CIRS R&D Briefing 87

A Roadmap for Regulatory Strengthening: CIRS Tools for Measuring and Optimising Regulatory Performance to Support Practices in Line with the World Health Organization Global Benchmarking Tool Indicators

OpERA
*Op*timising *E*fficiencies in *R*egulatory *A*gencies

CIRS Centre for Innovation in Regulatory Science

Contents

Introduction: the importance of regulatory strengthening

The role of the World Health Organization Global Benchmarking Tool

Regulatory systems play a key role in assuring the quality, safety, and efficacy of medical products. When effective, these systems are an essential component of health systems and contribute to desired public health outcomes and innovation. National regulatory authorities (NRAs) of all sizes and maturity levels face challenges with ensuring that their systems are sufficiently robust, adaptable, and reflective of the needs of the emerging regulatory environment. In order to address their need to ensure that their regulatory system is "fit-for-purpose" for their stated mission, regulatory systems rely on optimising the effectiveness and efficiency of regulatory processes. Among regulators' many diverse roles and responsibilities, perhaps most important is the authorisation of medicines. Through this function, regulators ensure that safe, effective, and quality medicines are made available in a timely and efficient manner to their population.

To ensure that an NRA is operating at a level consistent with its purpose, mission, and capabilities, the World Health Organization (WHO) has developed the Global Benchmarking Tool (GBT) to assess and compare the practices of regulatory systems (WHO, 2021). Sub-indicators of the WHO GBT support enhanced regulatory performance when embedded within regulatory systems. The GBT represents the primary means by which the WHO objectively evaluates regulatory systems, a process mandated by WHA Resolution 67.20 on Regulatory System Strengthening for medical products.

The GBT and its methodology enable the WHO and regulatory authorities to:

- Identify strengths and areas for improvement
- Facilitate the formulation of an institutional development plan (IDP) to build upon strengths and address the identified gaps and prioritise IDP interventions
- Monitor progress and achievements against formal indicators

The GBT represents the first truly 'global' tool for benchmarking regulatory systems (WHO, 2021). It is designed to evaluate the overarching regulatory framework and the component regulatory functions through a series of indicators and sub-indicators across themes, such as quality, risk management, and others.

The GBT also incorporates the concept of "maturity level" (ML), allowing WHO and regulatory authorities to assess the overall "maturity" of their regulatory system on a scale of 1 (existence of some elements of regulatory system) to 4 (operating at advanced level of performance and continuous improvement). The WHO aims for NRAs to reach ML-3.

The WHO has introduced a framework for designating and publicly listing a regulatory authority as a WHO Listed Authority (WLA). This is in response to Member States' requests to develop a transparent and evidence-based pathway for regulatory authorities operating at an advanced level of performance to be globally recognised, thereby replacing the procurement-oriented concept of stringent regulatory authorities.

The experience of Centre for Innovation in Regulatory Science through Optimizing Efficiencies in Regulatory Agencies

Over the last 20 years, CIRS has been developing regulatory science tools to increase transparency of processes, support quality regulatory decision making, and provide global advocacy in support of regulatory and HTA strengthening. CIRS' tools have been developed with companies, NRAs, and academics, validated and implemented by organisations, and applied practically in projects. In a recent study, CIRS tools have supported the goals of specific GBT sub-indicators in assessing

and improving the performance and the scientific competencies of NRAs (Keyter et al., 2020)

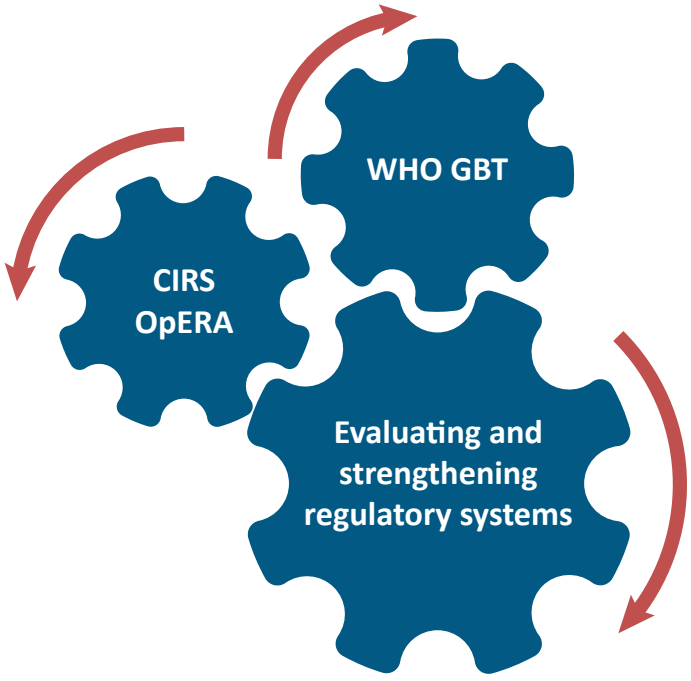
These tools form part of a comprehensive toolkit to support the CIRS "Optimizing Efficiencies in Regulatory Agencies (OpERA)" programme, a multi-year programme supported in part by the Bill and Melinda Gates Foundation, for NRAs to support regulatory monitoring and strengthening.

