health Canada (SBD) | USFDA (Summary Review) | SAHPRA's appraisal of BR |
|---|---|---|---|---|---|---|
| 2.1.1 | Quality conclusion | Section III. Quality findings – Quality summary and conclusion and Section VII. Overall conclusion and risk/benefit assessment – Quality | Section 2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects | Section 7.3: Quality Basis for Decision | Section 3: Product Quality | 6.31: Section 2 |
| 2.1.2 | Non-clinical conclusion | Section IV. Non-clinical summary and conclusion and Section VII. Overall conclusion and risk/benefit assessment – Nonclinical | Section 2.3.7 Conclusion on the non-clinical aspect | Section 7.2: Non-Clinical Basis for Decision | Section 4: Nonclinical Pharmacology/ Toxicology | CRT: Section 4.2<br>6.31: Section 1.1 |
| 2.1.3 | Human pharmacology conclusion | Section IV. Pharmacology and Section VII. Overall conclusion and risk/benefit assessment – Pharmacology | Section 2.4.5 Conclusions on clinical pharmacology | Section 7.1: Clinical Basis for Decision – Pharmacology | Section 5: Clinical Pharmacology | CRT: Section 4.1 |
| 2.1.4 | Assessment of ethnic factors | Section V. Clinical findings - Evaluator's conclusions on safety / Special Populations | Section 2.6 Safety in special populations | Section 2: Why was <product> approved? | Not available | CRT: Section 4.3.1 |
| **3.1** | **Clinical study summary** | Section V. Clinical findings - Contents of the clinical dossier | Section 2.4 Clinical Aspects Section 3.1.3 Main clinical studies | Section 7.1: Clinical Basis for Decision – Clinical Efficacy | Section 7: Clinical/statistical efficacy and Section 8: Safety | CRT: Section 4.3.1 |
| **3.2** | **Clinical conclusion** | Section V. Clinical findings and Section VII. Overall conclusion | Section 2.5.4 Conclusions on clinical efficacy and Section 2.5.6 | Section 7.1: Clinical Basis for Decision | Section 7: Efficacy Conclusion and Section 8: Safety Conclusion | CRT: Section 4.3.2 |

| UMBRA BR Summary Template: Content | | TGA (AusPAR) | EMA (EPAR) | Health Canada (SBD) | USFDA (Summary Review) | SAHPRA's appraisal of BR |
|---|---|---|---|---|---|---|
| | | and risk/benefit assessment – Clinical | Conclusions on clinical safety | | | |
| **4.1** | **Risks: Overall summary** | Section V. Clinical findings: First and second round risk assessment | Section 2.6 Clinical Safety - Adverse events and Section 3.4 Unfavourable effects | Not available | Section 1: Benefit-Risk Dimensions – Risk and Section 8: Safety – safety conclusions | Not available |
| **5.1** | **Identified benefits and risks** | | | | | |
| 5.1.1 | Benefits documented: Listing of all benefits, and justification for inclusion and exclusion | Section V. Clinical findings: First and second round benefit assessment | Section 3.2 Favourable effects and Section 3.3 Uncertainties and limitations about favourable effects | Not available | Section 1: Benefit-Risk Dimensions - Benefit | Not available |
| 5.1.2 | Risks documented: Listing of all risks, and justification for inclusion and exclusion | Section V Clinical findings. First and second round risk assessment | Section 3.4 Unfavourable effects and Section 3.5 Uncertainties and limitations about unfavourable effects | Not available | Section 1: Benefit-Risk Dimensions – Risk and risk management | Not available |
| **6.1** | **Weighting and valuing of benefits and risks** | Not available | Section 3.7.1 Importance about favourable and unfavourable effects | Not available | Not available | Not available |
| **7.1** | **Conclusion** | | | | | |
| 7.1.1 | Effects table and conclusion: Listing the relative importance and valuing the options of the | Not available | Section 3.6 Effects table | Not available | Not available | Not available |

| UMBRA BR Summary Template: Content | | TGA (AusPAR) | | EMA (EPAR) | | Health Canada (SBD) | | USFDA (Summary Review) | | SAHPRA's appraisal of BR | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | effects of each benefit and risk and commenting on any strengths or uncertainty | | | | | | | | | | |
| 7.1.2 | For negative benefit–risk balance, discussion on the harm | | Section VII. Overall conclusion and risk/benefit assessment – Risk-benefit analysis | | Section 3.7.2 Balance of benefits and risks | | Not available | | Section 1: Benefit-Risk Dimensions - Risk and risk management | | Not available |
| 7.1.3 | Discussion on evolution of the benefit-risk balance | | Section VII. Overall conclusion and risk/benefit assessment – Risk-benefit analysis | | Section 3.7.1 Importance about favourable and unfavourable effects | | Not available | | Section 1: Benefit-risk integrated assessment | | Not available |
| 7.1.4 | Evaluation of the pharmacovigilance plan and risk minimisation plan | | Section VI: Pharmacovigilance findings and Section VII. Overall conclusion and risk/benefit assessment – RMP | | Section 2.6 Risk management plan and Section 2.7 Pharmacovigilance | | Section 2: Why was <product> approved? And Section 5: What post-authorization activity has taken place for <product>? | | Section 1: Benefit-Risk Dimensions - Risk and risk management and Section 12/13/14: Post-marketing recommendations | | CRT: Section 4.4<br>6.31: Section 1.1 |
| 7.1.5 | Discussion on outstanding issues and other significant information (hearings, advisories, patients, consumers, stakeholder inputs) | | Section VII. Overall conclusion and risk/benefit assessment – Specific conditions of registration applying to these goods and Summary of issues | | Section 3.7.1 and Section 4 Recommendations | | Section 4: What follow-up measures will the company take? | | Section 12/13/14: Post-marketing recommendations | | Not available |
| 7.1.6 | Discussion on need for further studies | | Section VII. Overall conclusion and risk/benefit assessment – Specific conditions of registration applying to | | Section 3.7.3 Additional considerations on the benefit-risk balance | | Section 4: What follow-up measures will the company take? | | Section 12/13/14: Post-marketing recommendations | | Not available |

| UMBRA BR Summary Template: Content | | TGA (AusPAR) | EMA (EPAR) | Health Canada (SBD) | USFDA (Summary Review) | SAHPRA's appraisal of BR |
|---|---|---|---|---|---|---|
| | | these goods and Summary of issues | | | | |
| 7.1.7 | Any other information relevant to the benefit-risk decision | Section VII. Overall conclusion and risk/benefit assessment – Risk-benefit analysis | Section 3.7.3 Additional considerations on the benefit-risk balance | Section 3: What steps led to the approval of <product>? (Limited) (Reference made to reference agency PARs from USFDA and EMA) | Section 1: Benefit-risk integrated assessment | Not available |
| 7.1.8 | Conclusion on the benefit-risk balance for proposed indication | Section VII. Overall conclusion and risk/benefit assessment – Concluding remarks | Section 4 Recommendations | Section 2: Why was <product> approved? | Section 1: Benefit-risk integrated assessment | CRT: Section 4.4<br>6.31: Section 1.1 |
| 7.1.9 | Recommendation indication | Section VII. Overall conclusion and risk/benefit assessment – Outcome | Section 4 Recommendations | Section 7.1: Clinical Basis for Decision – Indication | Section 1: Benefit-risk integrated assessment | Not available |
| 7.1.10 | Indicate if the approved indication is the same as the reference agencies used for this review | Not available | Not available | Not available | Not available | Not available |

Legend: Available | Available but information is limited | Not available

Abbreviations: AusPAR, Australian Public Assessment Report; BR, Benefit-Risk; CRT, Clinical Report Template; EMA, European Medicines Agency; EPAR, European Public Assessment Report; SBD, Summary Basis of Decision; SAHPRA=South African Health Products Regulatory Authority; TGA, Therapeutic Goods Administration of Australia; UMBRA, Universal Methodology for Benefit-Risk Assessment; USFDA, United States Food and Drug Administration

## Part II – Review of the appraisal initiated by SAHPRA to document and communicate BR decisions

The appraisal initiated by SAHPRA to document and communicate the BR decisions to sponsors was evaluated by comparing the SAHPRA guidelines and templates, used to support the assessment of NASs, against the section headings of the UMBRA BR Summary Template (Table 7.2). A description of the treatment options evaluated (Section 1.1.2 of the BR Template) is included in Section 4.3.1 of the CRT. The description is limited to comments on the stratification between treatment naïve and treatment experienced patients. Information pertaining to the review of the API by a reference agency (Section 1.1.6 of the BR Template) is included in Section 3 of the CRT, however, the information requested is limited to an indication of the registration status of the medicine with regulators with which SAHPRA aligns itself. An assessment of ethnic factors (Section 2.1.4 of the BR Template) is included in Section 4.3.1 of the CRT, but is limited to comments on patient demographics stratified by ethnic groups and how this is related to or affected the intended use described in the professional insert. The CRT: Section 4.4 makes provision for a summary of the BR analysis and assessors are required to provide information pertaining to the risk management plan or risk minimisation measures and implementation plan. The clinical study summary is required to be presented as a narrative within the CRT and is limited in that the key benefits and risks, identified in each clinical study, are not documented. The benefits and risks are not listed, no effects table is available and the relative importance, valuing and justification for inclusion/exclusion are not documented. The discussion on the harms, the evolution of the BR balance, outstanding issues, the need for further studies, the conclusion on the BR balance and the recommended indication are not documented. An evaluation of the risk minimisation plan is only applicable for applications for abridged review and an evaluation of the pharmacovigilance plan is not documented.

The SAHPRA Clinical Guideline confirmed that the sponsor is required to provide the reference agencies' regulatory history to SAHPRA, however this requirement is limited to applications for abridged reviews only (SAHPRA, 2019a). The internal SAHPRA Guideline for Clinical Reviewers provides instruction to SAHPRA clinical reviewers on the required format and content of a full clinical review report (SAHPRA, 2019d). Clinical reviewers are required to ensure that review reports are sufficiently detailed to allow for secondary assessment by other expert clinical reviewers. During the review of clinical data, reviewers are required to comment on:

- Whether the BR balance at maximum dose was acceptable;
- The BR balance presented by the applicant;
- Whether or not the suggested risk management plan and risk mitigation measures addressed the safety issues identified within the BR analysis of the safety information of the clinical studies;
- Whether quality of life issues were addressed in the clinical studies; and
- The safety issues reflected in the periodic safety update report (PSUR) or periodic benefit-risk evaluation report (PBRER) or changes in the BR balance, risk management plan and risk minimisation measures when a phase IV post-marketing study was submitted for a medicine that was registered by an NRA with to which SAHPRA aligned itself.

While these requirements are listed in the internal SAHPRA Guideline for Clinical Reviewers as elements to be reviewed, provision is not made to document the reviewer's assessment of these elements within the CRT.

**PART III – Outcomes of focus group**

The outcome of the focus group that was held in Virginia in June 2019 resulted in recommendations for consideration in the use of PARs as potential knowledge management tools for stakeholders such as other NRAs, HTA agencies, industry, civil society and patients in understanding a reference agency's decision-making. The participants identified the need for reference agencies, producing PARs, to ensure that regulatory decisions were documented in a structured and systematic manner. The participants endorsed and agreed that a harmonised PAR template would support improved transparency in regulatory decision-making by aiding the understanding of how the regulatory decision was made and by allowing for easy comparison of the regulatory decisions made by different reference agencies. The participants also

endorsed initiatives supporting an effective approach to communicate regulatory decisions to NRAs that placed reliance on the decisions made by these reference agencies. It was further recommended that reference agencies should consider publishing PARs or releasing information related to negative regulatory decisions (i.e. the rejection of an application for medicine registration) and regulatory decisions made regarding applications for extension of medicine indications. The focus group concluded that the strengths of this work is that it had now compared the PARs produced by reference agencies against a structured, systematic BR template.

## DISCUSSION

National regulatory authorities (NRAs) publish PARs in an effort to enhance transparency and accountability in the regulatory decision-making process. In the public healthcare sector, the publication of PARs contributes towards building public confidence in the regulator and demonstrating the regulator's ability to ensure that medicines available on the market are safe, effective and of good quality. Patients may refer to PARs to better understand the benefits and risks associated with the medicines that have been prescribed to them and practitioners may use them to guide their decisions in selecting one treatment option over another (Leong et al., 2014). The pharmaceutical industry and applicants submitting dossiers to NRAs for medicine registration use such reports to better understand the basis of the regulatory decision and the regulator's rationale for supporting the final BR balance (Leong et al., 2014). Their availability allows stakeholders to better understand any differences in data interpretation and the regulatory opinions that exist amongst NRAs in different jurisdictions (Leong et al., 2014). Other smaller NRAs, particularly in the emerging markets, place reliance on reference NRAs or recognise the decisions of reference NRAs when making local decisions on BR and the local summary basis of the decision to register a medicine in their jurisdiction (McAuslane et al., 2017).

Public assessment reports (PARs) have been recognised by various stakeholders as good knowledge management tools in understanding regulatory decision-making. National regulatory authorities (NRAs) may have legislative duties to make certain information available in the public domain through the publication of PARs or may publish these to support the goals of enhanced public transparency (McAuslane et al.,

2017). The preparation and publication of PARs may inherently contribute to the effective and timely documenting of regulatory decisions by NRAs to support regulatory performance efforts to build quality into regulatory decision-making and maintain the consistency of decisions and scientific advice (Skerritt, 2019). Documenting the regulatory decision-making process, including both internal and external decisions and commitments, is crucial and may serve as a platform whereby past decisions may be used to inform future decisions in a consistent manner while contributing to evolved regulatory pathways that enlist accelerated review processes.

Regulatory decision-making involves the assessment of the benefits and risks and culminates in the final regulatory judgement on the BR balance. It is recognised that several structured approaches to performing the BR assessment exist (Levitan et al., 2014; Leong et al., 2014) through the identification of the initial set of clinical endpoints for the medicine under review and may be illustrated through the use of visualisation tools such as the value tree (Levitan et al., 2014). The importance of incorporating the perspectives of different stakeholders, notably that of the patient, has been emphasised as a result of the influence of patient reported outcomes on the relevance of each endpoint for the decision and the consequent reassessment of the clinical endpoints within the value tree (Levitan et al., 2014; Leong et al., 2014; McAuslane et al., 2017). The data for such endpoints should be assessed and the relative importance should be assigned to each endpoint. This should be indicative of the relative clinical importance of the endpoint in order to support and contextualise the final decision in terms of the BR balance. Furthermore, the preparation of an effects table and the listing of key benefits and risks has been demonstrated to support structured discussion through focused gap analysis and supports the identification of critical issues (Levitan et al., 2014). The decision-making process should also document the framing of the benefits and risks that should be assessed and the justification for their inclusion or exclusion should be recorded (Leong et al., 2014).

In the study conducted by Leong et al. (2014) it was noted that there were discrepancies in the information provided through the PARs prepared by reference agencies when compared to the UMBRA BR Summary Template. Since then these NRAs have taken steps to enhance their PARs, however, the results of this case study indicate that these may be further improved to enhance communication of the BR

decision to intereseted stakeholders. As a result of this study it has been noted that the following key elements should be considered for inclusion in the PARs in order to effectively communicate the summary basis of the regulatory decisions and the key discussion points that lead to the BR decision to accept or reject the application for the registration of a medicine:

- A clinical study summary of the key benefits and risks identified in the clinical studies;
- An effects table, listing each of the benefits and risks identified and a record of the justification for the inclusion or exclusion of the benefits and risks assessed;
- Documented valuing of the options and a record of the strengths and uncertainties identified for each benefit and risk;
- Documented assigned weighting (relative importance) of each of the benefits and risks taking into consideration relevant stakeholder perspectives;
- A record of the expected evolution of the BR balance over time;
- A record of the regulatory history of the medicine; and
- A record of the indication of the medicine in comparison with that approved by the reference agency.

The results of the study conducted by Leong et al. (2014) and of this case study confirm that the PARs prepared by the NRAs were similar in purpose, format and context and supports the use of a universal template for documenting and communicating BR decisions (Leong et al., 2014). The UMBRA framework made provision for the listing of benefits and risks, assigning relative importance and valuing the options. It also provides a platform for structured discussion and a documented appraisal of the BR parameters through the use of a common language and presentation. By using the UMBRA BR Summary Template, the interested stakeholder will be able to clearly understand the key messages presented by the NRA as the summary basis of the regulatory decision would be prepared in a format that was suitable for public consideration (Leong et al., 2014; McAuslane et al., 2017; Walker et al., 2014).

The UMBRA BR Summary Template provides a mechanism for NRAs to document their BR assessment and build quality into their decision-making practices in a structured way as part of their efforts to ensure GRevPs (McAuslane et al., 2017;

WHO, 2015). This approach could be used as an assessment template for NRAs wanting to enhance their BR assessment and could potentially serve as a guidance on BR assessment and a training tool for both regulatory reviewers and industry stakeholders responsible for the assessment of new medicines (McAuslane et al., 2017). Making use of the UMBRA BR Summary Template as an outline for a PAR would enhance consistency in regulatory decision-making and provide an effective tool for the review of past regulatory decisions. The UMBRA BR Summary Template supports the clear articulation of each of the benefits and risks and contributes towards the ease of comparison of regulatory outcomes for medicines of the same class and the decisions by different NRAs for the same medicine (Leong et al., 2014; McAuslane et al., 2017).

The SAHPRA has initiated development of an appraisal document to be used for considering BR balance during the review of NASs. This study has identified a number of deficiencies in that appraisal. The current guidelines and report templates used by SAHPRA do not contribute fully to the comprehensive, structured, consistent evaluation of each of the benefits and risks and do not provide documented justification for the final decision on the BR balance or the decision to accept or reject the registration of the medicine.

National regulatory authorities (NRAs) worldwide, irrespective of size and expertise have or are considering the implementation of FRPs; entering into work sharing arrangements with other NRAs and placing reliance on or recognising the regulatory decisions of other NRAs (Azatyan, 2019; Liberti, 2017, unpublished thesis; Liberti et al., 2018; Ward, 2019). A study by McAuslane et al. (2017) demonstrated that making use of a common approach to BR assessment and decision-making was pivotal in the implementation of work sharing models and in enabling the effective utilisation of information and expertise (McAuslane et al., 2017). Considering the drive by SAHPRA to embrace reliance models and the involvement of SAHPRA in work-sharing initiatives such as Zazibona, it may be valuable for SAHPRA to consider using a universal template and common approach to BR decision-making.

Key recommendations for SAHPRA for the implementation of an effective approach for communicating BR decisions include:

- Ensuring that the BR assessment is performed in a structured, systematic documented manner in alignment with GRevPs in order to build quality into decision-making;
- Preparation and publication of a South African public assessment report (ZAPAR) in order to effectively communicate the BR decision to stakeholders and to ensure consistency, transparency and accountability in regulatory decision making; and
- A consideration of the UMBRA BR Summary Template as guidance for BR assessment and as an outline for the ZAPAR which may further contribute towards:
    - Ease of comparison of regulatory decisions made by SAHPRA and other NRAs for the same medicine or for decisions made by SAHPRA for medicines in the same class;
    - The review of past regulatory decisions to ensure consistency and objectivity in post-market assessments and medicine life cycle management; and
    - The use of documented BR assessments as a reference to facilitate expedited review times; as a result of better understanding of past decisions that may support faster decision-making in line with the goals of accelerated review times for NASs.

The implementation of an effective approach for communicating BR decisions by SAHPRA, based on these recommendations, should have a major impact on ensuring consistency in the BR assessment of NASs through the use of a structured template that supports transparent quality decision-making. Communicating the regulatory decisions of SAHPRA in the public domain will also enhance their goals of being a trusted, responsive, accountable regulator in which all stakeholders such as the industry and public may rely on and in which have confidence.

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**SUMMARY**

- National regulatory authorities (NRAs) make a decision to register a medicine based on an assessment of the overall benefits and risks of a medicine

- Reference agencies publish PARs in order to communicate the basis for the regulatory decision

- Many NRAs in emerging economies place reliance on the PARs of reference agencies to inform their own regulatory decisions

- The PARs from the TGA, EMA, Health Canada and US FDA were compared to the validated UMBRA BR Summary Template to determine whether the BR decision had been documented in a systematic and structured manner

- A focus group was conducted to discuss the use of PARs as potential knowledge management tools for stakeholders

- The approach initiated by SAHPRA to document and communicate the BR decisions was evaluated

- The results of this case study indicated that the following key elements should be considered for inclusion in the PARs: a record of the regulatory history of the product, an effects table, the valuing of the options and a record of the strengths and uncertainties identified for each benefit and risk

- The participants in the focus group agreed that a harmonised PAR template would support improved transparency in regulatory decision-making

- The approach initiated by SAHPRA to communicate BR decisions could be improved and communicating the regulatory decisions of SAHPRA in the public domain would enhance their goals of being a trusted, responsive, accountable regulator

# CHAPTER 8

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# A Roadmap for the Implementation of a Proposed Model for Regulatory Reliance in South Africa

## INTRODUCTION

Disparities in the regulatory capacity of NRAs between low and high-income countries and the lack of collaboration and work sharing in medicines regulation between NRAs have been previously identified (Azatyan, 2019). Approximately 30 % of NRAs do not have the necessary capacity in terms of expertise, QMS and human and financial resources to fulfil core regulatory functions (Azatyan, 2019). The WHO has initiated the development of guidelines on GRPs to support NRAs' efforts of increased efficiency of regulatory systems, higher quality regulation, improved decision-making and better public health outcomes (Azatyan, 2019; WHO, 2016).