The objectives of OpERA are to:

- Understand the regulatory processes that drive assessment and approval times
- Encourage systematic re-assessment of the medicines' review processes
- Provide a basis for comparison across processes used in the review of marketing authorisations
- Provide a simple process to collect benchmarking data specific to the regulatory review and assessment processes
- Encourage the development of a systematic approach to self-monitoring and continuous improvement
- Support regulators as they integrate best practices that are fit for purpose and within the agency remit, while ensuring the safety, efficacy, and quality of their products, in line with the WHO GBT

Over 30 national regulatory authorities and several regional initiatives have participated in the OpERA Programme since its inception in 2013, and many have subsequently utilised and implemented CIRS tools. The programme has successfully built a culture of measurement and refinement within participating NRAs, helping them to define their performance goals for medicines' review and optimise review processes.

While several approaches can help NRAs meet the GBT's stated goals, the OpERA tools provide an opportunity for an NRA to conduct a deep-dive assessment of its registration processes, in alignment with the GBT and in a detailed and comprehensive manner not offered by other tools. The OpERA tools described here also offer approaches that go beyond checklists to support the implementation of key indicators in the GBT and help NRAs achieve the goals as described by the sub-indicator. Together, OpERA tools allow NRAs to build an ongoing process of self-assessment and improvement into their systems in line with the WHO GBT.



Overview of the CIRS OpERA tools

The CIRS OpERA toolkit is comprised of seven key tools focusing on evaluating the regulatory review process and practices, implementing a structured approach to benefit-risk, and establishing good review and decision-making practices.

CIRS OpERA regulatory tools that contribute to the performance of sustainable and efficient regulatory systems

Evaluate the regulatory review process and practices

1. Country report
2. Metrics tool
3. Process Effectiveness & Efficiency Rating (PEER)

Implement a structured and systematic approach to benefit-risk

4. Unified Methodologies for Benefit-Risk Assessment (UMBRA) framework and template

Establish good review and decision-making practices

5. Quality Scorecard
6. GRevP Embeddedness Survey
7. Quality of Decision Making Orientation Scheme (QodOS)

Supporting agencies in implementing WHO GBT indicators and attaining ML-3 status

The CIRS tools have been developed together with major global NRAs and validated using rigorous scientific methods. Over the last 30 years, they have been utilised by NRAs globally in Africa, Asia, the Americas, Australia, Europe, and Middle East to support the creation of efficient, effective, and fit-for-purpose regulatory systems. The tools assist NRAs in efforts to attain WHO ML-3 status by demonstrating the NRAs' capabilities in specific GBT indicators, in addition to providing a mechanism for compliance with GBT record keeping requirements.

1. Country report

Background:

In 2009, CIRS developed a standardised reporting approach to identify key characteristics that impact regulatory performance. The resulting country report is used to map the regulatory processes and practices:

1) Organisation of the NRA

2) The types of review models used to assess medicines

3) Key milestones in the review process

4) Elements of Good Review Practices in place at the NRA

5) Quality decision-making practices used to make regulatory decisions (McAuslane et al., 2009; Rodier et al., 2020)

Goal of the tool: Enable transparent NRA processes and practices aligned with best practice.

Objectives:

- Accurately define the NRA processes and practices
- Provide context to enable interpretation of quantitative metrics (see Metrics Tool)
- Enable global comparisons to similar NRAs open to sharing their profile (Sithole et al., 2021)
- Encourage transparent publication of information related to the NRA and promote alignment with best practice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ORIGINAL RESEARCH

OPEN ACCESS

Comparison of the registration process of the medicines control authority of Zimbabwe with Australia, Canada, Singapore, and Switzerland: benchmarking best practices

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ABSTRACT

Background: Benchmarking regulatory systems of low- and middle-income countries with mature systems provides an opportunity to identify gaps, enhance review quality, and reduce registration timelines, thereby improving patients' access to medicines. The aim of this study was to compare the medicines registration process of the Medicines Control Authority of Zimbabwe (MCAZ) with the regulatory processes in Australia, Canada, Singapore, and Switzerland.

Methods: A questionnaire that standardizes the review process, allowing key milestones, activities and practices of the five regulatory authorities was completed by a senior member of the divisions responsible for issuing marketing authorizations.

Results: The MCAZ has far fewer resources than the regulatory authorities in the comparator countries, but employs three review models, which is in line with international best practice. The MCAZ registration process is similar to the comparator countries in key milestones monitored, but differs in the target timelines for these milestones. The MCAZ is comparable to the comparator authorities in implementing the majority of good review practices, although it significantly lags behind in transparency and communication.

Conclusion: This study identified the MCAZ strengths and opportunities for improvement, which if implemented, will enable the achievement of its vision to be a leading regulatory authority in Africa.