The review of quality, efficacy and safety of medicines is considered to be one of the key functions of NRAs (Liberti et al., 2018) and the timely review of applications for registration of NASs can significantly improve patients' access to medicines and consequently impact public health (WHO, 2015). The implementation of GRevPs supports improved regulatory performance and contributes to the advancement of convergence of regulatory requirements of NRAs (WHO, 2015). This coupled with the alignment of the ICH technical guidelines would create opportunities for reliance based on the regulatory decisions of other NRAs and supports possibilities for work-sharing and joint regulatory initiatives (EFPIA, 2017).

The WHO has defined reliance as "an act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision" (Ward, 2019). The NRAs in resource-limited settings may apply facilitated regulatory pathways (FRPs) to meet patients' expectations of timely access to medicines and accelerate the regulatory review process by condensing the elements considered in the review of new medicines. Such NRAs remain responsible for the regulatory decisions made through FRPs and in this way are able to maintain sovereignty in making regulatory decisions (Ward, 2019). The application of FRPs should be developed on appropriate legal frameworks and within the bounds of commensurate resources.

The WHO has developed draft guidance for good reliance practices (GRelPs). These GRelPs are derived from GRevPs and fit within the remit of best practices for the regulation of medical products as prescribed by the WHO (Azatyan, 2019). The

GRelPs may be implemented across all regulatory processes and applied to all medicines throughout the whole product life cycle, while contributing to an improved healthcare environment through the promotion of fully functional national regulatory systems (Azatyan, 2019). Furthermore, NRAs may apply GRelPs in order to advance good governance, transparency and regulatory convergence that in turn supports good quality decisions by NRAs and presents opportunities for leveraging the regulatory effort of other NRAs, while promoting the conservation of limited regulatory resources (Azatyan, 2019).

This study aimed to provide recommendations for the implementation of an abridged review process and a framework for GRelPs in South Africa. This review is the first to be carried out in determining the current practices of NRAs in performing an abridged review of a NAS while considering the practicality of the implementation of GRelPs.

**Study objectives**

The main objectives of this study were to:

- Identify the criteria and current practices within a number of NRAs for implementing an abridged review process;
- Conduct focus groups on the practical implementation of an abridged review process for new medicines in the light of the WHO's GRelPs; and
- Develop recommendations in the light of the WHO roadmap for the implementation of an abridged review process based on GRelPs in South Africa.

## METHODS

### Data Collection

***Questionnaire*:**

**Criteria and current practices for implementing an abridged review process**

A questionnaire (see Appendix 2), the abridged review process profile (ARPP), was developed by the CIRS (CIRS, 2017; McAuslane, 2019) to identify the criteria and current practices that were applied by NRAs for implementing an abridged review process. A number of NRAs have already implemented processes to facilitate an abridged review. The countries recruited into the study were Australia, Brazil, Canada,

the Gulf Health Council, Indonesia, Israel, Thailand, Saudi Arabia and Singapore and the ARPP was distributed to each for completion.

The ARPP consists of five parts:

Part I: NRA information

This part of the questionnaire describes the mandate and scope of the NRA as well as its size and type, including information on the number of reviewers within the NRA and their areas of expertise.

Part II: Criteria for product inclusion and reliance on reference agency

The specific criteria applied to determine which products were eligible for inclusion in the abridged review process were recorded. The criteria for the selection as well as how many reference agencies on which to rely were also described.

Part III: Data requirements

This part of the ARPP lists the data requirements for the abridged review. The type of assessment report from the reference agency that would be used to facilitate the abridged review and the level of detail of information that would be required were described.

Part IV: Clinical Factors

The clinical factors considered in the BR evaluation were recorded.

Part V: Enablers and Barriers

The perceived enablers and barriers to the implementation of an abridged review were also listed.

***Focus group:***

**Practical implementation of an abridged review process for new medicines and GRelPs**

Two focus group sessions were conducted with representatives from NRAs, industry, academia and patient groups from different jurisdictions. The focus group sessions held in South Africa and Singapore consisted of 16 and 13 participants respectively, a moderator for facilitating the discussion and a rapporteur who was responsible for

consolidating the results and reporting on the outcomes of the discussion. A brief guideline was prepared for the participants of each focus group. The guideline described the discussion topic, provided background information and outlined the objectives of the focus group discussion. A list of questions and issues for consideration were developed and made available to each of the focus groups to further stimulate the discussion.

The first focus group was held at a workshop convened by the CIRS in South Africa in March 2018. The topic of discussion was "The practical implementation of an abridged review process for new medicines: where should an agency focus and what are the practical steps needed to change process and mind-sets?" The second focus group was held at a workshop convened by the CIRS in Singapore in March 2019. The topic of discussion was "The draft Good Reliance Practice Guideline – how practical is it? A stakeholder's review and discussion."

The SAHPRA initiated an abridged review process in July 2019 in an effort to reduce the evaluation time that was currently around six years. In addition, it introduced a new clinical guideline together with a SCoRE document that was required to be submitted with all new applications for registration to SAHPRA. These documents were examined, in the light of the abridged study described, in order to make recommendations regarding an appropriate framework for such reviews in South Africa in line with GRelPs.

**RESULTS**

For the purpose of clarity, the results were presented in three parts:

- Part – I: Criteria and current practices for implementing an abridged review process
- Part – II: Outcomes of focus groups
- Part – III: Review of the abridged review process initiated in South Africa

**Part - I: Criteria and current practices for implementing an abridged review process**

Six out of the nine NRAs recruited into the study completed the ARPP including: Australia; Brazil; Canada; the Gulf Health Council; Israel; and Thailand. In addition, information from the public domain, such as documents published by SAHPRA for public comment and the CIRS workshops held in Singapore and South Africa, were included.

***National regulatory authority information***

This part of the questionnaire provided insight into the scope, regulatory mandate and size of the participating NRAs (Table 8.1).

***Criteria for product inclusion and reliance on reference agency***

The participating NRAs concurred that one of the key criterion for product inclusion was the submission of an application for an NAS that was identical to that approved by, or submitted to, the reference agency. The application submitted had to be identical in terms of dosage form, strength, formulation and manufacture. Three of the participating NRAs reported that the proposed indication for the medicine would need to be based on broadly similar population demographics, disease profiles and expectations regarding public health outcomes between the NRA and the reference agency. Most of the participating NRAs confirmed that NASs were eligible for inclusion but one NRA stated that the abridged review would only be applicable to biological products, while biosimilars would be excluded. One NRA specified that the NAS in question had to be approved as well as being available on the market in the reference agency country.

The participating NRAs documented inclusion criteria relating to the time frame between the submission of the NAS application to the reference agency and the submission to the NRA. Two of the NRAs did not impose restrictions in terms of this time frame while two NRAs indicated that applications that had been submitted to the reference agency, more than two years before, would not be considered. One NRA indicated that a new guideline had been drafted that echoed this requirement. One NRA stated that a timeframe of not more than one year would be applied for the quicker evaluation route.

**Table 8.1. Scope, size and regulatory mandate of participating national regulatory authorities (NRAs)**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Type of agency** | | | | | | | |
| Autonomous agency, independent from the Health Ministry administration | 2 | | | Operates within the administrative structure of the Health Ministry | | | 4 |
| **Size of agency** | | | | | | | |
| Total staff in the agency for medicinal products for human use | | | 731 | 1958 | 186 | 565 | 40 | 38 |
| Number of reviewers for applications for marketing authorisations/ product licences | | | 115 | 134 | 186 | 247 | 29 | 17 |
| **Scope and remit of the agency** | | | | | | | |
| Medicinal products for human use | 6 | Medicinal products for veterinary use | 4 | Medical devices and *in vitro* diagnostics | 4 | Blood and Blood Products | 1 |
| **Main activities that are covered by the agency** | | | | | | | |
| Marketing authorisations/ Product licences | 6 | Post-marketing surveillance | 4 | Laboratory analysis of samples | 2 | Clinical trial authorisations | 4 |
| Regulation of advertising | 4 | Price regulation | 3 | Site inspections (site visits) | 4 | Other | 1 |

The participating NRAs indicated the following as key considerations in selecting a reference agency: utility and compliance to global standards and technical guidelines; the availability of reference agency assessment report, integrity in decision-making and transparent communication.

Six of the participating NRAs selected the USFDA and the EMA as reference agencies on which reliance would be placed for the purposes of implementing an abridged review. Four of the NRAs indicated that reliance was also placed on the MHRA of the United Kingdom and the Swiss agency for therapeutic products (Swissmedic) while other reference countries considered for reliance included Australia (3), Canada (3), Japan (3), New Zealand (1), Norway (1), Singapore (1), Iceland (1) and the WHO prequalification of medicines programme. Six of the participating NRAs stated that reliance would be placed on only one reference agency in the application of the abridged review process and one NRA stated two reference agencies, namely the USFDA and the EMA. In the event that reliance was placed on more than one reference agency and a difference in the regulatory decisions of the two reference agencies was noted, the NRA would apply the reference regulatory decision most appropriate to the requirements of the jurisdiction.

***Data requirements***

*Assessment report* - Five of the participating NRAs stated that un-redacted assessment reports would be required in order to facilitate the abridged review process. Three of the six NRAs indicated that redacted reports could be used, provided that these reports were only lightly redacted and that all the necessary information was available. Also required was a list of questions to sponsors and their responses as well as post-marketing commitments. Three of the NRAs made use of PARs that were available in the public domain. Five of the six NRAs indicated that while only parts of the technical document would be reviewed during an abridged review, it was a requirement that a full ICH/Association of Southeast Asian Nations (ASEAN) CTD had to be submitted for the abridged review. All of the six participating NRAs provided insight into the depth of the CTD review during the abridged review (Table 8.2).

**Table 8.2. Depth of review of the common technical document (CTD) by the national regulatory authorities (NRA) in the abridged review**

| Area of the CTD reviewed | Only reviewed if there was a query | Verification for completeness of data | Selective detailed review | Detailed review and assessment report prepared |
|---|---|---|---|---|
| Quality / (CMC) | 0 | 0 | 3 | 3* |
| Human Pharmacology | 3** | 1 | 0 | 2** |
| Clinical | 1 | 1 | 0 | 4*** |
| Non-Clinical | 3** | 1 | 0 | 2** |

Abbreviations: CTD=Common Technical Document; CMC=Chemistry, Manufacturing and Controls

* Reflected the current situation, however in the new draft guidelines the NRA would only review the reference agency assessment report, but could review data in CTD if necessary.

** One NRA indicated that currently the level of review was dependent on the product and availability of the reference agency assessment report. The new draft guidelines stated that the NRA would only perform a review of the data in the CTD if an issue was identified by the reference agency.

*** One NRA stated that the new draft guidelines described that only the pivotal studies would be reviewed

*Application* - In support of the requirement for an abridged review, participating NRAs verified that applications submitted should be identical to that approved by the reference agency. All of the participating NRAs required the dosage form and strength of the NAS to be identical with that of the NAS submitted to the reference agency. All of the six participating NRAs required that the ingredients of the respective NAS be identical and four of the NRAs required that the indications, dose as well as the warnings and precautions of the NAS be identical.

All of the NRAs accepted a closely similar product label to that submitted to the reference agency. During the abridged review process, NRAs may choose to perform a detailed review of the reference agency assessment reports in lieu of performing an internal review of the CTD or review areas of the reference agency assessment report in the event that the reviewer identifies an issue. Five of the participating NRAs indicated that a detailed review of the reference agency assessment report was performed during the abridged review. The areas of the reference agency assessment report relating to quality/CMC, human pharmacology, clinical and non-clinical data were reviewed in detail by the NRAs as part of the abridged review.

***Clinical factors***

The majority of the participating NRAs indicated that clinical factors such as differences in medical practice, national disease patterns and unmet medical needs were taken into account during the clinical evaluation and the benefit-risk assessment that was conducted during the abridged review. The majority of the NRAs indicated that ethnic factors were also, sometimes, considered during an abridged review.

***Enablers and barriers***

In Part V of the questionnaire the participating NRAs provided insight into the perceived enablers and barriers that impacted on the implementation of an abridged review (Table 8.3).

**Table 8.3. Enablers and barriers identified by national regulatory authorities (NRAs) in implementing an abridged review**

| Enablers | Barriers |
|---|---|
| Availability of the un-redacted reference agency assessment reports | Not receiving the un-redacted reference agency assessment reports from the applicant |
| Availability of the list of questions from the reference agency to the applicant and post-approval commitments | Resistance from applicants to apply for the abridged review process as requirements for supporting documents could not be met |
| Approval of a NAS within two years from the reference agency | Inadequate transparency with regard to reference agency decision making process |

| | |
|---|---|
| Applicants who are willing to answer questions throughout the course of the review rather than at the end of the review | Benefit-risk assessment is not sufficiently detailed and presents challenges in application to the local NRA population |
| Increased communication and interaction with other agencies | Differences or diversity in regulatory requirements between the NRA and the reference agency |
| Saves resources as the assessment report of the reference agency may be used for the review instead of contracting an external expert to conduct the review | The reliance on work conducted by another agency requires a culture shift; unease that reliance will result in a loss of local expertise |

Abbreviations: NAS=New Active Substances; NRA=National Regulatory Authority

**Part - II: Outcomes of focus group discussions**

The outcomes of the first focus group session that was held in South Africa in March 2018 resulted in recommendations for consideration in the practical implementation of an abridged review process for NASs. The participants concluded that the elements constituting an abridged review had to be identified. It was recognised that the requirements for applications submitted for abridged review to the NRAs participating in the discussion, were similar. The participants agreed that while information such as reference agency assessment reports were available in the public domain, these were often heavily redacted and ill equipped to support regulatory decisions made by NRAs during the abridged review process. The participants endorsed the recommendation to perform a study to identify what NRAs evaluate when performing an abridged review.

The outcomes of the second focus group session that was held in Singapore in March 2019 resulted in recommendations for consideration in the review of the practicality of the draft WHO GRelPs guideline. The participants agreed that reliance practices were largely based on the use of information or regulatory decisions of a trusted source/reference agency. Through the discussion it was acknowledged that reliance practices were used in diverse applications and participants commented that shared inspection reports and CMC reports could be used to confirm the quality of an NAS without duplicating regulatory efforts. Participants endorsed the application of a phased-approach in the implementation of GRelPs and commented positively regarding the requirement to provide a summary of the BR assessment and findings and/or recommendations prepared by the reference agency. The participants

endorsed the outcomes of the study that identified which NRAs have implemented reliance pathways and what the requirements were for such pathways.

**Part III: Evaluation of the abridged review process initiated in South Africa**

The SAHPRA initiated an abridged review process in 2019 in an effort to limit the evaluation time of medicines that had been registered by reference agencies recognised by SAHPRA. All NASs including biological medicines, generic medicines, type II variations and MLEs would be eligible for an abridged review (SAHPRA, 2019a). Similar to the requirements of the participating NRAs in this study, SAHPRA required the submission of an application that was materially the same as that submitted to a reference agency recognised by SAHPRA. The EMA was considered as the default reference agency by SAHPRA for reliance, however the USFDA, PMDA, Health Canada, Swissmedic, the TGA and MHRA were also listed as recognised agencies. Sponsors were required to submit the full CTD and were also requested to submit un-redacted assessment reports from reference agencies. Where these were not available, applicants were requested to submit a request to the reference agency to make the relevant un-redacted assessment reports available to SAHPRA. SAHPRA also requested the submission of any correspondence between the applicant and the reference agency relating to safety and efficacy or queries regarding the risk management plan or BR decisions (SAHPRA, 2019a). The clinical guideline published by SAHPRA in July 2019 described the requirements for the clinical evaluation of medicines using the abridged review (SAHPRA, 2019a). The guideline indicated that only the overviews of the pre-clinical and clinical data described in CTD modules 2.4 and 2.5 would be reviewed, however, reviewers were at liberty to perform a full review of CTD modules 4 and 5 if it was deemed necessary (SAHPRA, 2019a).

The new SAHPRA Clinical Guideline indicated that the summary basis for registration (SBR) document, which was previously required by SAHPRA to support clinical evaluation of a medicine, was no longer required and would be replaced by the clinical overviews and summaries and the SCoRE document. The SCoRE document was required to be submitted with all new applications for registration (SAHPRA, 2019b) and was required to be submitted as part of CTD module 3.2.R.8 (Other) in addition to the Quality Overall Summary. Applicants were also required to submit the latest PSUR/PBRER and reference package insert approved by the reference agency. The

SAHPRA also indicated that two additional reliance pathways had been developed for medicines that had been pre-qualified by the WHO and for medicines that had been reviewed through the Zazibona collaborative review procedure (SAHPRA, 2019b).

## DISCUSSION

### Practical implementation of an abridged review process

Strategies initiated by NRAs to leverage international collaboration in the form of reliance and referencing to enhance regulatory performance have been endorsed by the WHO (Azatyan, 2019). The participants in the focus groups identified that there is a definite need for NRAs to use FRPs such as an abridged review to improve regulatory efficiencies. The abridged review is based on the premise that the review time would be decreased as reliance on the assessment report of a reference agency and placing weight on the regulatory decision of a trusted NRA eliminated the need to do a full assessment of the quality, safety and efficacy data provided in the technical dossier. Typically, NRAs rely on the decision of one reference agency in support of an abridged review. Applications submitted to NRAs for an abridged review should be identical to that submitted to the reference agency. An abridged review of a NAS relies on the scientific, evidence-based assessment of the NAS by a reference agency. Subsequently, the NRA may review the reference agency's assessment report and conduct an abridged review of certain parts of the technical dossier in support of local requirements. Enablers supporting the implementation of an abridged review include the availability of un-redacted reference agency assessment reports, increased communication and interaction between NRAs and reference agencies and continued efforts to ensure that regulatory decisions are based on sound regulatory processes and standards.

### Practical implementation of good reliance practices

"The recommendations from several WHO ICDRA meetings highlighted that the desired public health goals can only be achieved through collective efforts of regulators and other stakeholders" (Azatyan, 2019, p. 8). The WHO conducted a survey on reliance practices amongst members of the International Pharmaceutical Regulators Programme (IPRP) in October 2018 (Cooke, 2019). Responses to the survey were received from 8 member countries including Australia, Brazil, Canada, Japan,

Singapore, Switzerland, Taiwan and United States of America. Additional responses were also received from Cuba, Europe, Mexico, New Zealand, Russia and Turkey.

This survey set out to further understand the experience of the NRAs in implementing a reliance framework and what the perceived benefits, challenges and opportunities were (Cooke, 2019). The results of the survey echoed the findings of the current study in that the rationale for choice of reference agencies was similar. Perceived benefits of reliance included enhanced regulatory performance and shortened review times based on greater collaboration, the effective application of resources and opportunities for formalising reliance and work-sharing arrangements (Cooke, 2019).

The responses from the survey unveiled similar concerns as those identified through the questionnaire used in this study. Respondents identified the differences in regulatory systems and country-specific requirements as an area for improvement. National regulatory authorities (NRAs) relying on reference agencies were concerned about the lack of access to information from reference agencies. Emphasis was placed on challenges experienced with highly redacted assessment reports and the lack of information available to document the rationale for the reference agency's regulatory decisions. The formal implementation of common review templates and assessor's guides was recommended in order to optimise reliance frameworks.

The respondents noted that the implementation of a reliance framework supported a number of opportunities in the post-approval phase. These included proactive sharing of post-market safety data, work-sharing in terms of pharmacovigilance activities and enhanced efficiencies in monitoring activities and the standardisation of pharmacovigilance practices. A reliance framework would support routine work-sharing platforms and harmonisation in terms of templates for inspection and assessment and opportunities for emerging markets to gain experience in advanced regulatory practices (Cooke, 2019).

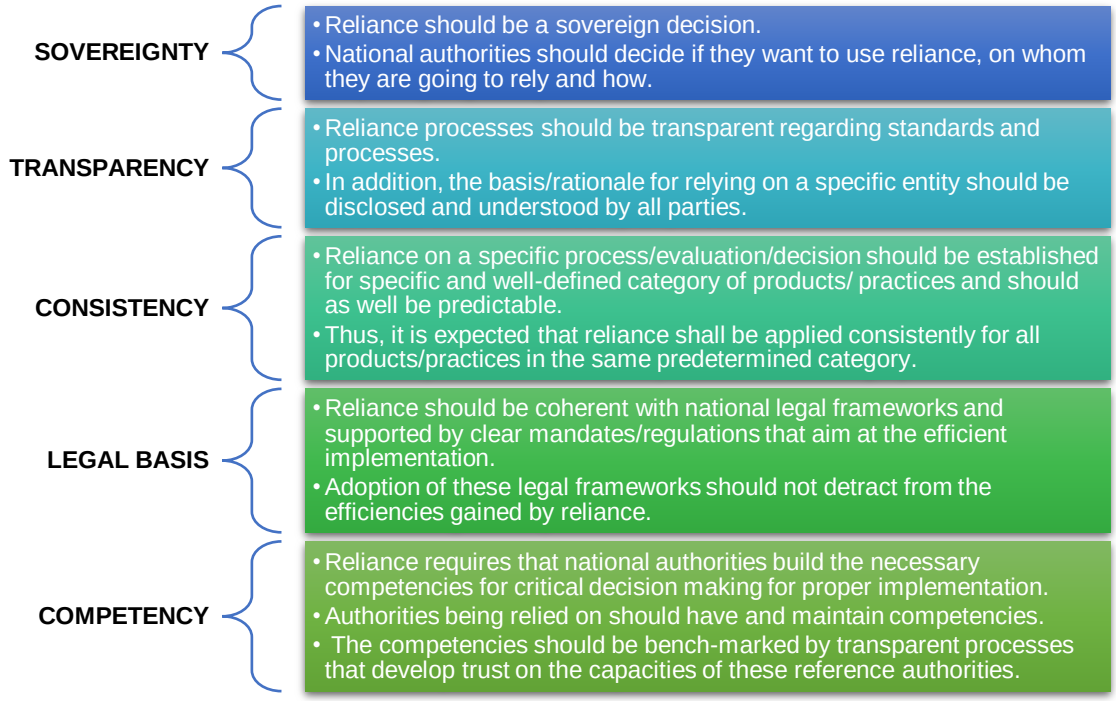
The National Academies of Sciences, Engineering, and Medicine assembled an expert committee to examine the challenges and opportunities facing NRAs, particularly in the context of mutual recognition agreements and other forms of regulatory reliance (National Academies of Sciences, Engineering, and Medicine, 2019). The findings of

the committee resonated with the outcomes of this study. National regulatory authorities (NRAs) are faced with challenges in applying finite resources to effect regulatory mandates. As such, NRAs have to explore opportunities to expand their capabilities and engage in collaborative initiatives. Information sharing and transparency amongst NRAs should be increased. Formal and informal reliance frameworks should be considered and developed on a co-created results-framework that highlights measuring, monitoring and performance metrics in order to quantify the impact of these strategies (National Academies of Sciences, Engineering, and Medicine, 2019).

The GRelPs have been drafted by the WHO to support the systematic and consistent implementation of a reliance framework within regulatory systems (Azatyan, 2019). Through the introduction of such GRelPs, NRAs are able to redirect limited resources to core regulatory functions that can only be performed by the NRA with an aim of accelerating patients' access to medicines. The implementation of GRelPs provides an opportunity for NRAs with limited expertise to rely on the technical assessment of reference agencies for complex medical products and consequently provide a solution for timely registration and access to advanced medicines by the local population (Azatyan, 2019). National regulatory authorities (NRAs) that implement a reliance framework remain responsible for their regulatory decisions and the outcomes thereof (Ward, 2019; WHO, 2016).

Current regulatory capacity, the needs of an efficient regulatory system and consideration of how the implementation of reliance models may contribute to enhancing the performance of an NRA should form the basis on which NRAs decide to adopt reliance models and implement GRelPs (PANDRH, 2018). "Understanding the key principles through which reliance models operate (Figure 8.1) should guide and inform decision-making by NRAs contemplating the adoption and implementation of reliance practices" (PANDRH, 2018, 10).

**Figure 8.1. Key operational principles of reliance models**



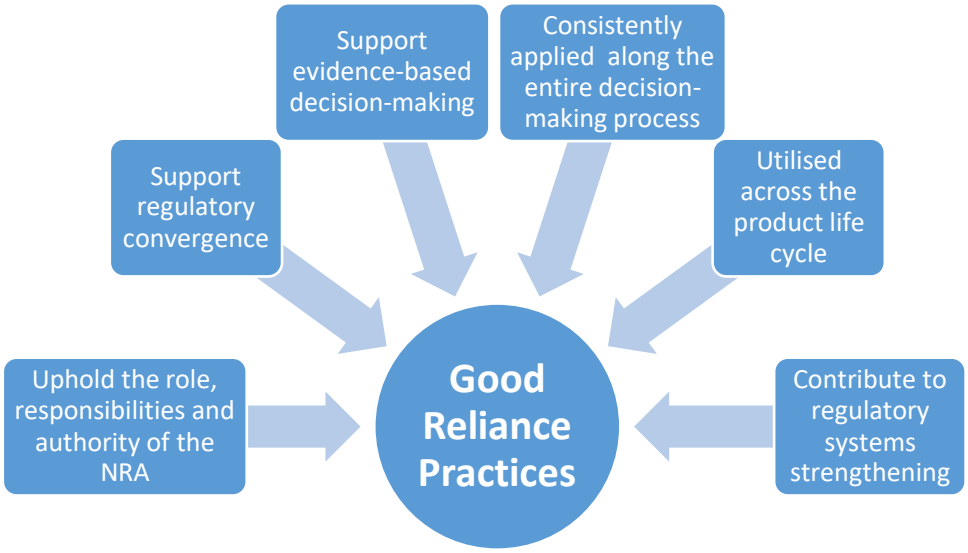

*Adopted from PANDRH, 2018*

National regulatory authorities (NRAs) can tailor the application of these principles to meet the individual needs of national health and regulatory systems (PANDRH, 2018). The foundation for the implementation of a reliance model is dependent on the knowledge of or information gained from a trusted source that has based regulatory reviews and decision-making on sound scientific evidence, global standards and robust regulatory frameworks. In this way, trust between NRAs becomes a critical component of reliance as confidence is built through trustworthy networks (PANDRH, 2018). Further initiatives to improve trust amongst NRAs have contributed to the reinforcement of reliance structures (PANDRH, 2018). These include the benchmarking of national regulatory systems of WHO Member States, using the standardised WHO GBT (WHO, 2020) and the evaluation of NRA inspection capacities by the PIC/S (PIC/S, 2019).

The principles of GRelPs are illustrated in Figure 8.2. The implementation of GRelPs should not undermine the authority of the NRA as underwritten by the relevant legal framework that supports the regulatory mandate (Bee, 2019). Convergence of regulatory requirements among NRAs underpins the success of GRelPs which in turn

facilitates enhanced decision-making (Bee, 2019). The reliance models used for regulatory decision-making should be applied consistently and the decision-making process must remain evidence-based and in compliance with GRevPs (Bee, 2019). Reliance models used to support regulatory decision-making should be extended across the product life cycle to support the post-market robustness of the decision with respect to the local population (Bee, 2019).

**Figure 8.2. The principles of good reliance practices (GRelPs)**




*Adopted from Bee, 2019*

Regulatory efficiency could be increased through the support of GRelPs which in turn contributes towards regulatory system strengthening (Bee, 2019). However, NRAs should continue to develop their regulatory capabilities and develop reliance models based on a set of key principles (Table 8.4) (Azatyan, 2019). Reliance models that may be used to facilitate the review of medicines include mutual recognition, referencing decisions using un-redacted assessment reports of reference agencies (e.g. use of assessment reports from reference agencies or WHO prequalification), work sharing (e.g. EU decentralised procedure and the Zazibona process in the SADC region; and joint assessment (e.g. WHO East African Community (EAC) joint assessments/inspections and the ASEAN joint assessments) (Azatyan, 2019; Bee, 2019).

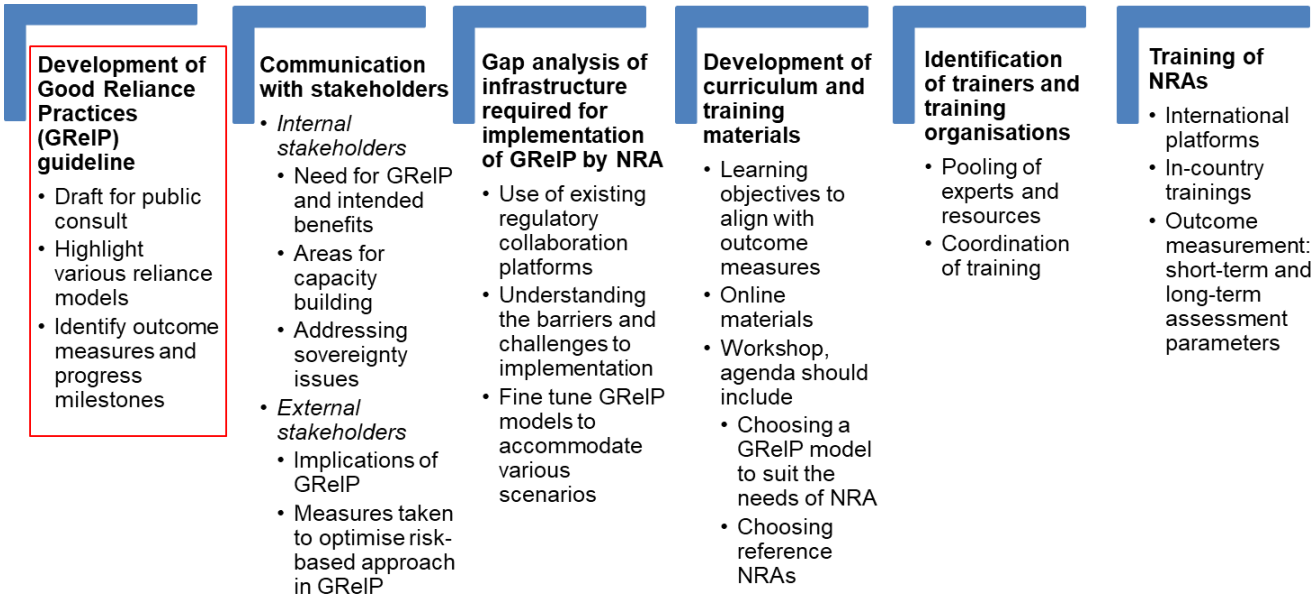
**Table 8.4. Key principles in the development of reliance models**

| | |
|---|---|
| **Outcome orientation** | Efforts should lead to measurable public health gains. |
| **Operational flexibility** | One approach may not be appropriate for all situations. |
| **Pragmatism** | Employing a step wise approach that builds on successes and lessons learned. |
| **Utilising best international practices** | Importance of common requirements and approaches based on international best practices and standards, such as the Common Technical Document (CTD), in achieving optimal outcomes. |
| **Accountability** | The work needs to be planned and staffed appropriately and the outputs need to be implemented consistently, predictably, and transparently. |

*Adopted from Azatyan, 2019*

The GRelPs must be integrated into the frameworks developed by NRAs to support the implementation of reliance models and a roadmap for the implementation of GRelP has been drafted (Figure 8.3) (Bee, 2019). It is, therefore, important that reliance models are built on a legal and regulatory foundation that supports international cooperation and exchange of information with other NRAs (Bee, 2019).

**Figure 8.3 Roadmap for the implementation of good reliance practices (GRelPs)**




Abbreviations: GRelP=Good Reliance Practices; NRA=National Regulatory Authority

*Adopted from Bee, 2019*

This might initially rely on NRAs leveraging existing international collaborative platforms to initiate and expedite the implementation of reliance models (Bee, 2019). National regulatory authorities (NRAs) should ensure that both internal and external stakeholders understand and accept the proposed reliance model (Bee, 2019). Thus, providing clear guidance to sponsors and defining the relevant requirements for eligibility criteria, submission requirements, time lines and registration pathways is recommended to facilitate the process and ensure the intended outcomes (EFPIA, 2017). Furthermore, NRAs should ensure that the implementation of reliance models is underpinned by capacity building strategies and rolled out effectively to support the success of such initiative while continuing to enhance regulatory competencies to complement reliance models (Bee, 2019). Reliance models may be used by NRAs to support the initial approval of a NAS as well as the management of post-approval variations. While NRAs may rely on the decisions made by reference agencies, they should remain cognisant of the possibility that certain NASs may be developed in a manner that allowed for expedited approval, based on an abbreviated data-set, supported by well-defined post-approval commitments (EFPIA, 2017). Transparent decision-making processes must be in place to ensure that the basis for the approval or rejection of a NAS is adequately documented.

While NRAs strive to improve regulatory performance and work towards achieving accelerated approval times for NASs, many NRAs continue to face challenges due to resource constraints. Increasing workloads, advancing technologies and limited expertise create the need for NRAs to leverage regulatory convergence initiatives, collaborative registration procedures and functional continental networks in order to fulfil their regulatory mandates (Azatyan, 2019).

The SAHPRA has faced similar challenges and has taken steps towards embracing reliance models and employing an abridged review process for NASs. Key recommendations to ensure the success of the proposed reliance model for an abridged review and the implementation of GRelPs by SAHPRA should include:

- Formalising the implementation of GRelPs;
- Continuing to place reliance on trusted reference agencies that have met the requirements of standardised regulatory benchmarking tools;

- The verification that the NAS applications submitted to SAHPRA are materially the same as that submitted to a reference agency recognised by SAHPRA;
- Limiting the scope of the abridged review to a:
    - Detailed review of clinical data including consideration of clinical factors such as differences in medical practice, national disease patterns, unmet medical needs and ethnic factors;
    - Review of the quality data and non-clinical data only in the event of query; and
    - Selective review of human pharmacology data.

The implementation of abridged reviews by SAHPRA based on these recommendations of GRelPs should have a major impact on regulatory review times which over the last four years (2015-2018) were in excess of five years. Thus, this approach, if continued and endorsed by SAHPRA, will ensure the timely patients' access to new medicines.

**SUMMARY**

- This study aimed to identify the criteria and current practices for implementing an abridged review process as well as understanding the challenges, enablers and barriers in utilising reliance models and to offer recommendations for the implementation of an abridged review process in South Africa based on GRelPs

- A questionnaire was completed by six NRAs to determine the criteria and current practices for implementing an abridged review process

- Two focus group discussions were conducted to discuss the practical implementation of an abridged review process for new medicines based on GRelPs

- The participating NRAs indicated that reliance would be placed on at least one reference agency

- Applications submitted to NRAs for an abridged review had to be identical to that submitted to the reference agency

- Un-redacted assessment reports from the reference agency would be required in order to facilitate the abridged review process

- The results of the focus group discussions indicated that the elements constituting an abridged review had been identified and that these should be considered in line with the implementation of GRelPs

- National regulatory authorities (NRAs) strive to improve regulatory performance and work towards achieving accelerated approval times for new active substances

- Recommendations for the implementation of an abridged review process and a framework for GRelPs have been made with a view to optimising regulatory review processes in South Africa

# CHAPTER 9

## General Discussion

## INTRODUCTION

The effective regulation of medicines, the strengthening of regulatory systems and the improvement of regulatory performance have become the focus for national regulatory authorities (NRAs) and governments worldwide. National regulatory authorities (NRAs) are responsible for protecting and promoting public health, implementing rigorous regulatory standards and maintaining an assured supply of medicines which are safe, effective and of good quality (Rago & Santoso, 2008; Ndomondo-Sigonda et al., 2017; WHO, 2018a). Global trends of mounting pressure on NRAs of all sizes and capacity have been noted due to the larger volumes of applications received, the complexity of the submissions and the increased categories of medicines (WHO, 2015). For many NRAs, particularly in emerging markets with resource-limited settings, achieving these types of results has not been a reality (WHO, 2014a). Efforts to address the challenges faced by NRAs in low and middle-income countries have focused on strategies for identifying and performing core regulatory functions that have to be undertaken directly by NRAs to meet country or regional needs (Ward, 2014; WHO, 2014a). National regulatory authorities (NRAs) have also been encouraged by the World Health Organization (WHO) to consider regulatory convergence and to collaborate with and recognise the work done by other NRAs in order to avoid the duplication of regulatory efforts and to ease the regulatory burden (Ward, 2014; WHO, 2014a).

The Medicines Control Council (MCC), the past NRA in South Africa, had historically faced similar difficulties. The increasing volume of applications received by the MCC, coupled with resource constraints, resulted in the development of a significant backlog in medicine registration and unprecedented extension of their respective review timelines. The approval timelines for new active substances (NASs) in South Africa were much longer than those achieved by NRAs in developed and comparable emerging markets. The MCC regulatory review process was deemed to be inherently slow as a result of insufficient human and financial resources, outdated manual document management systems and legislative constraints that did not support the use of facilitated regulatory pathways (FRPs). Undoubtedly, the delayed approval times for NASs in South Africa negatively impacted patients' access to medicines.

The need for a more effective regulatory framework in South Africa was prioritised and in June 2017 the Medicine and Related Substances Act, 1965 (Act 101 of 1965) was amended to allow for the transition of the MCC to the South African Health Products Regulatory Authority (SAHPRA). With the legislative support for regulatory re-form, the South African NRA was provided with an opportunity to study the past practices of the MCC with a view to enhance the regulatory performance of SAHPRA and make substantive contributions within the advancing regulatory landscape.

Research in this field has demonstrated that NRAs, of varying sizes and capacity, have been able to improve their regulatory performance and thus the objectives of this research were to identify the inefficiencies in the current regulatory framework of the MCC and the opportunities for improvement in the regulatory performance of the newly established SAHPRA. The key recommendations stemming from this research have been prepared as a proposed improved model for consideration and implementation by SAHPRA to support the goals of shortened approval timelines, enhanced regulatory performance and accelerated patients' access to new medicines.

Six studies were conducted as part of this programme of research; these included a review of the regulatory environment and legislative developments in medicine regulation in South Africa (Study 1: Chapter 3), an evaluation of the MCC review process (Study 2: Chapter 4), an assessment of the resultant MCC performance metrics (Study 3: Chapter 5), a comparison of the MCC against other similar NRAs (Study 4: Chapter 6), a study on the use of a universal benefit-risk (BR) assessment template (Study 5: Chapter 7) and an appraisal of reliance models and an abridged review process to support a transparent, predictable and timely review of NASs (Study 6: Chapter 8). The data collected from each study were analysed and reviewed individually to facilitate a thorough evaluation of the regulatory environment in South Africa with a view to improving the review process and patients' access to new medicines.

## RESEARCH OUTCOMES AND CONTRIBUTIONS

Despite the interest of stakeholders to register NASs in South Africa and the increasing backlog in medicine registration, no studies have previously been undertaken to

evaluate the performance of the MCC in terms of the regulatory review process and the overall median approval timelines for the registration of NASs. This programme of research has for the first time evaluated the regulatory review process of the MCC and has provided commentary and recommendations as the MCC transitioned to the newly established SAHPRA. This research commenced with an in-depth review of the regulatory environment in South Africa in terms of the enabling legislation that resulted in the establishment of SAHPRA, the new NRA in South Africa and provided an assessment of the differences in the operational models of the MCC and the newly established SAHPRA as documented in Chapter 3. The results of this study confirmed the challenges historically faced by the MCC and demonstrated the need for the formalisation of the SAHPRA quality management system, adoption of a risk-based approach to the evaluation of medicines and the implementation of routine and accurate metrics collection. Key recommendations for a new regulatory environment were developed and were considered to be fundamental elements that may contribute to the success of SAHPRA.

The evaluation of the status of the MCC, prior to the establishment of SAHPRA was the focus of Chapter 4, in terms of its organisational structure and the regulatory review process for NASs and included an assessment of the level of implementation of good regulatory practices (GRPs) and good review practices (GRevPs) by the MCC. The results of this study documented the regulatory approval time for NASs in South Africa and the associated milestones within the review process for the first time. This study provided an overview of the median approval timelines achieved by the MCC during 2015-2017 and highlighted for the first time that the MCC in its current capacity was not able to achieve the target timelines for the regulatory review of NASs. Recommendations were made to support the implementation of a risk-based regulatory review process and the formalisation of reliance on the regulatory efforts of reference NRAs.

A detailed account and evaluation of the NASs, including new chemical entities (NCEs), biologicals and major line extensions (MLEs), registered by the MCC during the period 2015-2017 as well as the NASs registered by SAHPRA during 2018 was provided in Chapter 5. This was the first review of the key milestones and metrics in the regulatory review process applied by the MCC and those embedded within the

transitional process applied by SAHPRA during 2018. The available data was collected and analysed in order to determine the overall median approval timelines for NASs. The challenges and opportunities for expediting the overall review timelines were reviewed and recommendations for an enhanced regulatory performance in South Africa were made.

The medicine review process applied by the MCC and its comparison with the medicine review processes applied by the NRAs in Australia, Canada, Singapore and Switzerland was described in Chapter 6. The results of this study indicated that the timelines for the MCC medicine review process were considerably longer than those achieved by the comparative agencies. Recommendations made as a result of this study echoed the need for the formalised implementation of GRevP, routine metrics collection and a template for BR assessment to support consistent, predictable, transparent and timely regulatory review.