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KEYWORDS
Medicines Control Authority of Zimbabwe (MCAZ); international best-practice; improved medicines access; registration of medicines; low- and middle-income countries (LMIC)

Approach and audience:

The Country Report is based on the Country Questionnaire completed by each NRA, with a particular focus on registration departments. The Country Questionnaire is a Microsoft Word-based tool available in English, Spanish, and French, which the NRAs complete with the help of CIRS. CIRS then develops the report using a standardised approach to identify the key components of the review and the practices, including characteristics that may impact regulatory performance and practices that bring quality to the registration processes.

Practical global experience:

CIRS has prepared over 30 Country Reports for NRAs and regional bodies in Asia, Africa, North and South America, Australia, Europe, and the Middle East. The NRAs have used these reports to conduct an internal gap analysis to identify alignment with best practice and opportunities for improvement. In addition, they use the reports to monitor changes to the process over time, as well as to undertake comparisons with other NRAs and enable transparent process sharing through publications.

This tool supports the following WHO-GBT indicators:

- GBT RS03.05: The NRA is required to promote good regulatory practices (GRPs)
- GBT RS01.02: Legal provision and regulations define the institutions that are involved as part of the regulatory system, as well as their mandates, functions, roles, responsibilities, and enforcement powers
- GBT RS03.04: Reliance on the decisions of other mature NRAs through documented policy, procedures, and/or mechanisms must be formalised
- GBT RS07.02: The amounts collected for fees, taxes, tariffs, or dues payable for the services provided are defined and publicly available

2. Metrics tool

Background:

CIRS has been benchmarking major NRAs since 2002 using a methodology developed with agencies (Hirako et al., 2007). The Metrics tool provides a simple starting point to track regulatory performance and measure the time it takes to review medicines, with the ability to assess key granular milestones as well as NRA time and company time.

Goal: Facilitate timeliness and effectiveness of the regulatory review process.

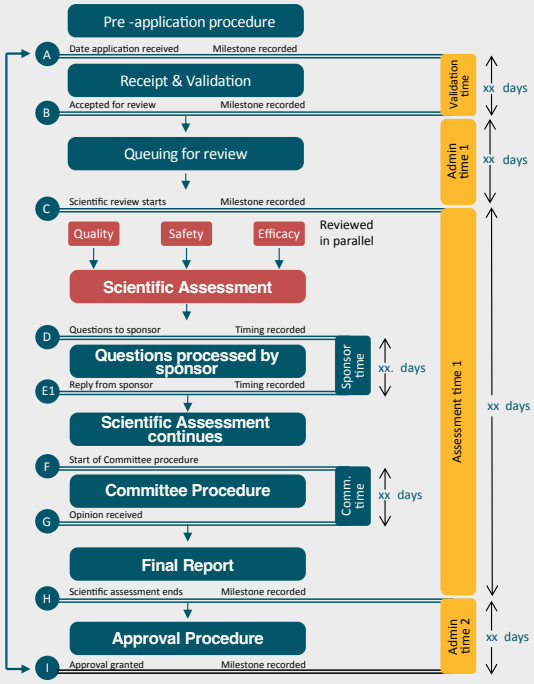
Objectives:

- Track regulatory timelines and performance and identify process limitations
- Facilitate strategic planning and decision-making within the approval process
- Provide a baseline against which the impact of change can be measured
- Gather feedback via independent analysis from a third-party that is comparative across other NRAs

Approach and audience:

Typically, the NRA registration or information management departments undertake Metrics collection. They either use a CIRS online data collection tool or receive data through a secure spreadsheet that CIRS then uploads into its system.

Milestones collected	Analysis by CIRS
Step 1: Submission and approval dates only and basic product characteristics	Overall approval time (median and variance) against NRA target; impact of characteristics and NRA pathways
Step 2: Additional dates to start scientific assessment and receive response from companies	Analysis based on review phases (validation, scientific assessment, authorisation) comparing NRA vs company time



Practical global experience:

CIRS has analysed regulatory review metrics for over 20 NRAs and regional bodies in Asia, Africa, North and South America, Australia, Europe, and the Middle East (CIRS, 2022; Liberti et al., 2020; Sani et al 2020; Patel et al., 2020.). Results have been published in NRA annual reports (TGA, 2015; Swissmedic 2020) and are used to monitor timelines and identify effective and ineffective tactics. NRAs also utilise this information to compare their efforts to other NRAs doing similar activities, then identify opportunities for learning.

This tool supports the following WHO-GBT indicators:

- GBT MA04.06: The establishment of timelines for the assessment of applications and an internal tracking system are required to follow the targeted timeframes
- GBT MA06: The use of a mechanism to monitor regulatory performance and output
- GBT MA06.02: The establishment and implementation of performance indicators for registration and/or market authorisation activities is required
- GBT RS09.04: Information on marketed medical products, authorised companies, and licensed facilities is publicly available
- GBT RS10.01: Requirements established to monitor, supervise, and review the performance of the NRA and affiliated institutions using key performance indicators

3. Process Effectiveness & Efficiency Rating (PEER)

Background:

Regional initiatives, joint procedures, and work sharing assessments are becoming increasingly important to ensure effective use of resources by regulators. CIRS has been evaluating and supporting the establishment of regional bodies through its Country Reports and Metrics to evaluate process characteristics and timelines. In order to further enhance efficiency and effectiveness within the regional initiatives, CIRS developed a tool (Ngum et al., 2022a, b; Sithole et al., 2022a, b, c) to gather information from the participating regulatory bodies as well as the industry to ensure a system that is fit for purpose and aligned with stakeholder expectations.

Goal: Support effectiveness and efficiency of regional bodies.

Objectives:

- Obtain views of the individual authorities and companies on the regional initiatives
- Identify challenges stakeholders experience
- Determine strengths and weaknesses of the initiatives
- Identify ways to improve the performance of the initiative and chart a path forward

Approach and audience:

Word-based questionnaire completed by NRA and analysed by CIRS

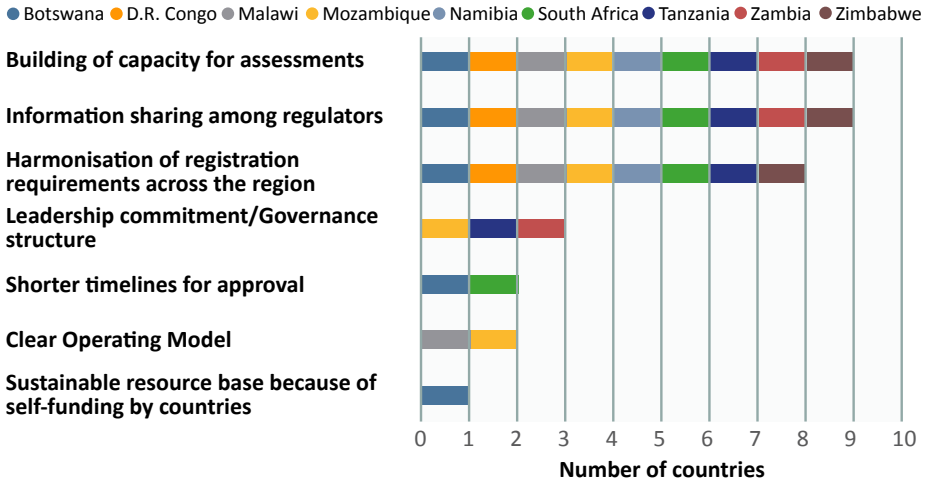
Practical global experience:

NRAs have used the approach to make recommendations on how to further strengthen ZaZiBoNa, the work-sharing initiative in the Southern African as well as the East African Community joint assessment procedure. Although the practical experience has focused on Africa so far, CIRS is planning to evaluate additional initiatives in Africa, Asia, Latin America, and the Middle East.

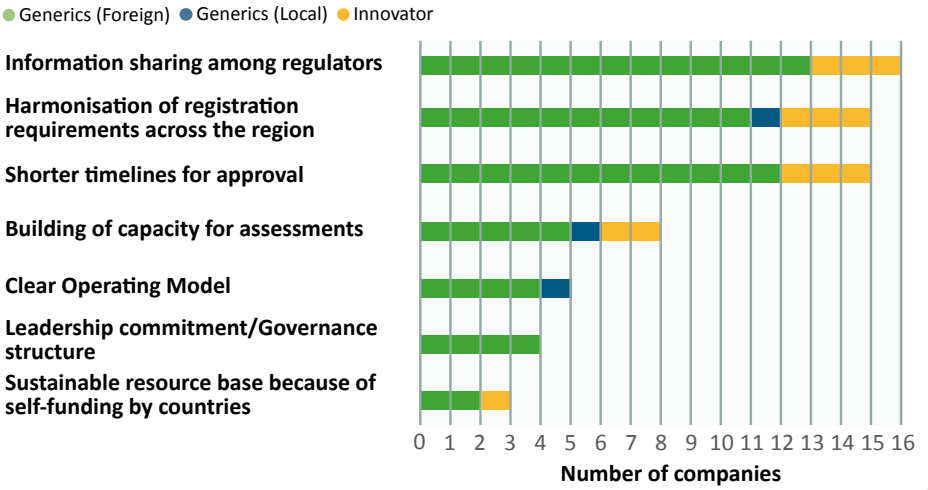
This tool supports the following WHO-GBT indicators:

- GBT RS03.04: Reliance on the decisions of other mature NRAs through documented policy, procedures, and/or mechanisms must be formalised
- GBT RS09.01: NRAs are encouraged to participate in a regional and/or global network in order to promote convergence and harmonisation efforts

Benefits of the ZaZiBoNa initiative according to regulatory authority respondents