The assessment of a benefit-risk (BR) framework was further explored in Chapter 7. The public assessment reports (PARs) from the Australian Therapeutic Goods Administration (TGA), European Medicines Agency (EMA), Health Canada and United States Food and Drug Administration (USFDA) were compared to the validated Universal Methodology for Benefit-Risk Assessment (UMBRA) BR Summary Template to determine whether the BR decision had been documented in a systematic and structured manner. A focus group was conducted to discuss the use of PARs as potential knowledge management tools for stakeholders in understanding the decisions made by reference agencies. The participants in the focus group agreed that a harmonised PAR template would support improved transparency in regulatory decision-making. The approach initiated by SAHPRA to document and communicate the BR decisions was evaluated. Key recommendations for SAHPRA for the implementation of an effective approach for communicating BR decisions were developed. These included consideration of the UMBRA BR Summary Template as guidance for BR assessment as well as this approach as an outline for the preparation of a South African public assessment report (ZAPAR). The publication of the ZAPAR would promote the transparency of SAHPRA's decision-making. It was also recommended that documented BR assessments, such as the PARs, may be relied on by other agencies in order to facilitate expedited review times. The criteria and

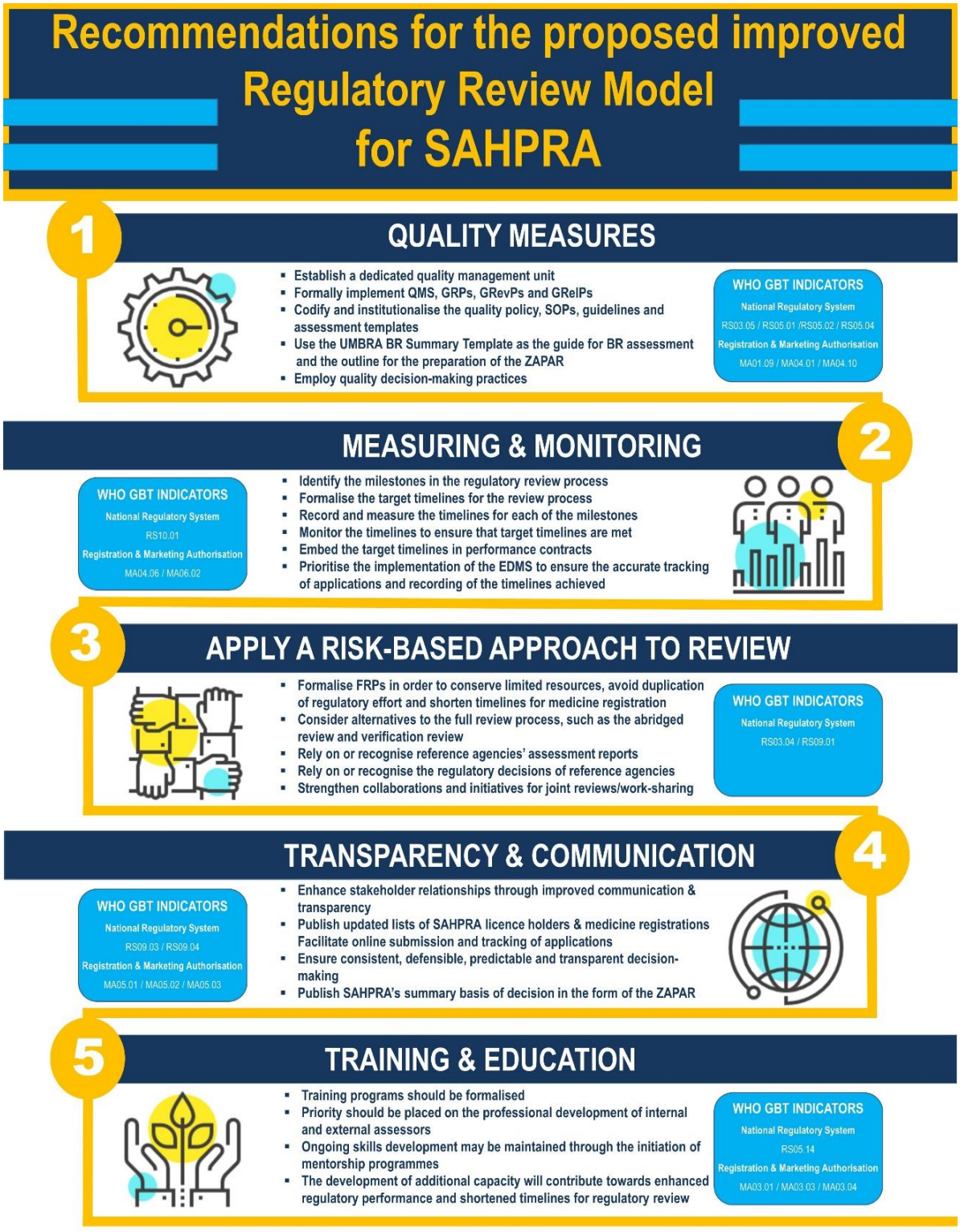
current practices for implementing an abridged review process as well as understanding the challenges, enablers and barriers in utilising reliance models were identified and documented in Chapter 8. Recommendations for the implementation of an abridged review process in South Africa based on good reliance practices (GRelPs) were developed through this study.

This programme of research has culminated in the development of a set of recommendations for a proposed improved regulatory review model for SAHPRA.

## RECOMMENDATIONS FOR AN IMPROVED REGULATORY REVIEW MODEL FOR SAHPRA

These recommendations have been based on an analysis of the results of the six studies conducted and are underpinned by GRPs, GRevPs and GRelPs. This research has contributed towards the identification of the challenges and opportunities for regulatory reform and improved regulatory responsiveness and performance by SAHPRA. A number of key recommendations have been developed throughout this programme of research and these recommendations have been identified as core elements required to support the proposed improved regulatory review model for SAHPRA. The implementation of these recommendations is considered crucial in meeting the requirements of several of the sub-indicators within the World Health Organization (WHO) Global Benchmarking Tool (GBT) that contribute towards the regulatory performance of a sustainable and efficient regulatory system. Furthermore; these recommendations are considered to be fundamental for SAHPRA in achieving a maturity level rating of either 3 or 4 and becoming a WHO-listed NRA. These recommendations have been illustrated in Figure 9.1 and include the following; quality measures, measuring and monitoring, risk-based approach to the evaluation of medicines, transparency and communication, training and education.

**Figure 9.1 Recommendations for the proposed improved regulatory review model for the South African Health Product Regulatory Authority (SAHPRA)**




Images adopted from: https://image.flaticon.com/sprites/new_packs/957317-corporate-business.png

Abbreviations: BR=Benefit-Risk; EDMS=Electronic Document Management System; FRP=Facilitated Regulatory Pathway; GBT= Global Benchmarking Tool; GRP=Good Regulatory Practice; GRevP=Good Review Practice; GRelP; Good Reliance Practice; MA=Marketing Authorisation; RS=Regulatory System; SAHPRA=South African Health Products Regulatory Authority; SOPs=Standard Operating Procedures; QMS=Quality Management System; UMBRA=Universal Methodologies for Benefit-Risk Assessment WHO=World Health Organization; ZAPAR=South African Public Assessment Report

**Quality measures**

A dedicated quality management unit should be established and a QMS be formally implemented and the quality policy, SOPs, guidelines and assessment templates should be codified and institutionalised into practice. These recommendations are endorsed by the WHO GBT sub-indicator RS05.01 that states that top management is required to demonstrate commitment and leadership to develop and implement a QMS; sub-indicator RS05.02 that requires the quality policy, objectives, scope and action plans for the establishment of the QMS to be in place and to be communicated to all levels; and sub-indicator RS05.04 that requires the assignment of enough competent staff to develop, implement and maintain the QMS (WHO, 2018b). It is recommended that SAHPRA consider following the WHO Guideline on the implementation of QMSs for NRAs (WHO, 2019) that was developed based on the principles of the ISO Standard 9001:2015 for QMSs. GRPs, GRevPs and GRelPs should also be formally implemented and maintained in order to build quality into the review process. This recommendation is supported by WHO GBT sub-indicator RS03.05 that requires the NRA to promote GRPs and to assure that the principles of GRP are applied to the regulation of medicines (WHO, 2018b) and the sub-indicator MA04.10 that requires the formal implementation of GRevPs (WHO, 2018c).

The WHO GBT sub-indicator MA01.09 specifies that guidelines on the quality, nonclinical/safety and clinical aspects should be established and implemented and should specify the requirements for registration/granting market authorisation (WHO, 2018c). The WHO GBT sub-indicator MA04.01 states that documented procedures/tools should be implemented for the assessment of different parts of the application and for the assessment of specific requirements of specific classes of medical products (quality, safety & efficacy) (WHO, 2018c). Both of these sub-indicators endorse the recommendation to formalise the use of the UMBRA BR Summary Template as the guide for BR assessment and the outline for the preparation of the ZAPAR. It is recommended that quality decision-making practices should be

employed to support transparent, consistent, predictable and defensible regulatory decisions as described in the requirements for sub-indicator MA04.10. The objective of sub-indicator MA04.10 is to ensure that regulatory decisions are adequately documented and to ensure consistency throughout the review process in terms of requirements and criteria for registration (WHO, 2018c).

**Measuring and monitoring**

SAHPRA should identify the milestones in the regulatory review process and formalise target timelines for individual milestones as well as the entire review process. The timelines for each of these milestones should be recorded and should be routinely and accurately measured. The data collected should be monitored regularly (Quarterly) in order to ensure that target timelines for the review process are continuously met and improved. The introduction of an electronic document management system (EDMS) should be prioritised to ensure the accurate tracking of applications through the milestones of the review process and to provide for the automated and assured collection of the timelines achieved throughout the review process. These recommendations are endorsed by the sub-indicator MA04.06 that requires the establishment of timelines for the assessment of applications and an internal tracking system to follow the targeted timeframes (WHO, 2018c). The target timelines for the review process should be embedded within the performance contracts and should be reflected as key performance indicators for personnel responsible for ensuring the timely review of medicines. This recommendation is supported by the sub-indicator MA06 that requires the use of a mechanism to monitor regulatory performance and output (WHO, 2018c); sub-indicator MA06.02 that requires the establishment and implementation of performance indicators for registration and/or market authorisation activities (WHO, 2018c); and the sub-indicator RS10.01 that requires the monitoring, supervision and review of the performance of the NRA and affiliated institutions using key performance indicators (WHO, 2018b).

**Risk-based approach to the evaluation of medicines**

SAHPRA should apply a risk-based approach to the regulatory review of medicines whereby the allocation of resources is commensurate with product risk. Facilitated regulatory pathways (FRPs) should be formalised in an effort to conserve limited resources, to avoid duplication of regulatory effort and shorten timelines for medicine

registration. SAHPRA should consider alternatives to the full review process, such as the abridged and verification review and should rely on or recognise the PARs of reference agencies as well as the assessment reports of the regulatory decisions of reference agencies. Initiatives for joint reviews or work-sharing should be further developed to support continued enhancement of regional such as Zazibona, continental and international collaborations. These recommendations are endorsed by sub-indicator RS03.04 that supports the formalisation of reliance on the decision of other NRAs through documented policy, procedures and/or mechanisms and the sub-indicator RS09.01 that encourages NRAs to participate in a regional and/or global networks in order to promote convergence and harmonisation efforts (WHO, 2018b).

**Transparency and communication**

SAHPRA should enhance stakeholder relationships through improved communication strategies and increased transparency. The SAHPRA website should be supplemented with the publication of updated lists of SAHPRA licence holders and medicine registrations as well as information pertaining to vigilance activities such as medicine recalls and safety alerts. SAHPRA should develop, implement and maintain enhanced ICT solutions to facilitate the online submission of applications supported by systems that allow the industry to track the progress of applications. These recommendations are supported by the WHO GBT indicator MA05 that highlights the need for the NRA to ensure that mechanisms exist to promote transparency, accountability and communication. These recommendations are further endorsed by the sub-indicator MA05.01 that requires the NRA to ensure the availability and of a website or other official publication that is regularly updated (WHO, 2018c); sub-indicator MA05.02 that requires the publication of an updated list of all medicines granted market authorisation (WHO, 2018c); and the sub-indicator RS09.04 that requires the publication of information on marketed medical products, authorised companies and licensed facilities (WHO, 2018b). SAHPRA should ensure consistent, defensible, predictable and transparent decision-making. This can be achieved through the application of the UMBRA BR Summary Template for BR assessment and the publication of SAHPRA's summary basis of decision in the form of the ZAPAR. This recommendation is endorsed by the sub-indicator MA05.03 that requires the publication of summary technical evaluation reports for approved applications of marketing authorisation in the public domain (WHO, 2018c) and the sub-indicator

RS09.03 that requires the publication of the NRA's decisions related to regulatory activities in the public domain (WHO, 2018b). The placement of the ZAPAR in the public domain will also support and strengthen the position of SAHPRA as an NRA whose regulatory decisions may be relied on or recognised by other NRAs in the emerging markets.

**Training and education**

Training programs should be formalised and priority should be placed on the professional development of internal and external assessors. Ongoing skills development may be maintained through the initiation of mentorship programmes. These recommendations are endorsed by the requirements of the following sub-indicators of the WHO GBT: MA03.01 states that enough competent staff (education training skills and experience) should be assigned to perform marketing authorisation; MA03.03 requires the development, implementation and annual updating of the training plan; MA03.04 describes the requirement of performing and maintaining records of staff training activities (WHO, 2018c); and RS05.14 requires the establishment of a mechanism to evaluate and demonstrate the effectiveness of training activities (WHO, 2018b). Ensuring the development of additional capacity will contribute towards enhanced regulatory performance and shortened timelines for regulatory review.

## STUDY LIMITATIONS

As with any research there are a number of limitations including the following:

- This programme of research was limited to an evaluation of the regulatory review process in South Africa for new active substances (NASs) including new chemical entities (NCEs), biologicals and major line extensions (MLEs). This study did not include a review of the overall approval timelines for applications for the registration of generic medicines, biosimilars or complementary medicines.
- The performance metrics data collected for NASs for the period 2015-2018 was limited to the information that was documented and made available by the South African NRA. While the dossier receipt date and date of allocation of the dossier

to a reviewer were recorded it was not possible to confirm the time taken to validate the document during the administrative and technical screening processes. The data provided did not allow for the accurate calculation of the clock stop, so it was not possible to determine the amount of time each application spent with each of the various scientific committees nor the time it took for the applicant to provide the required response/s.

- Chapter 5 documented the evaluation of the regulatory review times and products in South Africa for the period 2015-2018. The data collected indicated the characteristics and number of the NASs approved (including NCEs, biologicals and MLEs) and the overall median approval timelines for these NASs. Data collected for the period 2015-2017 represented the performance of the MCC and the results described for 2018 reflected the performance of SAHPRA during the initial stages of its establishment and transition. The results for 2018 did not reflect the re-engineered, streamlined processes developed by SAHPRA that were still in the process of being piloted prior to final implementation.
- Chapter 8 described the results following the distribution of a questionnaire to nine NRAs to gather information pertaining to the criteria and current practices for implementing an abridged review process. Responses to the questionnaire were received from six out of the nine NRAs to whom the questionnaire was sent. Nevertheless, the achieved 67% response rate in studies of such nature is rated as ‘very good’.

## FUTURE WORK

- This programme of research largely evaluated the regulatory performance of the MCC and has been valuable in providing a baseline against which the results of the recommended improvements to the reformed regulatory review process under SAHPRA may be quantitatively evaluated and presented. Following the implementation of the SAHPRA’s re-engineered processes it would be useful to:
    - Complete the questionnaire that was used in Study 2 (Chapter 4: Review of the Regulatory Review Process) to reflect on the organisational structure, regulatory review process and regulatory performance of SAHPRA

- Evaluate the performance metrics and overall median approval times for NASs (2019-2020)
- Compare the new registration process and regulatory review model of SAHPRA against other similar-sized NRAs

- Provided that the recommendation to identify and routinely measure and monitor the milestones in the regulatory review process is implemented, it would be useful to analyse the timelines achieved between these milestones in order to accurately determine the time taken by SAHPRA to review an application for the registration of NASs and the time taken by the applicant to provide the required response/s to SAHPRA.
- Considering the intention of SAHPRA to implement FRPs it would be valuable to study the overall median approval timelines achieved for different review types (including full review, abridged review and verification) and the impact thereof on patients' access to NASs
- The drive for the implementation of collaborative initiatives to support the appropriate allocation of limited resources and to reduce the duplication of regulatory effort is evident. SAHPRA has participated in such initiatives, most notably the regional Zazibona work sharing collaborative registration process. It would be valuable to study the regulatory performance and the opportunities for the enhancement of both regional and continental collaborative initiatives in Africa through:
    - The use of the questionnaire applied in Study 6 (Chapter 8) as well as interviewing regulatory agencies to determine the criteria and current practices for implementing an abridged review process by NRAs that have implemented these approaches in order to gain a better understanding of how FRPs may be used to strengthen regulatory performance of the Zazibona work sharing collaborative initiative or work-sharing/joint reviews in the SADC region or within the African continent
    - To assess the impact of the use of a structured universal template for BR assessment on the quality of review supporting predictable, transparent and quality decision making and provide an effective approach for communicating BR decisions made through the use of collaborative initiatives

## CONCLUSION

This programme of research has presented, in a seminal piece of work, an evaluation of the regulatory performance of the South African NRA. The studies undertaken have for the first time made recommendations for an improved regulatory review model for the South African Health Products Regulatory Authority (SAHPRA). Recommendations have been made for the implementation of a universal framework for benefit-risk (BR) assessment and an abridged review process as well as formalised reliance mechanisms. These recommendations may contribute towards enhancing global regulatory efficiencies and ensuring transparent, consistent and timey regulatory decision-making; ultimately resulting in accelerated patients' access to new medicines.

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Keyter, A., Salek, S. & Walker, S. (2020). Recommendations for an improved regulatory review model for SAHPRA. *Therapeutic Innovation & Regulatory Science* (Submitted for publication).

**Poster Presentations**

Keyter, A., Salek, S. and Walker, S. (2019). The South African regulatory environment: Challenges and opportunities for a reformed regulatory review process. Poster presentation at: School of Life and Medical Sciences (LMS) Research Conference 2019, 16 April 2019, Hatfield, United Kingdom. (Appendix 3).

Keyter, A., Salek, S. and Walker, S. (2019). The South African regulatory environment: Challenges and opportunities for a reformed regulatory review process. Poster presentation at: Drug Information Association (DIA) Global Annual Meeting 2019, 23-27 June 2019, San Diego, United States of America. (Appendix 4).

**Oral Presentations**

Keyter, A., Salek, S. and Walker, S. (2019). Managing change: Identifying policy needs. Oral presentation at: Workshop convened by the Centre for Innovation in Regulatory Science (CIRS), 26-28 March 2019, Singapore, Singapore.

Keyter, A., Salek, S. and Walker, S. (2019). The South African regulatory environment: Challenges and opportunities for a reformed regulatory review process. Oral presentation at: Postgraduate Research Seminar, 1 May 2019, Hatfield, United Kingdom.

# APPENDIX

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# APPENDIX 1:

# Questionnaire used to complete

# Study 2 (Chapter 4) and Study 4 (Chapter 6)

**CONFIDENTIAL**


# Characterising the Good Review Practice of the assessment and registration process for Medicines in Emerging Markets

## Review of key milestones, target times, Organisation, Review Process, Transparency, Predictability and Quality of decision-making.

# QUESTIONNAIRE

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**The Centre for Innovation in Regulatory Science (CIRS)**

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CIRS recognises that much of these data may be highly sensitive. CIRS has more than 20 years of experience in handling similar data provided by agencies regarding individual products in regulatory review. **All information collected from individual agencies will be kept strictly confidential. No data that will identify an individual agency will be reported or made available to any third party.** External reports or presentations of the data will include only blinded results and any appropriate analytical interpretations.

**REGULATORY REVIEW PROCESS IN EMERGING MARKETS**

## Review of key milestones, target times and quality of decision-making in the assessment and registration process

### BACKGROUND

This questionnaire represents an ongoing study of the CIRS Emerging Markets programme which is focusing on the regulation of new medicines in the Emerging Markets and looking at how regulatory agencies build quality into the review process.

The first phase was initiated in January 2004 to assess the current regulatory environment in some 30 countries, using comparative data, at the country and regional level, in order to identify the key issues for improving review practices and making new medicines available in an efficient and timely manner. Some of these, for example the timing and use of the Certificate of a Pharmaceutical Product (CPP) and the length of the review process were analysed in more detail in a smaller selection of countries. This study highlighted the need to understand more about the different steps in the review process and the way in which these affect the overall timeline. Regulatory authorities also showed an interest in having a greater understanding of how agencies are building quality into the review process.

The second phase of the study was carried out in 2006-2008 among the regulatory agencies in twelve regulatory authorities: *Argentina, Brazil, China, Egypt, India, Indonesia, Malaysia, Mexico, Saudi Arabia, South Africa, South Korea and Taiwan.*

Through this study, CIRS proposes to map the key milestones and associated activities, for each agency, for both marketing and clinical trial applications and to determine the quality measures employed by the agencies in their different procedures in Latin America.

As many agencies in the second phase have evolved, so have their review processes and practices. Therefore, third phase of the study, CIRS focuses on updating the process maps for the regulatory agency as many on establishing a baseline to understand of the current practices and procedures being undertaken by agencies to support their GRevP initiatives.

Through this study, CIRS proposes to map the key milestones and associated activities, for each agency, for marketing applications and to identify processes and procedures for GRevP. This would help provide a platform to enable information sharing including possibility of sharing assessment report in the future.

### OBJECTIVES

The objectives are to:

- To identify the organisation structure and capacity of each agency.
- To identify the key milestones and target times for each authority and the main activities between milestones for registration
- To identify the model(s) of the review which is being undertaken by each of the agencies.
- To assess how agencies are building GRevP into the assessment and registration process.
- To identify opportunities for the exchange of better practices amongst the regulatory authorities.

### OUTPUT

Participating agencies will receive a report from which they can compare their regulatory procedures with those of peer agencies across the regions. This will include an analysis of where time is spent in the review process with the opportunity to identify where time is lost.

The outcome will allow an analysis of the quality measures that are, or are not, in place for a certain type of review and provide a baseline for subsequent training in GRevP across agencies to establish a common framework for best practices that support timely, predictable and consistent assessment practices.