Benefits of the ZaZiBoNa initiative according to pharmaceutical industry respondents



4. Unified Methodologies for Benefit-Risk Assessment (UMBRA) framework and template

Background:

An important component of a quality decision-making system is the ability to document how a decision to approve (or not approve) a medicine came about. This decision is based on the reviewer's assessment of the product's benefits and risks; how these factors contributed to the assessment, how these were weighted in terms of relative importance, and how the overall decision outcome was reached need to be documented in a structured, systematic, simple manner. As a consequence, CIRS, together with other major NRAs, developed the Unifying Methodology for Benefit Risk Assessment (UMBRA) tool in 2015 to provide a structured approach to benefit-risk assessment of medicines (Leong et al., 2015; Walker et al., 2015; McAuslane et al., 2017).

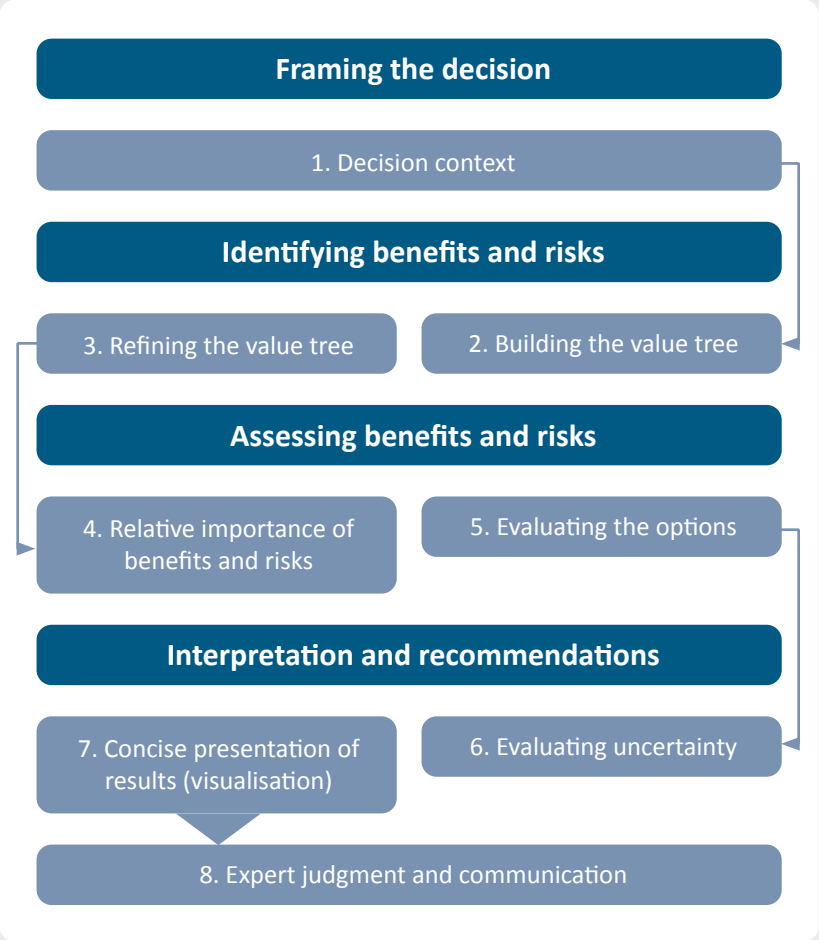
Goal: Enable a systematic and structured approach to benefit-risk.

Objectives:

- Provide a simple document through which all key aspects that contributed to the final decision can be clearly documented
- Improve the current NRA framework and template for benefit-risk and align with best practice
- Provide a structured platform for internal discussions on benefit-risk within an NRA, for NRA-to-company interactions, and for NRA-to-NRA interactions in the case of risk-based reliance reviews and work-sharing
- Serve as the basis for Public Assessment reporting

Approach and audience:

CIRS Shares the UMBRA eight-step framework and template as a paper-based PDF document, which NRA reviewers complete for specific products (internal to the NRA and including external advisor assessors or advisory committees).



Practical global experience:

The UMBRA framework and template have been completed by NRAs in Asia, Africa, Australia, North and South America, Europe, and the Middle East for retrospective and prospective case studies on the assessment of medicinal products. NRAs have also utilised the framework and template to modify their clinical assessment templates, ensure alignment of processes compared to other NRAs, and facilitate risk-based worksharing reviews and reliance.

This tool supports the following WHO-GBT indicators:

- GBT RS09.03: Information on decisions related to regulatory activities is available to the public
- GBT RS03.04: Reliance on the decisions of other mature NRAs through documented policy, procedures, and/or mechanisms must be formalised
- GBT MA05.03: NRAs are required to publish the summary technical evaluation reports for approved applications of marketing authorisation in the public domain

5. Quality scorecard

Background:

Measuring quality of the review is important as it increases trust amongst stakeholders and achieves a broader acceptability of the review conducted. Although it is very difficult to measure quality per se, it is possible to instead measure the different activities that are believed to make up a quality review. Consequently, in 2004, CIRS developed the concept of using a Quality Scorecard to get feedback from companies on the NRAs' reviews and from NRAs on the companies' submissions with regard to specific parts of the review/dossier (Salek et al., 2012)

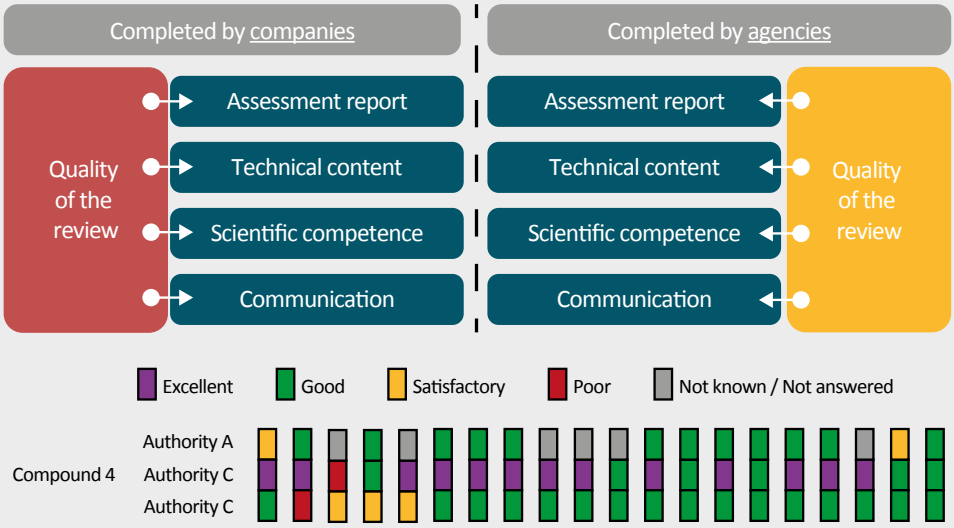
Goal: Enable improved quality of NRA review and company submission.

Objectives:

- Monitor the quality of regulatory submissions and their review
- Enable a transparent, timely, predictable, and good-quality review
- Provide a structured and detailed feedback provided by industry and NRAs that could enable optimisation of the regulatory process
- Encourage effective working relationships between industry and authorities by providing a means for open exchange of views, as well as enhancing dialogue

Approach and audience:

The survey is a paper-based Word-document that is used to assess the quality of the company submission and the quality of the dossier based on the assessment of individual products. CIRS collates the information and provides aggregated, anonymised results to the NRA and companies and undertakes a gap analysis across the responses.



Practical global experiencee:

The Quality Scorecards have been utilised by NRAs in Australia, North and South America, and Europe to identify major factors that affect the review and submission process. The results provided a gap analysis that was used for training purposes to build quality into the medicines assessment process and to strengthen regulatory activities overall.

This tool supports the following WHO-GBT indicators:

- GBT MA04.01: Documented procedures/tools are implemented for the assessment of the different parts of the application and for the assessment of specific requirements of specific classes of medical products (quality, safety, and efficacy)
- GBT MA04.10: The regulations and/or guidelines for good review practices (GRevP) are developed or recognized and implemented

6. Embeddedness Survey

Background:

CIRS has been working with NRAs over the last decade to improve the quality of their review processes. CIRS has initiated studies across the APEC counties to identify the status of GRevP within each country and identify training needs (Liu et al., 2013). In addition, CIRS have worked within NRAs to evaluate how embedded GRevP practices are into workflows so as to identify opportunities for additional training.

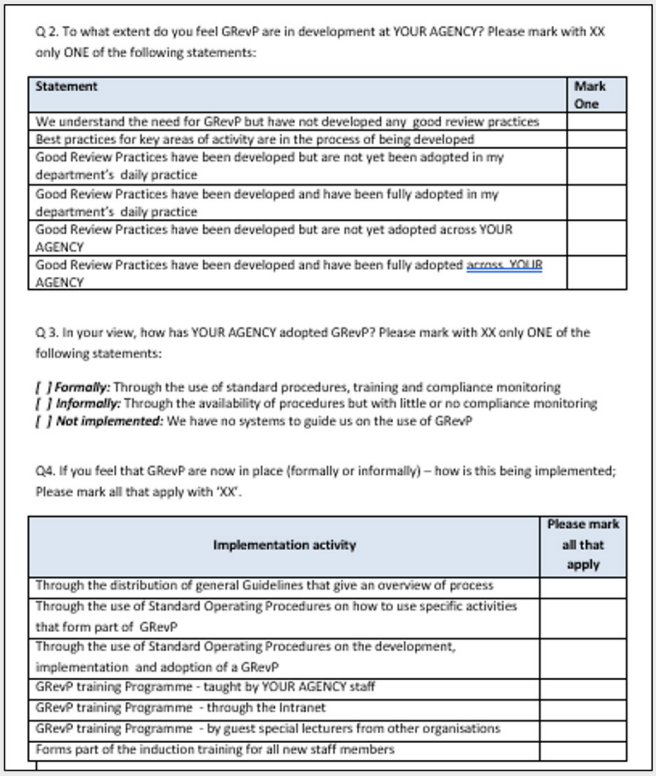
Goal: Facilitate implementation of good-review practices.