## ABOUT THE QUESTIONNAIRE

The attached questionnaire is divided into three sections:

**Part I: Organisation of the agency.** The **Introduction** to the questionnaire asks the Authority to provide current information on its structure, organisation and resources. It also explores ***review model(s)***for the ***scientific assessment of medicines*** in terms of the extent to which data is assessed in detail by the agency rather than relying on the results of assessments and reviews carried out elsewhere

**Part II: Key Milestones in the registration of medicines.** This part of the questionnaire is based on the General Model giving a process map and milestones that has been developed from studying procedures followed in 'established' and 'emerging' regulatory agencies. It captures the main steps in the review and approval process and identifies key 'milestone' dates in the process for monitoring and analysing timelines

**Part III: Good Review Practice (GRevP): Building quality into the assessment and registration process** looks at the activities that contribute to the quality of the decision-making process and those measures that have been adopted to improve consistency, transparency, timeliness and competency in the review processes

The **Introduction** to the questionnaire asks the Authority to provide current information on its structure, organisation and resources. It also explores ***review model(s)*** for the scientific assessment in terms of the extent to which data is assessed in detail by the agency rather than relying on the results of assessments and reviews carried out elsewhere. The questionnaire is intended to be used as the basis for a face-to-face interview between Agency staff and CIRS.

## Focus of the Study

The study is intended, primarily, to document procedures and practices that relate to medicines that are the subject of **major** applications, i.e., new active substances and major line extensions.

***New Active Substance***

A new chemical, biological or pharmaceutical active substance including:

- a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product;
- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance not previously authorised as a medicinal product but differing in properties with regard to safety and efficacy from that chemical substance previously authorised;
- a biological substance previously authorised as a medicinal product, but differing in molecular structure, nature of the source material or manufacturing process;
- a radiopharmaceutical substance which is radio nucleotide, or a ligand not previously authorised as a medicinal product, or the coupling mechanism to link the molecule and the radio nucleotide has not been previously authorised

***Major line extension***

A major line extension is a change to an authorised Medicinal Product that is sufficiently great that it cannot be considered to be a simple variation to the original product, but requires a new product authorisation. Such changes include major new therapeutic indications or new disease states, extension to new patient populations (e.g., paediatrics), a new route of administration or a novel drug delivery system.

## PART I: ORGANISATIONAL STRUCTURE & TYPE OF REVIEW

### 1. Information on the Regulatory Authority

As background to the discussions about your agency, its practices and procedures it would be helpful to have the following basic information on its structure and the way it is established:

***Title of the Agency/Division*** *responsible for the regulation of medicinal products for human use*

South African Health Products Regulatory Authority

If this is part of a parent agency with a wider remit (e.g., Food and Drugs) please give the title:

N/A

***Scope and remit***

*1.1 Please indicate the scope of responsibility of the Agency:*

| | | |
|---|---|---|
| Medicinal products for human use | ☐ **YES** | ☐ **NO** |
| Medicinal products for veterinary use | ☐ **YES** | ☐ **NO** |
| Medical devices and *in vitro* diagnostics | ☐ **YES** | ☐ **NO** |

*1.2 Indicate the main activities that are covered by the agency*

| | |
|---|---|
| ☐ Marketing authorisations/Product licences | ☐ Clinical trial authorisations |
| ☐ Post-marketing surveillance | ☐ Regulation of advertising |
| ☐ Laboratory analysis of samples | ☐ Price regulation |
| ☐ Other ☐ Site inspections (site visits) | |

***Type of agency***

*1.3 Indicate which of the following best describes this agency*

☐ Autonomous agency, independent from the Health Ministry administration

☐ Operates within the administrative structure of the Health Ministry

Date of establishment of the current agency ☐

***Size of agency***

Please note that the following questions refer to the regulation of **medicinal products for human use.**

*1.4 Please provide information on staff numbers*

- Total staff in the agency ☐
- Number of reviewers for applications for marketing authorisations/ product licences ☐

*1.5 Please indicate the professional background and numbers of the **technical** agency staff assigned to the review and assessment of medicinal products.*

External evaluators are appointed at the discretion of the Council and information pertaining to their professional background is not available. Internal evaluators are required to be suitably qualified as pharmacists or scientists.

| | ***Number Employed as assessors (Degree/Expertise)*** | | | |
|---|---|---|---|---|
| | *Total:* | *with PhD or PharmD:* | *with MS:* | *Other:* |
| • Physicians | | | | |
| • Statisticians | | | | |
| • Pharmacists | | | | |

| | | | | |
|---|---|---|---|---|
| • Other Scientists | | | | |
| • Project Managers | | | | |

***Fee structure***

*1.6 Are fees charged to sponsors for the review and assessment of applications for medicinal products for human use?* ☐ **YES** ☐ **NO**

If **YES**, please provide the following information:

| ***Marketing Authorisation Application fee for*** | ***Local currency*** | ***US$ (rounded)*** |
|---|---|---|
| ☐ New Active substance | | |
| ☐ Established ingredient - proprietary product | | |
| ☐ Generic product | | |
| ☐ Variations | | |
| ☐ Major line extension | | |
| ☐ Other (Please specify) | | |
| Does the agency charge a fee for Scientific Advice<br>☐ **YES** ☐ **NO**: If Yes please provide | | |

***Budget***

Please indicate whether the following data ☐ are in the **public domain** *or*

☐ Should be treated as **confidential**

*1.7 Please provide the following information on the agency budget for the regulation of medicinal products for human use*

| | ***Local currency*** | ***US$*** |
|---|---|---|
| ☐ Total annual budget | | |
| ☐ Year for which data are given | | |

If the budget is sub-divided according to different activities, please specify: N/A

| | ***% of total budget*** |
|---|---|
| ☐ Clinical trial authorisations | |
| ☐ Marketing authorisations | |
| ☐ Pharmacovigilance | |
| ☐ Other post-marketing controls | |
| ☐ Other activities (specify) | |

***Sources of funding***

*1.8 Please provide the following information in relation to the way the agency is funded*

| | | |
|---|---|---|
| Funded entirely by the government | ☐ **YES** ☐ **NO** | |
| Self-funded entirely from fees | ☐ **YES** ☐ **NO** | |
| Partially funded from different sources (please give proportions of total budget) | % Government<br>% Other (specify) | % Fees |

***Additional documentation***

*To assist CIRS to better understand your organisation please provide copies of any **organisation charts** that show the structure of the agency and its relationship to other regulatory bodies, e.g., medical device agency. It would also be very useful to have copies of any background papers that describe the **functions**, **remit** and **mission** of the agency.*

## 2. Type of data assessment

Three basic types of scientific review have been identified as a result of discussions with regulatory agencies and presentations at the CMR International Institute Workshop on *The Emerging Markets: Regulatory issues and the impact on patients' access to medicines,* Geneva, Switzerland, March 2006. Many agencies apply a different level of data assessment to different applications, according to the type of product and/or its regulatory status with other agencies. The data assessment models for scientific review are described in section 2.1 below and further questions are set out in 2.2 to analyse the types of scientific review in more detail.

***2.1 Please indicate by checking the boxes below, which descriptions fit the model(s) used by your agency in the assessment of major applications i.e., new active substances (NASs) and major line extensions as described on page 2.***

### Data Assessment Type 1

This model is used to reduce duplication of effort by agreeing that the importing country will allow certain products to be marketed locally once they have been authorised by one or more recognised reference agencies, elsewhere. The main responsibility of the agency in the importing country is to 'verify' that the product intended for local sale has been duly registered as declared in the application and that the product characteristics (formulation, composition) and the prescribing information (use, dosage, precautions) for local marketing conforms to that agreed in the reference authorisation(s)

**TYPE 1** ☐ Not used ☐ Used for all major applications
☐ Used for selected applications (please specify)

### Data Assessment Type 2

This model also conserves resources by not re-assessing scientific supporting data that has been reviewed and accepted elsewhere but includes an 'abridged' independent review of the product in terms of its use under local conditions. This might include a review of the pharmaceutical (CMC) data in relation to climatic conditions and distribution infrastructure and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/culture and patterns of disease and nutrition.

Approval by a recognised agency elsewhere is a pre-requisite before the local authorisation can be granted but the initial application need not necessarily be delayed until formal documentation such as a Certificate of a Pharmaceutical Product (CPP) is available.

**TYPE 2** ☐ Not used ☐ Used for all major applications
☐ Used for selected applications (please specify)

### Data Assessment Type 3

In this model the agency has suitable resources, including access to appropriate internal and external experts, to carry out a 'full' review and evaluation of the supporting scientific data (quality, pre-clinical, clinical) for a major application. A Type 3 assessment could be carried out on a new application that has not been approved elsewhere but, in practice, legal requirements may dictate that the product must be authorised by a reference agency before the local authorisation can be finalised.

**TYPE 3** ☐ Not used ☐ Used for all major applications
☐ Used under the following conditions (please specify)

☐ Full review conducted but product must still be authorised by a reference agency prior to final authorisation

If your agency has recognised 'reference agencies' (as in Types 1 and 2) please provide the list:

## 2.2 Data requirements and assessment

| **Regulatory Status:** | **Type I** | **Type II** | **Type III** | **Priority/fast track products** |
|---|---|---|---|---|
| ***Evidence of authorisation by other authorities*** | | | | |
| Requirements for a CPP as part of the review | ☐ with application<br>☐ before authorisation<br>☐ not essential | ☐ with application<br>☐ before authorisation<br>☐ not essential | ☐ before local authorisation<br>☐ not essential<br>☐ if available at the time of submission | ☐ with application<br>☐ before authorisation<br>☐ not essential |
| Other documentation from the authorising agencies accepted as evidence of registration | ☐ letter of authorisation<br>☐ copy of full authorisation<br>☐ Internet evidence | ☐ letter of authorisation<br>☐ copy of full authorisation<br>☐ Internet evidence | ☐ letter of authorisation<br>☐ copy of full authorisation<br>☐ Internet evidence | ☐ letter of authorisation<br>☐ copy of full authorisation<br>☐ Internet evidence |
| Other evidence accepted | | | 1. | |
| ***Verification of identity between the authorised product and the local application: THIS VERFICATION IS NOT PERFORMED*** | | | | |
| *The following are checked:* | Information must be:<br>*Identical Closely similar* | Information must be:<br>*Identical Closely similar* | **Not applicable** | Information must be:<br>*Identical Closely similar* |
| Dosage form | ☐ ☐ | ☐ ☐ | | ☐ ☐ |
| Strength | ☐ ☐ | ☐ ☐ | | ☐ ☐ |
| Ingredients | ☐ ☐ | ☐ ☐ | | ☐ ☐ |
| Indications and dose | ☐ ☐ | ☐ ☐ | | ☐ ☐ |
| Warnings and precaution | ☐ ☐ | ☐ ☐ | | ☐ ☐ |
| Product label | ☐ ☐ | ☐ ☐ | | ☐ ☐ |
| Other (specify) | | | | |
| ***Scientific data required to support the application*** (Reference is made below to sections of the ICH Common Technical Document (CTD) as an example of the level of detail but does not imply that the CTD in necessarily accepted) | | | | |
| Pharmaceutical quality/CMC | ☐ Summary data (Mod 2.3)<br>☐ Summary + full stability<br>☐ Full data (Mod 3) | ☐ Summary data (Mod 2.3)<br>☐ Summary + full stability<br>☐ Full data (Mod 3) | ☐ Summary data (Mod 2.3)<br>☐ Summary + full stability<br>☐ Full data (Mod 3) | ☐ Summary data (Mod 2.3)<br>☐ Summary + full stability<br>☐ Full data (Mod 3) |

| **Regulatory Status:** | **Type I** | **Type II** | **Type III** | **Priority/fast track products** |
|---|---|---|---|---|
| | | | | |
| ***Scientific data required to support the application*** (continued) | | | | |
| Nonclinical data | ☐ Written summary (2.4)<br>☐ Tabulated data (2.5)<br>☐ Full data (Module 4) | ☐ Written summary (2.4)<br>☐ Tabulated data (2.5)<br>☐ Full data (Module 4) | ☐ Written summary (2.4)<br>☐ Tabulated data (2.5)<br>☐ Full data (Module 4) | ☐ Written summary (2.4)<br>☐ Tabulated data (2.5)<br>☐ Full data (Module 4) |
| Clinical data | ☐ Written summary (2.5)<br>☐ Tabulated data (2.6)<br>☐ Full data (Module 5) | ☐ Written summary (2.5)<br>☐ Tabulated data (2.6)<br>☐ Full data (Module 5) | ☐ Written summary (2.5)<br>☐ Tabulated data (2.6)<br>☐ Full data (Module 5) | ☐ Written summary (2.5)<br>☐ Tabulated data (2.6)<br>☐ Full data (Module 5) |
| ***Extent of Scientific Review*** | | | | |
| Quality/CMC data | ☐ Only examined if there is a query<br>☐ 'Check list' review for completeness of data<br>☐ Selective review in detail (e.g. stability, specification)<br>☐ Detailed assessment and evaluation report | ☐ Only examined if there is a query<br>☐ 'Check list' review for completeness of data<br>☐ Selective review in detail (e.g. stability, specification)<br>☐ Detailed assessment and evaluation report | ☐ 'Check list' review for completeness of data<br>☐ Selective review in detail (e.g. stability, specification)<br>☐ Detailed assessment and evaluation report | ☐ Only examined if there is a query<br>☐ 'Check list' review for completeness of data<br>☐ Selective review in detail (e.g. stability, specification)<br>☐ Detailed assessment and evaluation report |
| Comment | | | | |
| Non-clinical data | ☐ Only examined if there is a query<br>☐ 'Check list' review for completeness of data<br>☐ Detailed assessment and evaluation report | ☐ Only examined if there is a query<br>☐ 'Check list' review for completeness of data<br>☐ Detailed assessment and evaluation report | ☐ 'Check list' review for completeness of data<br>☐ Detailed assessment and evaluation report<br>☐ Not at all | ☐ Only examined if there is a query<br>☐ 'Check list' review for completeness of data<br>☐ Detailed assessment and evaluation report |
| Comment | | | | |

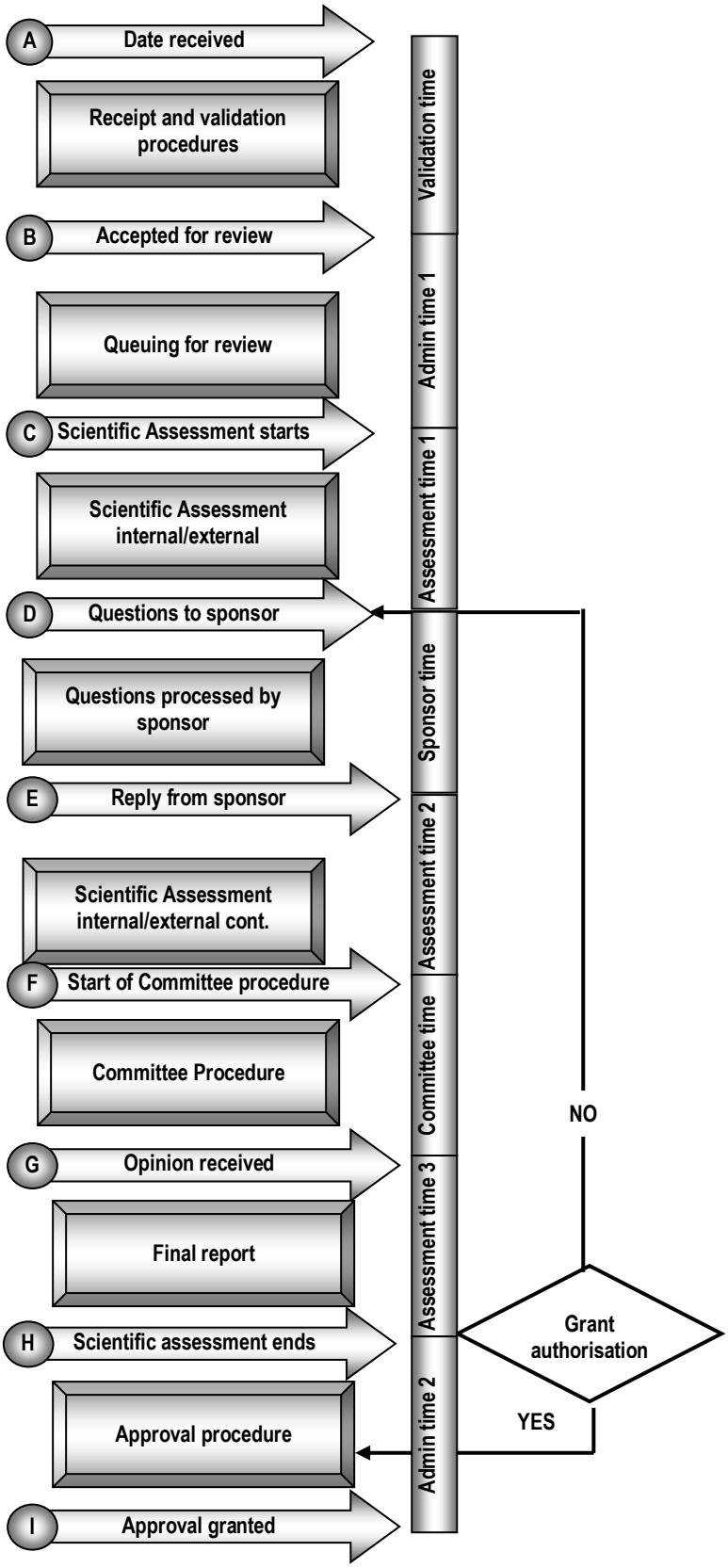
| **Regulatory Status:** | **Type I** | **Type II** | **Type III** | **Priority/fast track products** |
|---|---|---|---|---|
| | | | | |
| Clinical data | ☐ Only examined if there is a query<br>☐ 'Check list' review for completeness of data<br>☐ Selective review in detail (e.g. bridging studies)<br>☐ Detailed assessment and evaluation report | ☐ Only examined if there is a query<br>☐ 'Check list' review for completeness of data<br>☐ Selective review in detail (e.g. bridging studies)<br>☐ Detailed assessment and evaluation report | ☐ 'Check list' review for completeness of data<br>☐ Selective review in detail (e.g. bridging studies)<br>☐ Detailed assessment and evaluation report | ☐ Only examined if there is a query<br>☐ 'Check list' review for completeness of data<br>☐ Selective review in detail (e.g. bridging studies)<br>☐ Detailed assessment and evaluation report |
| Comment | | | | |
| ***Clinical evaluation: factors included in the risk-benefit assessment*** | | | | |
| *The clinical opinion takes account of:* | *Never sometimes always* | *Never sometimes always* | *Never sometimes always* | *Never sometimes always* |
| Differences in medical culture/practice | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ |
| Ethnic factors | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ |
| National disease patterns | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ |
| Unmet medical need | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ |
| ***Additional information, not in the application***: | | | | |
| *The agency tries to obtain* | Information is sought:<br>*Never sometimes always* | Information is sought:<br>*Never sometimes always* | Information is sought:<br>*Never sometimes always* | Information is sought:<br>*Never sometimes always* |
| Other agencies' internal assessment reports | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ |
| Reports available on the Internet (e.g., EPARS) | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ |
| General Internet search | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ |

| **Regulatory Status:** | **Type I** | **Type II** | **Type III** | **Priority/fast track products** |
|---|---|---|---|---|
| Other data (specify: ) | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ | ☐ ☐ ☐ |

## PART II - KEY MILESTONES IN THE REGISTRATION OF MEDICINES

### Review Process Map and Milestones

This part of the questionnaire is based on the General Model below giving a process map and milestones that has been developed from studying procedures followed in 'established' and 'emerging' regulatory agencies. It captures the main steps in the review and approval process and identifies key 'milestone' dates in the process for monitoring and analysing timelines.




***Notes***

**Receipt and validation** may include administrative registration (reference number) and checks on legal requirements, status of company, local agent, manufacturer etc. as well as a 'checklist' validation of the application content (e.g., technical sections, CPP status).

**Queuing for review**: *Administrative time 1* is a measure of the 'backlog' time (if any) while valid applications wait for action to begin.

**Scientific Assessment** extends from milestone C to milestone H and is a measure of 'review time'. In some systems the 'clock' stops when questions are asked and ***Sponsor time***(milestone D to milestone E) can be measured and deducted from the agency review time.

**Questions to sponsor** may be batched and sent at one time or asked throughout the review process, in which case the *Sponsor time* is not easily measured.

In some systems, questions may only be sent to the sponsor after the end of the 'first cycle' scientific assessment (at milestone H).

**Committee Procedure**: Most review procedures for major applications include a step where the opinion of an expert advisory committee is sought. In this scheme, the Committee procedure is 'nested' within the Scientific Assessment but it may take place after the Agency's scientific assessment is complete.

**Second cycle:** If the application cannot be granted immediately, on technical grounds, it enters a second review cycle (new data point D: questions to sponsor) and a further scientific assessment is made of the additional data. The Committee Procedure may or may not need to be included in the second and subsequent review cycles.

**Approval procedure:** The time interval after scientific review (*Admin time 2*) while the formal authorisation is issued may be extended by pricing negotiations and finalisation of analytical and GMP checks.

**Approval time** is measured from milestone A to milestone I

## Review stages and milestones

This section of the questionnaire is based on the ***General Model*** shown on page 6.

We recognise that not all systems conform to the general model and it would be very helpful if you could provide an outline of the model used by your authority. If this differs according to the **Type of data assessment** (see page 5) please provide information on the different models

When information is given on target or actual times please indicate here whether these are counted in:

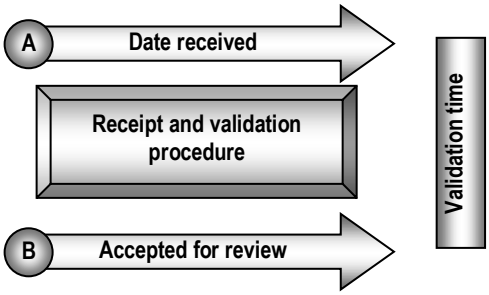
☐ **Calendar days** ☐ **Working days**

When 'milestone' dates are recorded during the review process is the information entered into an electronic tracking/recording system?

☐ **YES,** System in current use ☐ **NO,** System in development (Target date: 2018)

☐ **NO,** A manual system will be used for the foreseeable future

## 3. Receipt and Validation




***Pre-submission requirements***

*3.1. Are there any formal requirements before an application is submitted, for example, notification of intent to submit, assignment of registration code etc.*

X **NO,** milestone A is the formal start of the application procedure

☐ **YES**

***Validation***

| | |
|---|---|
| *3.2 Is the date of receipt (milestone A) formally recorded?* | ☐ **YES** ☐ **NO** |
| *3.3 Are the following administrative items checked in the pre-review validation process?* | |
| • Legal status of applicant/local agent | ☐ **YES** ☐ **NO** |
| • GMP status of manufacturer | ☐ **YES** ☐ **NO** |
| • Patent/IP status of active ingredient | ☐ **YES** ☐ **NO** |
| • Whether company has paid the correct fee | ☐ **YES** ☐ **NO** |
| Other:<br>1. Sample of the product must be submitted<br>2. CPP must be made available | |
| *3.4 For those applications **where prior authorisation elsewhere is essential** (**see Section 2**) please answer the following questions about the **Certificate of a Pharmaceutical Product***(CPP)<br>Is the inclusion of a CPP an absolute requirement before accepting the application as valid?<br>☐ **YES** ☐ **NO** ☐ For some applications (please specify) | |
| If **YES** must the CPP be legalised by an Embassy or Consulate? | ☐ **YES** ☐ **NO** |
| If **NO**, please indicate which of the following apply | |
| • A CPP must be provided before the authorisation is issued | ☐ **YES** ☐ **NO** |
| • Other evidence of authorisation by other countries is accepted in place of the CPP (e.g., copy of authorisation, Internet reference) | ☐ **YES** ☐ **NO** |
| Comment | |

***Validation** (cont.)*

*3.5 Is the application also checked for the following items?*

Acceptable format (e.g. ICH CTD or local requirements) ☐ **YES** ☐ **NO**

Correct sections of scientific data (quality, safety, efficacy) ☐ **YES** ☐ **NO**

Other technical items:

The qualifications of the Responsible Pharmacist/Responsible Person as well as the relevant authorisation of the Responsible Pharmacist/Responsible Person must be submitted with the application.

***Acceptance for review/refusal to file***

*3.6 Is the date of acceptance (milestone B) formally recorded?* ☐ **YES** ☐ **NO**

*3.7 What happens if the application is incomplete?*

☐ **Refusal to file:** New application must be made

☐ **File pending:** A request for the missing data is sent to the applicant

What is the time limit for the applicant to reply?

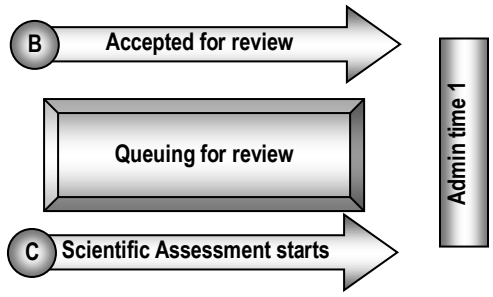
*Notes*:

*In the event that there is no response from the applicant within 10 days the file will be refused.*

***Target time for validation***

*3.8 Is there a target validation time?* ☐ **YES** ☐ **NO**

## 4. Queuing/backlog




*4.1 Which of the following applies to the queuing system for new applications?*

☐ Held in queue after validation (as in the General Model) after phase 1 validation

☐ Held in queue before validation starts (milestone A)

*4.2 What is the current queue time (approximately)?*

☐ Less than 2 weeks ☐ 2-8 weeks

☐ 2-6 months ☐ 6 months-1 year

☐ More than 1 year

*4.3 Are priority products taken out of turn in the queuing system*

☐ **YES,** always

☐ **YES,** sometimes

☐ **NO,** all applications await their turn

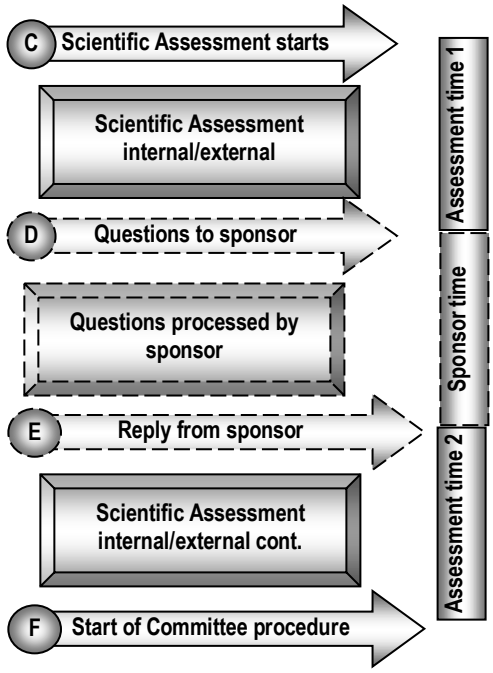
Comment:

*4.4 Does the Agency regard the backlog of applications as a problem* ☐ **YES** ☐ **NO**

If **YES**, how is this being addressed?

## 5. Scientific Assessment

### *5.1 Initiation of scientific review*




*5.1.1 Is the start of the Scientific Assessment formally recorded (milestone C)?* ☐ **YES** ☐ **NO**

*5.1.2 Is the scientific data separated into three sections (quality, safety, and efficacy) for review?* ☐ **YES** ☐ **NO**

*5.1.3 In what order are the different sections assessed:*

☐ In parallel ☐ In sequence

If in sequence, please give order

*5.1.4 Who carries out the **primary** scientific assessment?*

☐ Agency technical staff ☐ Sent to outside experts

☐ Different procedure for different sections

Please describe the process:

### *5.2 Use of outside experts*

*If outside experts are used for the assessment of scientific data (5.1.4 above) please complete the following:*

5.2.1 Number of experts on the agency's list or panel: ☐

5.2.2 Main responsibility:

☐ To provide a detailed assessment report and recommendation

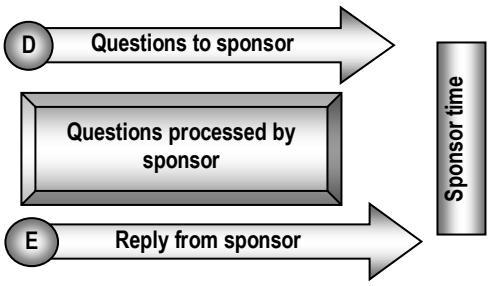
☐ To provide a clinical opinion on the product

☐ To provide advice to the agency staff on specific technical issues

☐ Other (specify)

5.2.3 Is there a contractual agreement on working within deadlines set by the agency? ☐ **YES** ☐ **NO**

### *5.3 Interaction with the Sponsor*




*5.3.1 How are questions sent to the Sponsor*

☐ as they arise during the assessment ☐ Collected into a single batch

*5.3.2 When are batched questions sent to the Sponsor*

☐ After the initial assessment but before reporting to the Scientific Committee (as in the General model)

☐ Not until the Scientific Committee has given its advice

☐ Before and after reference to the Scientific Committee

*5.3.3 Does the scientific review cease while questions are being processed by the Sponsor ('clock stop')* ☐ **YES** ☐ **NO**

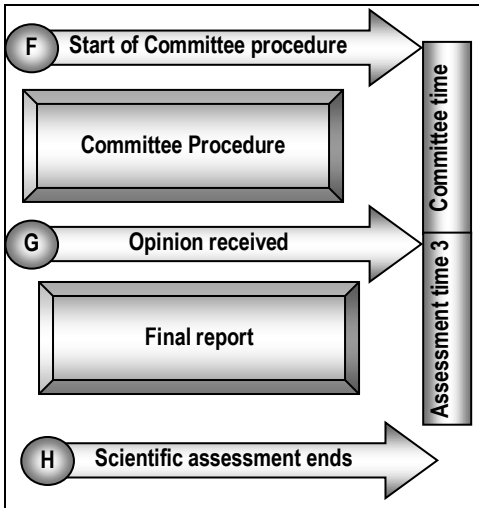
***5.3 Interaction with the Sponsor** (cont.)*

| | |
|---|---|
| *5.3.4 Can the sponsor time be calculated, i.e., are milestones D and E recorded?* | ☐ **YES** ☐ **NO** |
| *5.3.5 Is the sponsor given a time limit to reply* | ☐ **YES** ☐ **NO** |
| If **Yes**, what time is allowed? | |

***Meetings***

| |
|---|
| *5.3.6 Can the Sponsor hold meetings with the agency staff to discuss questions and queries that arise during the assessment* ☐ **YES** ☐ **NO** |
| If **Yes**, what conditions and restrictions (if any) are applied? |
| 1. Request formal meeting |
| 2. Require scientific argument to be provided beforehand |
| 3. Guideline is available to describe this procedure [IND Guideline] |

***5.4 Review by Scientific Committee***




*5.4.1 Is a Committee of Experts (internal and/or external) used in the review process* ☐ **YES** ☐ **NO**

*5.4.2 If **Yes**, at which stage in the review?*

- ☐ Responsible for the whole assessment of the dossier from the start of the review
- ☐ Integrated into the agency's own internal/external scientific review procedure
- ☐ Consulted after the agency has reviewed and reported on the scientific data
- ☐ Other (specify)

| | |
|---|---|
| *5.4.3 Are the dates at the start and end of the Committee Review recorded (milestones F and G)?* | ☐ **YES** ☐ **NO** |
| *5.4.4 Is the agency mandated to follow the Committee recommendation?* | ☐ **YES** ☐ **NO** |
| *5.4.5 Is there a time limit for the Committee Procedure?* | ☐ **YES** ☐ **NO** |
| If **YES**, please give the target | |
| If **NO**, what is the time range (e.g., 1-3 months) | |

*5.4.6 Is there an additional step in the scientific review process, after the Committee has given its opinion?* ☐ **YES** ☐ **NO**

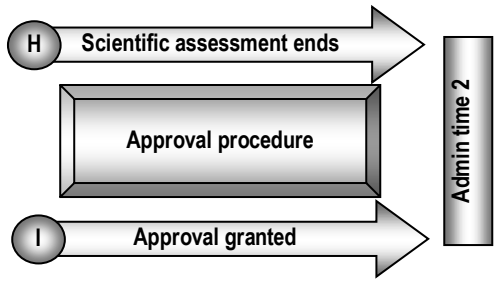
If **YES**, please describe briefly the work carried out at this stage (e.g., final report and agency opinion)

If **NO**, the milestone G will mark the end of the scientific review for the purpose of calculating the review time

***Target for scientific review***

| | |
|---|---|
| *5.4.7 Is a target time set for the scientific review (milestones C to H)* | ☐ **YES** ☐ **NO** |
| If **YES** please give target | |

## 6. Decision on the Application




At the end of the Scientific Review (see General Model, page 6) there is normally recommendation that either:

- The product meets the scientific criteria for authorisation (proceed to approval procedure) *or*
- Further data is required before the scientific criteria are met (application enters a **second cycle** at milestone D (questions to Sponsor) *or*
- The application should be refused (not shown in the General Model)

### *6.1 Responsibility for the authorisation decision*

*6.1.1 Who makes the decision that a marketing authorisation can be granted?*

☐ The Scientific Committee ☐ The Head of the Agency
☐ The Minister of Health

☐ Other

### *6.2 Other Criteria to be met*

*6.2.1 Is the issue of the authorisation dependent on a **pricing agreement*** ☐ **YES** ☐ **NO**

If **YES**, when are the pricing negotiations started?

☐ At the start of the scientific review ☐ After the end of the scientific review
☐ After the start but before the end of the scientific review

*6.2.2 Is the issue of the authorisation dependent on **sample analysis*** ☐ **YES** ☐ **NO**

If **YES**, when is the analytical work started?

☐ In parallel with the scientific review ☐ At the end of the scientific review
☐ After the start but before the end of the scientific review

*6.2.3 Is there a separate negotiation of the **product labelling/ product information** after the scientific opinion is given but before the approval is issued?* ☐ **YES** ☐ **NO**

Comments:

*6.2.4 Please specify any other legal/administrative matters that must be finalised before the approval can be issued*

### 6.3 Approval procedure

*6.3.1 Is the Sponsor informed of a positive scientific opinion at milestone G, i.e., before the authorisation is issued?* ☐ **YES** ☐ **NO**

*6.3.2 Approximately how long does it take from receiving a positive scientific opinion (at milestone H) to issuing an approval (milestone I)*

☐ Less than a month ☐ 1-3 months ☐ 3-6 months ☐ Over 6 months

*Comment:*

## 7. Metrics on the Approval Process for NAS

It would be very helpful to have the following information on processing times for marketing authorisations that have been received and/or determined in the three years 2014, 2015, 2016. Data available does not provide a clear distinction between NAS and Major Line Extension.

### *7.1 Applications received*

| | ***Number of applications received in each year*** | | | |
|---|---|---|---|---|
| **Type** | **2014** | **2015** | **2016** | **Current backlog** |
| **New Active Substance & Major line extension** | | | | |

### *7.2 Applications determined*

| | ***Number of applications determined in each year*** | | |
|---|---|---|---|
| **Type** | **2014** | **2015** | **2016** |
| **New Active Substances & Major line extension approved** | | | |
| **New Active Substances & Major line extension refused** | | | |

### *7.3 Average approval times*

| | ***Time from receipt of application to issue of approval*** | | |
|---|---|---|---|
| **Type** | **2014** | **2015** | **2016** |
| **New Active Substances & Major line extension** | | | |

### *7.4 Target for approval times*

*Is a target time set for the overall approval process (milestones A to I)* ☐ **YES** ☐ **NO**

If **YES** please give target

Please comment on the actual review times in relation to the authority's target time

## PART III-GOOD REVIEW PRACTICE (GREVP)

## BUILDING QUALITY INTO THE ASSESSMENT AND REGISTRATION PROCESS

Quality in the assessment and registration process is important to regulatory authorities as it ensures consistency, transparency, timeliness and competency in the review processes. Regulatory authorities are continuously developing and implementing a variety of measures to improve and achieve higher quality standards and to meet the expectations of industry and the general public.

The purpose of this section of the questionnaire is to obtain an insight into the strategies, measures and resources that agencies have in place to develop and maintain quality in their review processes.

### 8. General Measures used to achieve quality

Please indicate the quality measures currently in place and, where none, plans to introduce such measures in the foreseeable future.

**Good Review Practice** (GRevP): A code about the process and the documentation of review procedures that aims to standardise and improve the overall documentation and ensure timeliness, predictability, consistency and high quality of reviews and review reports

8.1 *How does your agency define GRevP?:*
Is it different from the Glossary? ☐ **Yes** ☐ **No**

If different, please define in here:
Please Outline the key elements that make up GRevP in your agency:

*Has the Agency* **formally or informally i***mplemented GRevP?*

☐ **YES (Formally)**
☐ **Yes (Informally)**
☐ **NO**

.If **YES** please give the title and date of **formal** implementation:

.

How has this been implemented: (Please tick the appropriate Box(s))

☐ Guidelines ☐ Standard Operating Procedure ☐ GRevP Training Program
☐ Other: Please specify:

Are these documents open and available to the Public? ☐ **Yes** ☐ **No**
If Yes please describe: All relevant Guidelines are available on the MCC website (www.mccza.com)

Was the establishment of your GRevP based on other agencies or International standards? ☐ **YES** ☐ **NO**

If Yes: please state the name of the agency(ies)/ or Internationals standards on which your GRevP has been based:

Are you satisfied with your existing GRevP framework?
☐ Satisfied ☐ Could be improved ☐ Unsatisfied
If **could be improved** or **Uns*atisfied*,** please select reason(s) that best describes your situation.
☐ System still evolving
☐ Requires additional training to understand and learn about Good Review Practice
☐ Poor acceptance/utilization by staff
☐ Benefits of implementing GRevP are not apparent so far
☐ other (please provide details)

| | |
|---|---|
| If you **do not have** a formal GRevP system in place are there plans to establish this within the next two years? | ☐ **Yes** ☐ **No** |
| **Quality Policy:** Overall intentions and direction of an organisation related to quality as formally expressed by top management. | |
| *8.2 Does the Agency have an internal Quality Policy?* | ☐ **Yes** ☐ **No** |
| If **NO** are there plans to establish this within the next two years? | ☐ **Yes** ☐ **No** |
| **SOPs** (Standard Operating Procedures) are written documents that describe in detail the routine procedures to be followed for a specific operation. | |
| *8.3 Are there SOPs for the guidance of scientific assessors* | ☐ **Yes** ☐ **No** |
| If **NO** are there plans to establish SOPs within the next two years? | ☐ **Yes** ☐ **No** |
| *8.4 Are there SOPs for the advisory committee consulted during the review process* | ☐ **Yes** ☐ **No**<br>☐ **No committee** |
| If **NO** are there plans to establish SOPs within the next two years? | ☐ **Yes** ☐ **No** |
| *8.5 Are SOPs used for any other procedures in the regulatory review process (e.g., validation)?*<br>Please specify: | ☐ **Yes** ☐ **No** |
| **Assessment Templates** set out the content and format of written reports on scientific reviews. | |
| *8.6 Are there Assessment Templates for reports on the scientific review of a NAS?* | ☐ **Yes** ☐ **No** |
| If **NO** are there plans to establish this within the next two years? | ☐ **Yes** ☐ **No** |
| If **Yes** are these based on another agencies assessment template | ☐ **Yes** ☐ **No** |
| If Yes, which agency was the assessment template based? Please specify: | |
| Is there an SOP for completing an assessment template | ☐ **Yes** ☐ **No** |
| Can you tick what elements from the list below are included in your agency assessment template? | |
| ☐ Drug Substance<br>☐ Drug Product<br>☐ Comments on label<br>☐ Non clinical GLP Aspects<br>☐ Non clinical Pharmacokinetic<br>☐ Toxicology<br>☐ Regulatory background (worldwide status on regulatory agencies)<br>☐ Other (please specify): | ☐ GCP aspects<br>☐ Clinical Pharmacology (PK & PD)<br>☐ Clinical Efficacy<br>☐ Clinical Safety<br>☐ List of questions for sponsors<br>☐ Benefit Risk Reduction<br>☐ Ethnic factors (e.g. consideration of bridging studies |
| Would the agency be open to sharing their assessment template or points to consider with CIRS? | ☐ **YES** ☐ **NO** |
| Do you produce an assessment report (AR) following the review? | ☐ **YES** ☐ **NO** |

| | |
|---|---|
| If Yes : | |
| Is there an SOP for completing the AR: | ☐ **YES** ☐ **NO** |
| What language is the AR prepared in: | ☐ **Local language English** |
| Do you share your AR with other regulatory authorities | ☐ **YES** ☐ **NO**<br>☐ **SOMETIMES** |
| Do you put your full AR on the website | ☐ **YES** ☐ **NO**<br>☐ **SOMETIMES** |
| Do you put your abridged AR on the website | ☐ **YES** ☐ **NO**<br>☐ **SOMETIMES** |
| Do sponsors get a copy of the **full** assessment report? | ☐ **YES** ☐ **NO** |
| Do Sponsors have any involvement in the following in relation to AR: | |
| Preparation of assessment reports | ☐ **YES** ☐ **NO** |
| Comments on the assessment reports | ☐ **YES** ☐ **NO** |
| Translation of assessment reports | ☐ **YES** ☐ **NO** |
| Distribution of Assessment reports | ☐ **YES** ☐ **NO** |
| **Peer Review** is an additional evaluation of an original assessment that is carried out by an independent person or committee. Peer review can occur either during assessment of a dossier or at the time of sign-off. | |
| *8.7 Are **external** peer reviews carried out when a NAS is assessed?* | ☐ **Yes** ☐ **No** |
| If **NO** are there plans to introduce these within the next two years? | ☐ **Yes** ☐ **No** |
| *8.8 Are **internal** peer reviews carried out when a NAS is assessed?* | ☐ **Yes** ☐ **No** |
| If **NO** are there plans to introduce these within the next two years? | ☐ **Yes** ☐ **No** |
| Do you have **target times** for following activities and if so can you provide your target times? | ☐ **Yes** ☐ **No** |
| Overall approval times | ☐☐ 36 MONTHS |
| Validation of dossier | ☐☐ N/A |
| Scientific assessment | ☐☐ 3 MONTHS |
| Company (clock stop), time | ☐☐ 6 MONTHS |
| Other: Please specify: | ☐☐ |
| If Target times given are they in working days? | ☐☐ calendar days |
| *8.9 Are there other general procedures in place to monitor the quality of the review process?*<br>*What other tools does your agency use to build quality into the assessment process?*<br>(e.g. Internal procedure could include; Quality assurance and quality control meeting; Stakeholder meeting; Channel for grievance; Survey of performance from sponsors) Please specify: | |

## 9 Quality Management

***Reasons for introducing quality measures in the authority***

*9.1 Please select, from the following list, the **three** most important reasons for the introduction of quality measures*

☐ To be more efficient

☐ To minimise errors

☐ To ensure consistency

☐ To increase transparency

☐ To achieve stakeholder satisfaction

☐ To improve communications in the authority

☐ To improve process predictability

☐ To allocate the regulatory resources

☐ Other (please specify)

***Monitoring to improve quality***

*9.2 Which of the following activities are undertaken by the authority to bring about continuous improvement in the assessment and registration process?*

- Reviewing assessors' feedback and taking necessary action ☐ **Yes** ☐ **NO**
- Reviewing stakeholders' feedback (e.g. through complaints, meetings or workshops) and taking necessary action ☐ **Yes** ☐ **NO**
- Using an internal tracking system to monitor (e.g. consistency, timeliness, efficiency and accuracy) ☐ **Yes** ☐ **NO**
- Carrying out internal quality audits (e.g. self-assessments) and using findings to improve the system ☐ **Yes** ☐ **NO**
- Having external quality audits by an accredited certification body to improve the system ☐ **Yes** ☐ **NO**
- Having a 'post approval' discussion with the sponsor to provide feedback on the quality of the dossier and obtain the company's comments ☐ **Yes** ☐ **NO**

***Management responsibility***

*9.3 Does the authority have a dedicated department for assessing and/or ensuring quality in the assessment and registration process?* ☐ **Yes** ☐ **NO**

If **YES**, how many staff are involved?