Objectives:

- Identify perspectives of the NRA reviewers on the use of GRevP by the NRA in general
- Provide a baseline on NRA's implementation of GRevP
- Assess the review team's knowledge of and attitude toward GRevP and their perspective on the value of GRevP to the NRAs' operations
- Explore the processes and procedures currently in place that underpin GRevP to determine how these relate to continuous process improvement

Approach and audience:

This tool has been constructed to survey individuals involved with regulatory activities in an NRA and gather their perception of how well their department and organisation follow GRevP. It is a Word-based questionnaire completed by individuals and analysed by CIRS.



Q 2. To what extent do you feel GRevP are in development at YOUR AGENCY? Please mark with XX only ONE of the following statements:

Statement	Mark One
We understand the need for GRevP but have not developed any good review practices	
Best practices for key areas of activity are in the process of being developed	
Good Review Practices have been developed but are not yet been adopted in my department's daily practice	
Good Review Practices have been developed and have been fully adopted in my department's daily practice	
Good Review Practices have been developed but are not yet adopted across YOUR AGENCY	
Good Review Practices have been developed and have been fully adopted across YOUR AGENCY	

Q 3. In your view, how has YOUR AGENCY adopted GRevP? Please mark with XX only ONE of the following statements:

[ ] ***Formally:*** Through the use of standard procedures, training and compliance monitoring
[ ] ***Informally:*** Through the availability of procedures but with little or no compliance monitoring
[ ] ***Not implemented:*** We have no systems to guide us on the use of GRevP

Q4. If you feel that GRevP are now in place (formally or informally) – how is this being implemented; Please mark all that apply with 'XX'.

Implementation activity	Please mark all that apply
Through the distribution of general Guidelines that give an overview of process	
Through the use of Standard Operating Procedures on how to use specific activities that form part of GRevP	
Through the use of Standard Operating Procedures on the development, implementation and adoption of a GRevP	
GRevP training Programme - taught by YOUR AGENCY staff	
GRevP training Programme - through the Intranet	
GRevP training Programme - by guest special lecturers from other organisations	
Forms part of the induction training for all new staff members	

Practical global experience:

The Embeddedness Survey has been utilised by NRAs in Asia, Europe, and South America. The results provided a gap analysis that was used for training to build quality into the medicines assessment process and to strengthen regulatory activities overall.

This tool supports the following WHO-GBT indicators:

- GBT RS03.05: The NRA is promoting GRP
- GBT MA04.10: The regulations and/or guidelines for good review practices (GRevP) are developed or recognized and implemented

7. Quality of Decision-Making Orientation Scheme (QodOS)

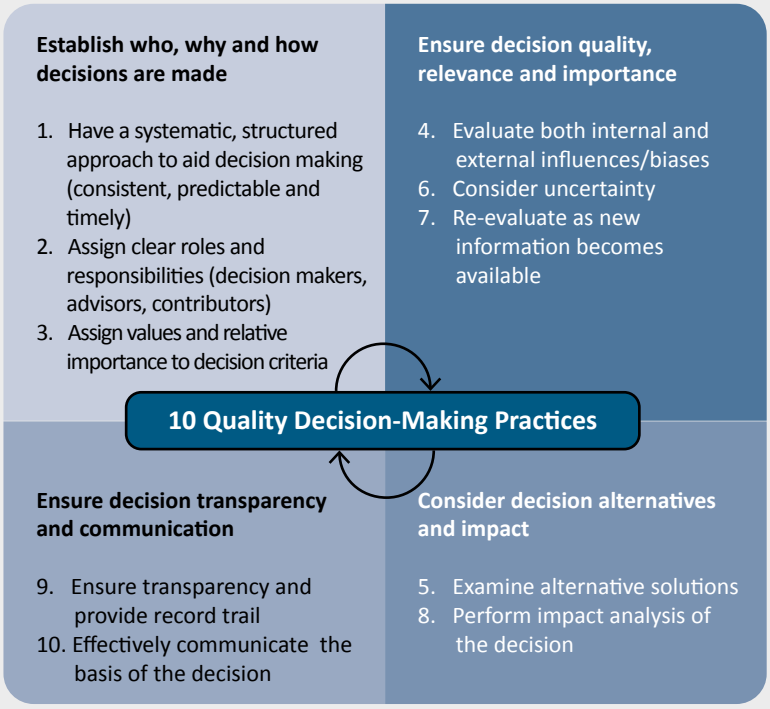
Background:

NRAs make various critical decisions ot ensure that safe and effective medicines become available in an efficient, timely manner. Despite this, there has been a paucity of research into the quality aspect of decision-making in medicines' research and development. The CIRS Quality of Decision Orientation Scheme (QoDOS) survey tool has been developed to assess the quality of decision-making by companies and NRAs (Donelan et al., 2016; Walker et al., 2017; CIRS, 2019).