***How often do you assess and/or ensure quality in assessment and registration process?***

☐ **Annually** ☐ **Semi-Annually** ☐ **Adhoc** ☐ **Other (please specify)**

To whom does this section report (e.g. the Chief Executive Officer of the authority)?

If **NO**, is the Authority thinking of setting up such a department? ☐ **Yes** ☐ **NO**

## 10. Quality in the Review and Assessment Process

***Improving the quality of applications***

*10.1 Does the authority have official guidelines to assist industry in the registration of medicinal products?* ☐ **Yes** ☐ **NO**

If **YES**, how are these guidelines made available? (Please indicate all that apply)

☐ Through the authority's website ☐ Through official publications

☐ On request ☐ Through Industry Associations

☐ Other, please specify:

What language are the guidelines available in:

☐ Local language only ☐ English ☐ Other, please specify:

***Improving quality through interaction with applicants***

*10.2 Does the authority provide pre-submission scientific advice to applicants* ☐ **Yes** ☐ **NO**

If **YES** how is the quality of that advice monitored?

*10.3 Is the applicant given details of technical staff that can be contacted to discuss an application during review?* ☐ **Yes** ☐ **NO**

*10.4 Please indicate which of the following best describes the level of contact that companies have with agency staff or outside experts during development and during the agency's assessment.*

| | *Development* | *Assessment* |
|---|---|---|
| **Extensive formal** contact (including scheduled meetings) | ☐ | ☐ |
| **Extensive informal** contact (frequent telephone or email contact) | ☐ | ☐ |
| **Some formal** contact (possibility of meetings) | ☐ | ☐ |
| **Some informa**l contact (possibility of telephone or email contact) | | ☐ |
| **None, or minimal formal** contact (rare occurrences of contact, via letter or fax) | ☐ | ☐ |
| **None, or minimal informal** contact (rare telephone or email contact) | ☐ | ☐ |

Please comment on general policy for contact with applicants:

The Authority endeavours to have an open-door policy through quarterly meetings with industry associations, workshops and one-on-one discussions with sponsors on the product reviews, general guidelines developed and new requirements as applicable.

***Committee Procedure***

*10.5 If your review procedure includes obtaining the advice of a scientific committee of internal and/or external experts (as in Section 5.4) please complete the following:*

Name of the Committee :

Number of Committee Members :

How frequently does the Committee meet?

☐ Once a week ☐ Once a month ☐ Other, please specify: Approximately every 8 weeks

For NAS applications and major line extensions does the Committee review?

☐ All applications ☐ Selected dossiers (specify)_____

Does the Committee review?

☐ The complete dossier ☐ Assessment reports from the reviewers

***Shared and Joint reviews with other Regulatory Agencies outside of your country***

A ***shared review*** is one where each participating authority takes responsibility for reviewing a separate part of the dossier. A ***joint review*** is one where the whole dossier is reviewed by each authority and the outcome is discussed before a decision is taken.

Is your agency part of any regional alignment initiatives? ☐ **Yes** ☐ **NO**

If **Yes**, please specify:

Are bilateral-multilateral information sharing agreements in place with other jurisdictions?

☐ **Yes** ☐ **NO**

If Yes, What is the general nature of those agreements?

*10.6 Does your authority conduct shared or joint reviews with other regulatory authorities?*

☐ **YES regularly. Please state which authorities**

☐ **YES Occasionally. Please state which authorities**

☐ **NO this has never been undertaken**

If **YES** do you have formal measures in place to ensure consistent quality during the review? ☐ **Yes** ☐ **NO**

If **Yes**, please specify

If **NO**, do you anticipate undertaking such reviews within the next two years? ☐ **Yes** ☐ **NO**

10.7 Have these joint reviews influenced the way in which your authority conducts reviews in general? If so, please comment ☐ **Yes** ☐ **NO**

## 11. Training and continuing education as an element of quality

The following questions relate to training and continuing education of assessors working within the authority, including those employed on a full-time basis and those contracted for specific assessments were necessary.

*11.1 Do you have a formal training programme for assessors?* ☐ **Yes** ☐ **NO**

*11.2 Which of the following methods are used for training assessors?*

☐ Induction training

☐ On job training

☐ External courses

☐ Post-graduate degrees

| | |
|---|---|
| ☐ Placements and secondments in other regulatory authorities<br>☐ External speakers invited to the authority<br>☐ Other, please specify: | ☐ Participation in international workshops/ conferences<br>☐ In-house courses |
| *Does your authority seek **direct** assistance of more experienced agencies for development of SOPs and Guidelines?*<br>If Yes please give details: | ☐ **YES** ☐ **NO** |
| *Does your authority mainly develop SOP, Guidelines etc. based on information published by more experienced agencies:* | ☐ **YES** ☐ **NO** |
| *11.3 Does your authority collaborate with other agencies in the training of assessors?*<br>If **Yes**, please give details: | ☐ **Yes** ☐ **NO** |
| *11.4 Is training tested in examination situations once completed?* | ☐ **Yes** ☐ **NO**<br>☐ **Partly** |
| *11.5 Is completion of training courses required for professional advancement?* | ☐ **Yes** ☐ **NO**<br>☐ **Partly** |

## 12. Transparency of the review procedure

This section examines 'transparency' in terms of the ability and willingness of the agency to assign time and resources to providing information on its activities to both the informed public (which includes health professionals) and industry.

*12.1 What priority does your agency assign to being open and transparent in relationships with the public, professions and industry?*

☐ High priority ☐ Medium priority ☐ Low priority

Please comment:

*12.2 What are the main drivers for establishing transparency? Please indicate the top three incentives for assigning resources to activities that enhance the openness of the regulatory system*

☐ Political will

☐ Public Pressure

☐ Press and media attention

☐ Need to increase confidence in the system

☐ Need to provide assurances on safety safeguards

☐ Better staff morale and performance

☐ Other, please specify:

***Transparency to the public***

The following questions explore the availability of information to the general public on the performance of regulatory authorities

*12.3 Please indicate which of the following information items about the assessment and registration of marketing applications is available to the public.*

☐ Approval of products

☐ Approval times

☐ Summary of the grounds on which the approval was granted

☐ Advisory Committee meeting dates

☐ Other, please specify

*12.4 How is this information made available*

☐ Official Journal/periodical publication

☐ From an official Internet website

☐ On request

☐ Other, please specify:

***Transparency to companies on application progress***

*12.5 Are companies able to follow the progress of their own applications?* ☐ **Yes** ☐ **NO**

If **YES** please indicate the mechanisms available to industry

☐ Electronic access to the status of applications

☐ Telephone contact

| | | |
|---|---|---|
| ☐ E-mail contact | ☐ Other, please specify | |
| *12.6 Are companies given detailed reasons for rejecting an application for registration?* | | ☐ **Yes** ☐ **NO** |

***Facilities for providing information***

| | |
|---|---|
| *12.7 Is there an electronic system for registering and tracking applications* | ☐ **Yes** ☐ **NO** |
| If **YES** please indicate whether it has the following capabilities | |
| • Tracing applications that are under review and identifying the stage in the process | ☐ **Yes** ☐ **NO** |
| • Signalling that target review dates have been exceeded | ☐ **Yes** ☐ **NO** |
| • Recording the terms of the authorisation once granted | ☐ **Yes** ☐ **NO** |
| • Archiving information on applications in a way that can be searched | ☐ **Yes** ☐ **NO** |
| If **NO** are there plans to introduce such a system? | ☐ **Yes** ☐ **NO** |
| If so, please give target date for implementation: | |

## PART IV – IDENTIFICATION OF ENABLERS AND BARRIERS

The purpose of the following two questions is to try to identify the Agency's own perception of its unique positive qualities and the major impediments it faces in carrying out the review of new medicines and making them available to meet patients' needs.

| *13.1 List three factors that make a major contribution to the effectiveness and efficiency of your agency's review procedures and decision-making processes for NAS applications* |
|---|
| 1. |
| 2. |
| 3. |
| *13.2 List three factors that act as barriers to making new medicines available in a timely manner through the regulatory process* |
| 1. |
| 2. |
| 3. |

13.3 Any important documents related to GRevP that you would like to share with CIRS?

☐ **YES** ☐ **NO**

**If yes please list and provide directly to CIRS**

**Thank you for completing this questionnaire**

*Please sign and date:*

| | |
|---|---|
| Signature | |
| | Position: |
| Name: | |
| Date: | Email address: |

## GLOSSARY AND ABBREVIATIONS

| | |
|---|---|
| **Additional information** | Additional data or additional analyses of existing data requested from the sponsor by the regulatory authority during the review process |
| **Advisory Committee** | An expert committee that advises the regulatory authority of the safety, quality and efficacy of new medicines for human use |
| **Approval** | The approval of a drug product by a regulatory authority, signified by the granting of a marketing authorisation, or the issue of a technical approval letter. However the product may still not be marketable until negotiations for pricing and reimbursement are concluded. |
| **Clinical summary** | Summary of clinical study data that typically includes biopharmaceutic studies and associated analytical methods, clinical pharmacology studies, clinical efficacy, clinical safety, literature references, and synopses of individual studies. Refers to Module 2.7 in CTD format. |
| **Common technical document (CTD) format** | Common technical document (CTD) as outlined in the ICH guideline M4 (Organisation of the common technical document for the registration of pharmaceuticals for human use; M4). |
| **CMC** | Chemistry, manufacturing and controls. All activities conducted to optimize, scale-up and validate the processes and technologies for transfer to manufacture and all QA, QC and CMC support activities (e.g. CMC project management including CMC contribution to project teams). This includes all drug substance R&D i.e. process research and process development, all drug product R&D i.e. formulation development and process development, all analytical work for drug substance R&D and drug product R&D, clinical supplies and CMC's involvement in the compilation of regulatory documentation. |
| **GCP** | Good Clinical Practice |
| **Good Review Practice (GRevP)** | A code about the process and the documentation of review procedures that aims to standardise and improve the overall documentation and ensure timeliness, predictability, consistency and high quality of reviews and review reports |
| **ICH** | International Conference on Harmonisation |

| | |
|---|---|
| **Internal reviewers** | Internal reviewers are employees of the Authority |
| **Joint review** | The whole dossier is reviewed by each authority and the outcome is discussed before a decision is taken. |
| **Marketing Authorisation** | Authorisation issued by a regulatory to launch a drug product on the market |
| **Marketing Authorisation Application (MAA)** | Authorisation application submitted to a regulatory authority to launch a drug product on the market to which the application has been submitted. |
| **Milestone** | A milestone must involve some form of dated written document to which the regulatory authority can refer. In addition, a milestone must be considered by the regulatory authority to be the point at which one event stops and the next one begins so that the times for events are interdependent. |
| **Major Line Extension** | A major line extension is a modification to an authorised Medicinal Product that is sufficiently great that it cannot be considered to be a simple variation to the original product, but requires a new product authorisation. Such modifications include major new therapeutic indications or new disease states, extension to new patient populations (e.g., paediatrics), a new route of administration or a novel drug delivery system. |
| **NAS (New Active Substance)** | A new chemical, biological or pharmaceutical active substance includes:<br><br>a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product;<br><br>an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance not previously authorised as a medicinal product but differing in properties with regard to safety and efficacy from that chemical substance previously authorised;<br><br>a biological substance previously authorised as a medicinal product, but differing in molecular structure, nature of the source material or manufacturing process;<br><br>a radiopharmaceutical substance which is radio nucleotide, or a ligand not previously authorised as a medicinal product, or the coupling mechanism to link the molecule and the radio nucleotide has not been previously authorised. |

| | |
|---|---|
| **Non-clinical summary** | Summary of non-clinical data including: pharmacology, pharmacokinetics and toxicology. Refers to Module 2.6 in CTD format. |
| **Peer review** | Peer review means an additional evaluation of an original assessment carried out by an independent person or committee. Peer review can occur either during assessment of a dossier, or at sign-off. |
| **Quality control** | Quality control is operational techniques and activities that are used to fulfil requirements for quality. It involves techniques that monitor a process and eliminate causes of unsatisfactory performance at all stages of the quality cycle. |
| **Quality policy** | Overall intentions and direction of an organisation related to quality as formally expressed by top management. |
| **Questions to sponsor** | The process of asking the sponsor for additional data or additional analyses of existing data. The requests are made by the regulatory authority during the review process. |
| **Scientific assessment** | Review of the dossier in terms of safety, quality and efficacy of data submitted. |
| **Shared review** | Each authority takes responsibility for assessing a separate part of a dossier. |
| **Sponsor** | A company, person, organisation or institution that takes responsibility for initiating, managing or financing a clinical study. |
| **Standard Operating Procedures (SOPs)** | Detailed, written instructions to achieve uniformity of the performance of a specific function |
| **Validation of a dossier** | The process whereby the authority verifies that all parts of the submitted dossier are present and complete and suitable to be assessed as part of the assessment and registration process. |

# Appendix 2:

# Questionnaire used to complete Study 6 (Chapter 8)

**CONFIDENTIAL**

# Implementing an Abridged Review: What are the Criteria and current practice?

## Regulatory Agencies Pilot Study

## Review of inclusion criteria, documentation required, depth of review and milestones/target times

## QUESTIONNAIRE

**May, 2017**


The Centre for Innovation in Regulatory Science

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## CONTENTS

**The Centre for Innovation in Regulatory Science (CIRS)**

The Centre for Innovation in Regulatory Science Limited - is a neutral, independently managed UK based subsidiary company, forming part of Clarivate Analytics (UK) Limited. CIRS' mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science and to facilitate access to medical products through these activities. This is CIRS' purpose. CIRS is operated solely for the promotion of its purpose. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, special projects and grants

### Confidentiality

CIRS recognises that much of these data may be highly sensitive. CIRS has more than 25 years of experience in handling similar data provided by agencies regarding individual products in regulatory review. **All information collected from individual agencies will be kept strictly confidential. No data that will identify an individual agency will be reported or made available to any third party.** External reports or presentations of the data will include only blinded results and any appropriate analytical interpretations.

# Implementing an Abridge Review: What are the Criteria and current practice?

## BACKGROUND

**Abridged review procedure: "***This model relies on assessments of scientific supporting data that has been reviewed and accepted by SRA's, but includes an 'abridged' independent review of a certain part of the registration dossier of the product (e.g. relevant to use under local condition). This might include a review of the pharmaceutical quality (CMC) data in relation to climatic conditions and distribution infrastructure and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/culture and patterns of disease and nutrition." [Liberti, 2017].*

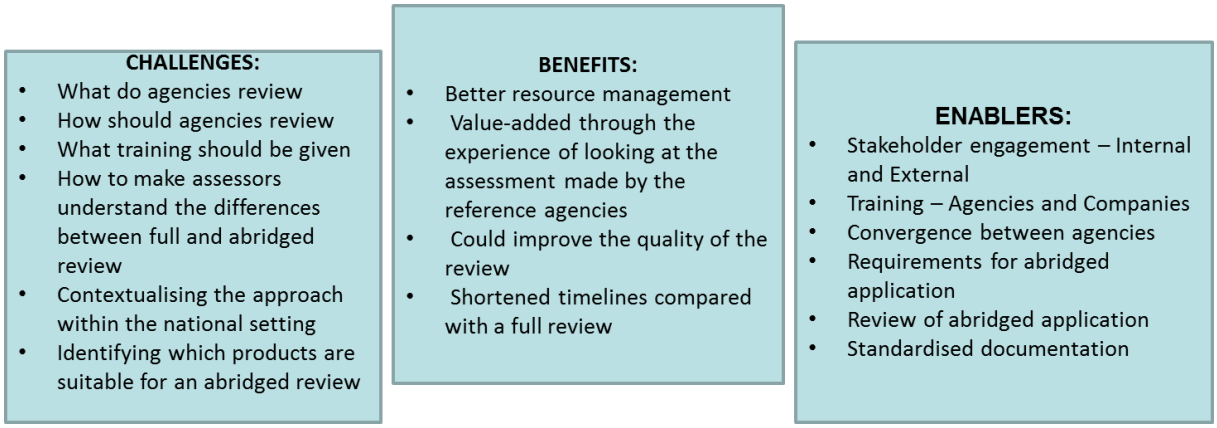
At the 2017 CIRS Workshop in Sao Paulo on this topic, it became clear that many agencies are interested in risk-based evaluations and would like to understand when and how they could and should practically implement a reliance model within their jurisdictions. It has been suggested that countries developing regulatory capabilities should consider a risk-based approach to the review of new medicines. Indeed, a number of agencies have recently adopted verification and abridged routes of regulatory review (Saudi Arabia, Brazil, Indonesia), which include consideration of reviews undertaken by reference agencies and which have accelerated timelines compared with standard reviews. Accelerating the review process should not compromise the safety, quality and efficacy of medicines and irrespective of the reliance model, agencies still need to consider the local benefit-risk decisions as well as use of the medicine within their healthcare system. The disadvantages of such systems are the need to wait for a prior approval and appropriate documentation such as a Certificate of Pharmaceutical Product. However, the advantages are the ability to focus on locally critical issues and conserve regulatory resources and the opportunity to accelerate availability of medicines.

However specifically for the abridged process many agencies evaluating this approach or having recently adopted such an approach are evaluating; what does this look like for us in reality; what are the areas the agency should evaluate specifically and in what depth; How do we enable the reviewers to see that such approaches does not diminish the review quality or level of scrutiny; How much should the agency rely on the reference agency and what detailed information do we need from the reference agency.

At a CIRS workshop in March 2018 in South Africa, a roundtable discussion was held with both regulatory agencies and companies called "Practical Implementation of Reliance Models: What are the Barriers and Facilitators to the Successful Application of these Models for Innovative Medicines, Generics and Variations?" The Group addressed a number of issues including:

- Experience of the group with abridged-based approaches: Examining the challenges, benefits and enablers
- Elements that constitute an abridged application
- Requirements for documentation from reference agencies
- Which parts of the dossier should be focused on in an Abridged Review
- Change Management Approach: Moving from Full Review to Abridged Review

## TABLE 1: BENEFITS CHALLENGES AND ENABLERS OF AN ABRIDGED REVIEW PROCESS




The syndicate group discussed that it was important to clarify the elements that make up an abridged review in particular the need to understand what each agency may require in an abridged review and what is needed in terms of reference agencies assessment reports.

Therefore, there is a need to identify what agencies currently evaluate when performing an abridged review. As many agencies are currently considering establishing a risk stratification approach for their review and placing some reliance on the decision and assessment of reference agencies. A pilot study is being proposed by CIRs and outlined below

### OBJECTIVES

The objectives are to:

- To identify criteria that agencies use to determine which products should be considered for an abridged review
- To determine what elements of the submission are currently or intended to be reviewed and the detail that will be considered
- To develop a framework based on current criteria and elements to enable agencies who wish to implement and abridged review process.
- To recommend appropriate means to document the review

### PILOT STUDY

To be conducted amongst the following agencies Indonesia, Brazil, Singapore, Israel and Saudi Arabia and to collect information directly from the agencies via a questionnaire

### OUTPUT

Participating agencies will receive a report from which they can compare their regulatory procedures with those of other agencies conducting an abridged review. This information will also inform future discussions on the how agencies are approaching abridged reviews.

### ABOUT THE QUESTIONNAIRE

The attached questionnaire is divided into three sections:

**Part I: Organisation of the agency.** The **Introduction** to the questionnaire asks the Authority to provide current information on its structure, organisation and resources. It also explores ***review model(s)*** for the ***scientific assessment of medicines*** in terms of the extent to which data is assessed in detail by the agency rather than relying on the results of assessments and reviews carried out elsewhere

**Part II: Key Milestones in the registration of medicines.** This part of the questionnaire is based on the General Model giving a process map and milestones that has been developed from studying procedures followed in 'established' and 'emerging' regulatory agencies. It captures the main steps in

the review and approval process and identifies key ‘milestone’ dates in the process for monitoring and analysing timelines

The **Introduction** to the questionnaire asks the Authority to provide current information on its abridged review process. It also explores the depth of the ***review model(s)*** for the scientific assessment in terms of the extent to which data is assessed in detail by the agency and what is used from the reference agency. The questionnaire is intended to be used as the basis for a face-to-face interview between Agency staff and CIRS.

## Focus of the Study

The study is intended, primarily, to document procedures and practices that relate to medicines that are the subject of abridged reviews of **major** applications, i.e., new active substances and major line extensions.

***New Active Substance***

A new chemical, biological or pharmaceutical active substance including:

- a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product;
- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance not previously authorised as a medicinal product but differing in properties with regard to safety and efficacy from that chemical substance previously authorised;
- a biological substance previously authorised as a medicinal product, but differing in molecular structure, nature of the source material or manufacturing process;
- a radiopharmaceutical substance which is radio nucleotide, or a ligand not previously authorised as a medicinal product, or the coupling mechanism to link the molecule and the radio nucleotide has not been previously authorised

***Major line extension***

A major line extension is a change to an authorised Medicinal Product that is sufficiently great that it cannot be considered to be a simple variation to the original product, but requires a new product authorisation. Such changes include major new therapeutic indications or new disease states, extension to new patient populations (e.g., paediatrics), a new route of administration or a novel drug delivery system.

## PART I: ORGANISATIONA STRUCTURE & TYPE OF REVIEW

### 1. Information on the Regulatory Authority

As background to the discussions about your agency, its practices and procedures it would be helpful to have the following basic information on its structure and the way it is established:

***Title of the Agency/Division*** *responsible for the regulation of medicinal products for human use*

If this is part of a parent agency with a wider remit (e.g., Food and Drugs) please give the title:

***Scope and remit***

*1.1 Please indicate the scope of responsibility of the Agency:*

| | | |
|---|---|---|
| Medicinal products for human use | ☐ **YES** | ☐ **NO** |
| Medicinal products for veterinary use | ☐ **YES** | ☐ **NO** |
| Medical devices and *in vitro* diagnostics | ☐ **YES** | ☐ **NO** |

*1.2 Indicate the main activities that are covered by the agency*

| | |
|---|---|
| ☐ Marketing authorisations/Product licences | ☐ Clinical trial authorisations |
| ☐ Post-marketing surveillance | ☐ Regulation of advertising |
| ☐ Laboratory analysis of samples | ☐ Price regulation |
| ☐ Other | ☐ Site inspections (site visits) |

***Type of agency***

*1.3 Indicate which of the following best describes this agency*

☐ Autonomous agency, independent from the Health Ministry administration
☐ Operates within the administrative structure of the Health Ministry

Date of establishment of the current agency ☐

***Size of agency***

Please note that the following questions refer to the regulation of **medicinal products for human use.**

*1.4 Please provide information on staff numbers*

- Total staff in the agency ☐
- Number of reviewers for applications for marketing authorisations/ product licences ☐

*1.5 Please indicate the professional background and numbers of the **technical** agency staff assigned to the review and assessment of medicinal products*

| | ***Number Employed as assessors (Degree/Expertise)*** | | | |
|---|---|---|---|---|
| | *Total:* | *with PhD or PharmD:* | *with MS:* | *Other:* |
| • Physicians | | | | |
| • Statisticians | | | | |
| • Pharmacists | | | | |
| • Other Scientists | | | | |
| • Project Managers | | | | |

***Fee structure***

*1.6 Are fees charged to sponsors for the review and assessment of applications for medicinal products for human use?* ☐ **YES** ☐ **NO**

If **YES**, please provide the following information:

| ***Marketing Authorisation Application fee for*** | ***Local currency*** | ***US$ (rounded)*** |
|---|---|---|
| ☐ New Active substance (Full Review) | | |
| ☐ New Active substance (Abridged Review) | | |
| ☐ Major line extension (Full) | | |
| ☐ Major line extension (Abridged Review) | | |

***Sources of funding***

*1.7 Please provide the following information in relation to the way the agency is funded*

| | | |
|---|---|---|
| Funded entirely by the government | ☐ **YES** ☐ **NO** | |
| Self-funded entirely from fees | ☐ **YES** ☐ **NO** | |
| Partially funded from different sources (please give proportions of total budget) | ____% Government<br>____% Other (specify) | ____% Fees |

***Additional documentation***

*To assist CIRS to better understand your organisation please provide copies of any **organisation charts** that show the structure of the agency and its relationship to other regulatory bodies, e.g., medical device agency. It would also be very useful to have copies of any background papers that describe the **functions**, **remit** and **mission** of the agency.*

## 2. Abridged Review - Inclusion Criteria and Reference agency

### Data Assessment: Abridged Review

This model also conserves resources by not re-assessing scientific supporting data that has been reviewed and accepted elsewhere but includes an 'abridged' independent review of the product in terms of its use under local conditions. This might include a review of the pharmaceutical (CMC) data in relation to climatic conditions and distribution infrastructure and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/culture and patterns of disease and nutrition.

Approval by a recognised agency elsewhere is a pre-requisite before the local authorisation can be granted but the initial application need not necessarily be delayed until formal documentation such as a Certificate of a Pharmaceutical Product (CPP) is available.

☐ Used for all NAS and Major Line Extensions applications
☐ Used for selected applications meeting specific criteria on request by sponsoring companies
☐ Used for selected applications meeting specific criteria but agency designated

Inclusion Criteria used by your agency

Does your agency have specific inclusion criteria, please tick all that apply

☐ Identical to that approved by, or submitted to, reference agency (i.e. dosage form, strength, formulation and manufacture)
☐ The proposed indication for the medicine would need to be based on broadly similar population demographics, disease profiles, and expectations regarding public health outcomes between your jurisdiction and Reference agency
☐ Criteria for timeframe between Reference agencies and submission to agency (if yes please specify: _____

☐ Other - Please Specify:

**Reference Agencies**

If your agency has recognised 'reference agencies' please tick which ones accepted:

☐ US FDA
☐ European Medicines Agency (EMA)
☐ PMDA Japan
☐ WHO listed agencies?
☐ Health Canada
☐ Swissmedic
☐ UK MHRA
☐ Australian TGA
☐ Other Please Specify:

How Many Reference agencies are required for an application: _____

In selection reference agencies – what are your key considerations?

☐ Risk tolerance,
☐ Objectives and goals,
☐ Standards and technical guidelines,
☐ Predictability in review process,
☐ Integrity of decision making and
☐ Transparent communication of processes and decision making.
☐ You have an MOU with the reference agency(ies)

☐ Reference agency conduct their business and release reports in English
☐ Other – Please specify

What information is required from the reference agency (tick all that apply)
☐ Assessment report
- ☐ Un Redacted
- ☐ Redacted can be submitted
- ☐ Public Assessment reports

Please state level of detailed required. E.g. include correspondence related to the application (e.g. questions asked of, and deliberations by, advisory bodies).

What other types of documents need to be submitted from a reference agency:

☐ Certificate of Pharmaceutical Product
☐ Approval letter
☐ Other: Please specify

## 2.2 Data requirements and depth of assessment

| **Regulatory Status:** | **Abridged Review** | **Full review** |
|---|---|---|
| ***Evidence of authorisation by other authorities*** | | |
| Requirements for assessment report and other documentation eg CPP as part of the review | ☐ with application<br>☐ before authorisation<br>☐ not essential | ☐ before local authorisation<br>☐ not essential<br>☐ if available at the time of submission |
| Other evidence required/accepted | | |
| ***Verification of identity between the authorised product and the local application*** | | |
| *The following are checked:* | Information must be:<br>*Identical Closely similar* | **Not applicable** |
| Dosage form | ☐ ☐ | |
| Strength | ☐ ☐ | |
| Ingredients | ☐ ☐ | |
| Indications and dose | ☐ ☐ | |
| Warnings and precaution | ☐ ☐ | |
| Product label | ☐ ☐ | |
| Other (specify) | | |
| ***Scientific data required to support the application*** (Reference is made below to sections of the ICH Common Technical Document (CTD) | | |

| **Regulatory Status:** | **Abridged Review** | **Full review** |
|---|---|---|
| as an example of the level of detail but does not imply that the CTD in necessarily accepted) | | |
| Pharmaceutical quality/CMC | ☐ Summary data (Mod 2.3)<br>☐ Summary + full stability<br>☐ Full data (Mod 3) | ☐ Summary data (Mod 2.3)<br>☐ Summary + full stability<br>☐ Full data (Mod 3) |
| ***Scientific data required to support the application*** (continued) | | |
| Nonclinical data | ☐ Written summary (2.4)<br>☐ Tabulated data (2.5)<br>☐ Full data (Module 4) | ☐ Written summary (2.4)<br>☐ Tabulated data (2.5)<br>☐ Full data (Module 4) |
| Clinical data | ☐ Written summary (2.5)<br>☐ Tabulated data (2.6)<br>☐ Full data (Module 5) | ☐ Written summary (2.5)<br>☐ Tabulated data (2.6)<br>☐ Full data (Module 5) |
| ***Extent of Scientific Review*** | | |
| Quality/CMC data | ☐ Only examined if there is a query<br>☐ 'Check list' review for completeness of data<br>☐ Selective review in detail (e.g. stability, specification)<br>☐ Detailed assessment and evaluation report | ☐ 'Check list' review for completeness of data<br>☐ Selective review in detail (e.g. stability, specification)<br>☐ Detailed assessment and evaluation report |
| What Quality/CMC data is not reviewed? | | |
| Comment | | |
| Non-clinical data | ☐ Only examined if there is a query<br>☐ 'Check list' review for completeness of data<br>☐ Detailed assessment and evaluation report | ☐ 'Check list' review for completeness of data<br>☐ Detailed assessment and evaluation report<br>☐ Not at all |
| What Non Clinical Data is not reviewed? | | |
| Comment | | |
| Clinical data | ☐ Only examined if there is a query<br>☐ 'Check list' review for completeness of data<br>☐ Selective review in detail (e.g. bridging studies) | ☐ 'Check list' review for completeness of data<br>☐ Selective review in detail (e.g. bridging studies)<br>☐ Detailed assessment and evaluation report |

| **Regulatory Status:** | **Abridged Review** | | | **Full review** | | |
|---|---|---|---|---|---|---|
| | ☐ Detailed assessment and evaluation report | | | | | |
| What Clinical data is not reviewed? | | | | | | |
| Comment | | | | | | |
| ***Clinical evaluation: factors included in the risk-benefit assessment*** | | | | | | |
| *The clinical opinion takes account of:* | *Never* | *sometimes* | *always* | *Never* | *sometimes* | *always* |
| Differences in medical culture/practice | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Ethnic factors | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| National disease patterns | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Unmet medical need | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| ***Additional information, not in the application***: | | | | | | |
| *The agency tries to obtain* | Information is sought: *Never* | *sometimes* | *always* | Information is sought: *Never* | *sometimes* | *always* |
| Other agencies' internal assessment reports | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Reports available on the Internet (e.g., EPARS) | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| General Internet search | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Other data (specify: ) | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

**Thank you for completing this questionnaire**

*Please sign and date:*

| | |
|---|---|
| Signature | |
| | Position |
| Name | |
| Date | Email address |

# APPENDIX 3:

## Poster presented at the School of Life and Medical Sciences (LMS) Research Conference 2019,

## 16 April 2019,

## Hatfield, United Kingdom

University of Hertfordshire UH

School of Life and Medical Sciences

# The South African Pharmaceutical Regulatory Environment: Challenges and Opportunities for a Reformed Regulatory Review Process

Andrea Keyter[1,2], Sam Salek[2] and Stuart Walker[2,3]

1. South African Health Products Regulatory Authority, Pretoria, South Africa;
2. Department of Pharmacy, Pharmacology & Postgraduate Medicine, University of Hertfordshire, Hatfield, UK;
3. Centre for Innovation in Regulatory Science (CIRS), London, UK.

## BACKGROUND

***INCREASED TIMELINES FOR REGISTRATION OF MEDICINES***

- Increased demands on regulatory system & resource constraints
- Informal Quality Management System (QMS) & Good Review Practices

***AMENDMENT OF LEGISLATION***

- Transition from the Medicines Control Council (MCC) to the South African Health Products Regulatory Authority (SAHPRA)
- Opportunity to address challenges

**The National Regulatory Authority (NRA) in South Africa, the MCC, is responsible for the SAFETY, QUALITY and EFFICACY of medicines**

## AIM

This study aims to review the regulatory environment in South Africa and to recommend the changes for the improved regulatory performance of SAHPRA

## METHOD

**1 QUESTIONNAIRE**
Part 1 – Organisational Structure / Part 2 – Review Process
Part 3 – Quality Management System / Part 4 – Decision-making
Completed by 4 comparative NRAs selected on size & function

**2 DATA COLLECTION**
Overall regulatory review times achieved by the MCC for New Active Substances for the period 2015 - 2017

### REGULATORY REVIEW PROCESS MAP

For MCC & comparative National Regulatory Authorities

#1 Receipt & Validation → #2 Queue Time → #3 Scientific Assessment → #4 Regulatory Decision

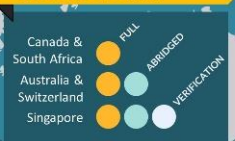
## RESULTS

- Pre-submission scientific advice
- Technical staff contact details
- Approval of products
- Feedback to industry on submitted dossiers
- Approval times
- Advisory Committee meeting dates
- Industry can track application progress
- Guidelines for industry
- Publication of grounds upon which product was approved

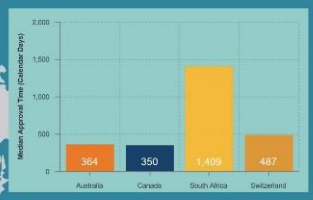
67% Singapore · 78% South Africa · 89% Canada · 100% Australia & Switzerland

**TRANSPARENCY & COMMUNICATION**

**TYPE OF ASSESSMENT**




**OVERAL MEDIAN APPROVAL TIME: 2015 - 2017**




**QUALITY MEASURES**

- Internal Quality Policy
- Shared and Joint Reviews
- Guidance for assessors
- Dedicated Quality Department
- Scientific Committee
- Assessment Templates
- Good Review Practice System


**CONTINUOUS IMPROVEMENT INITIATIVES**

- Internal quality audits
- External quality audits
- Internal tracking system
- Review of assessors feedback
- Review of stakeholders feedback

Canada 60 % · Australia, Singapore & South Africa 80 % · Switzerland 100 %

## RECOMMENDATIONS

**These recommendations endorse SAHPRA's vision for improved transparency, consistency and accountability. Enhanced regulatory performance will support access, availability and affordability of quality, safe and effective health care products in South Africa.**

**MEASURING & MOITORING**
Systematic metrics collection of overall approval time and key milestones in regulatory review process

**QUALITY MANAGEMENT SYSTEM (QMS)**
Formally implement and continuously improve QMS and Good Review Practices

**TRAINING**
Ongoing skills development for internal staff
Mentorship programmes
Contribute to enhanced regulatory performance

**RISK-BASED APPROACH**
Use reliance pathways
Reduce duplication of regulatory effort

**TRANSPARENCY**
Enhance stakeholder communication
Improve document management system
Publish basis for approval of medicine

**REFERENCES**

Keyter, A., Gouws, J., Salek, S. and Walker, S. (2018). The Regulatory Review Process in South Africa: Challenges and Opportunities for a New Improved System. *Therapeutic Innovation & Regulatory Science*, 1-10

Keyter, A., Banoo, S., Salek, S. and Walker, S. (2018). The South African regulatory system: past, present and future. *Front. Pharmacol.*, 9:1407

Keyter A, Salek S, Banoo S and Walker S (2019). The South African Medicines Control Council: Comparison of Its Registration Process With Australia, Canada, Singapore, and Switzerland. *Front. Pharmacol.*, 10:228

# APPENDIX 4:

## Poster presented at the Drug Information Association (DIA) Global Annual Meeting 2019,

## 23-27 June 2019,

## San Diego, United States of America

# The South African Regulatory Environment: Challenges and Opportunities for a Reformed Regulatory Review Process

Andrea Keyter[1,2], Sam Salek[2] and Stuart Walker[2,3]

1. South African Health Products Regulatory Authority, Pretoria, South Africa;
2. Department of Clinical and Pharmaceutical Sciences, University of Hertfordshire, Hatfield, UK;
3. Centre for Innovation in Regulatory Science (CIRS), London, UK.

## BACKGROUND

- The national regulatory authority (NRA) of South Africa, the Medicines Control Council (MCC), was mandated to ensure efficient, effective and ethical assessment of medical products that meet defined standards of quality, safety, efficacy and performance.
- Over the past two decades the MCC has experienced challenges in achieving these objectives which has resulted in extended timelines for registration of new medicines. This has been as a result of increased demands on the regulatory system and resource constraints.
- Legislative changes enacted in 2017 allowed for the transition of the MCC to the newly established South African Health Products Regulatory Authority (SAHPRA).

## AIM

- To review the regulatory environment in South Africa and to recommend changes for an improved regulatory review process.
- To compare the regulatory performance of the South African NRA with four other established NRAs.

## METHODS

### QUESTIONNAIRE

A questionnaire was completed by the Head of the Agency to describe the organisational structure, the registration process, good review and decision-making practices within the MCC.

- Similar questionnaires were completed and validated by comparative national regulatory authorities; Australia, Canada, Singapore and Switzerland.

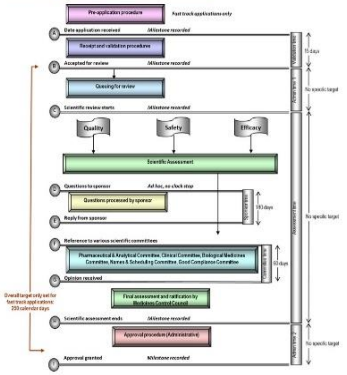
### DATA COLLECTION

Data was collected from the MCC for the period 2015 – 2017 using the OpERA data collection tool, developed by the Centre for Innovation in Regulatory Science (CIRS).

- These data reflect the overall approval timelines for new active substances (NAS) and were compared with similar datasets obtained directly from the comparative NRAs.

**The Optimising Efficiencies in Regulatory Performance (OpERA) programme provides the tools that help regulators integrate a practice of tracking and measuring regulatory performance within their agencies. This promotes continuous improvements and opportunities for work optimisation including potential reductions in review and approval times.**

**Figure 1: MCC Regulatory Review Process Map**



*Similar process maps were produced for the comparative NRAs.

## RESULTS

### Regulatory Review Process

**Figure 2: MCC Regulatory Review Process**

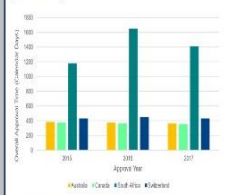

**Figure 3: Review Type**


- A comparison of the MCC regulatory review process with the four comparative agencies indicated that they all have similar requirements and procedures for medicine evaluation.
- The MCC conducted a full review of all applications, however they did not place any reliance on reviews performed by other NRAs and as such do not make use of abridged or verification reviews.
- The comparative agencies conduct a full review in addition to abridged or verification.

### Overall Review Time

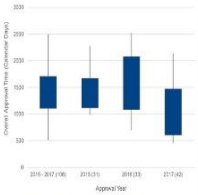
- The South African overall review timelines (approximately 1200 – 1600 calendar days) are substantially longer than the comparative NRAs (approximately 400 calendar days).
- Extensive review times in South Africa may be as a result of inappropriate operational processes, resource constraints as well as overcommitted external assessors.
- These results demonstrate the need to improve regulatory approval times and opportunities exist through SAHPRA to re-engineer the review process.

**Figure 4. Median Overall Review Times for NAS for Australia, Canada, Switzerland and South Africa (2015 – 2017)**




*Data from Singapore has been excluded as it represents the mean for their review which includes full review, abridged review and verification.

**Figure 5: Overall Review Times for NAS approved (2015 – 2017)**




*Number in bracket represents the number of applications approved in the approval year.

### Good Review Practices

#### Transparency & Communication


- Feedback to industry on submitted dossiers
- Publication of summary basis of approval
- Industry can track application progress
- Pre-submission scientific advice

#### Enablers and Barriers to Quality Decision-Making

| ENABLERS | BARRIERS |
|---|---|
| • Eagerness of the regulator to build confidence in the regulatory system<br>• Minimal staff turnover contributed toward the retention of institutional knowledge<br>• Support from scientific committees in the regulatory review of applications for market authorisation | • The lack of an electronic document management system<br>• Outdated review processes<br>• Fixed committee structures and decision-making processes |
| • Regulatory convergence<br>• Regulatory harmonisation<br>• Implementation of Good Review Practices | • Frustrations with incomplete submissions for market authorisation<br>• Need for appropriate electronic systems to support the review process and document management<br>• Full integration of electronic business systems |

### Good Review Practices

#### Continuous Improvement Initiatives


- Review of stakeholders feedback
- Internal tracking system
- Internal quality audits
- External quality audits
- Review of assessors feedback

#### Quality Measures

- Internal Quality Policy
- Shared and Joint Reviews
- Guidance for assessors
- Dedicated Quality Department
- Scientific Committee Assessment Templates
- Good Review Practices

Singapore
Australia, Canada & South Africa
Switzerland

**The five NRAs in this study implemented the majority of the essential elements of Good Review Practices.**

**The MCC differs in that there is no dedicated quality department. Internal quality audits were not performed, applicants were unable to track the progress of their applications and the summary basis of approval was not published.**

**These elements need to be addressed in order to strengthen the regulatory system in South Africa.**

## RECOMMENDATIONS

**These recommendations endorse SAHPRA's vision for improved transparency, consistency and accountability. Enhanced regulatory performance will support access, availability and affordability of quality, safe and effective health care products in South Africa.**


## CONCLUSIONS

This seminal study provides a baseline for monitoring the enhancement of the regulatory system in South Africa under the auspices of SAHPRA. It is hoped that enhanced regulatory performance will improve patients' access to new medicines.

## REFERENCES

## DISCLOSURE:

Author(s) have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this poster. A Keyter, S Salek and S Walker have nothing to disclose.