Goal: Enable improved decision-making processes and practices.

Objectives:

- Increase awareness of the 10 quality decision-making practices (QDMPs)
- Help organisations monitor decision-making across different teams or divisions
- Identify differences in decision-making between individuals and the organisation
- Identify strengths and weaknesses and measure change over time to determine the impact of training and improvement initiatives
- Reduce uncertainty around decision-making and improve quality and transparency to minimise reputational risk



Approach and audience:

The QoDOS is a Word-based questionnaire completed by individuals – such as Reviewers, managers, committee members – and analysed by CIRS to assess implementation of the 10 QDMPs. The tool measures how individuals implement QDMPs into their decision-making, as well as their perception of the organisation/department/committee.

Practical global experience:

The QoDOS tool has been completed by over 15 NRAs in Asia, Africa, North and South America, Australia, and Europe. The results provided a basis for discussion of decision-making issues within teams and the broader organisation. They also demonstrated how NRAs have implemented QDMPs and led to recommendations for improvement across reviewers in pre- and post- market departments, decision-making committees, regulatory management, and senior leadership. Companies and health technology assessment agencies have also used the tool (Bujar et al., 2020) to enable a global analysis of stakeholder decision-making practices.

This tool supports the following WHO-GBT indicators:

- GBT RS02.02: Channels of communication and decision-making are clearly established among the structures, institutions, and departments forming the NRA
- GBT MA04.01: Documented procedures/tools are implemented for the assessment of the different parts of the application and for the assessment of specific requirements of specific classes of medical products (quality, safety, and efficacy)

Summary table: CIRS tools for measuring and optimising regulatory performance to support evaluation by the World Health Organization (WHO) Global Benchmarking Tool (GBT)

	1. Country report	2. Metrics tool	3. PEER Survey	4. UMBRA framework and template	5. Quality Scorecard	6. GRevP Embeddedness Survey	7. QoDoS
Year established	2007	2002	2021	2015	2011	2013	2016
Goal	Enable transparent processes and practices aligned with best practice	Facilitate timeliness and effectiveness of the regulatory review process	Support effectiveness and efficiency of regional NRAs	Enable a systematic and structured approach to benefit-risk	Enable improved quality of NRA review and company submission	Facilitate implementation of good-review practices	Enable improved decision-making processes and practices
Example WHO GBT indicator that this tool supports	GBT RS03.05 GBT RS01.02 GBT RS03.04 GBT RS07.02	GBT MA04.06 GBT MA06 GBT MA06.02 GBT RS09.04 GBT RS10.01	GBT RS03.04 GBT RS09.01	GBT RS09.03 GBT RS03.04 GBT MA05.03	GBT MA04.01 GBT MA04.10	GBT RS03.05 GBT MA04.10:	GBT RS02.02 GBT MA04.01
Approach	Word-based questionnaire completed by NRA and translated into a report by CIRS	Online data collection tool and/or spreadsheet completed by NRA analysed by CIRS	Word-based questionnaire completed by NRA and analysed by CIRS	Word-based template completed by NRA and translated into a report by CIRS	Word-based questionnaire completed by NRA and analysed by CIRS	Word-based questionnaire completed by individuals and analysed by CIRS	Word-based questionnaire completed by individuals and analysed by CIRS
Target audience within the NRA	NRA in general as well as registration departments	Registration and information management departments	Registration departments	Reviewers within registration departments	Registration departments and reviewers	Reviewers within registration departments	Reviewers, managers, committee members
Practical global experience	Asia, Africa, North and South America, Australia, Europe, Middle East	Asia, Africa, North and South America, Australia, Europe, Middle East	Africa	Asia, Africa, North and South America, Australia, Europe, Middle East	Australia, North and South America, Europe	Asia, Europe, South America	Asia, Africa, North and South America, Australia, Europe
Key references	McAuslane et al., 2009 Rodier et al., 2020 Sithole et al., 2021	Hirako et al., 2007 Liberti et al., 2020 Sani et al. 2020 Patel et al., 2020	Ngum et al., 2022a, b Sithole et al., 2022a, b, c	Leong et al., 2015 Walker et al., 2015 McAuslane et al., 2017	Salek et al., 2012	Liu et al., 2013	Donelan et al., 2016 Walker et al., 2017 CIRS, 2019 Bujar et al., 2020
							

OpERA *Optimising Efficiencies in Regulatory Agencies*

CIRS Centre for Innovation in Regulatory Science

Case studies

CIRS has been working with 30+ NRAs and regional bodies globally and applying OpERA tools in Africa, Asia, North and South America, Australia, Europe, and the Middle East to support fit-for-purpose and strong regulatory systems, as well as to optimise regulatory efficiencies and effectiveness. Three examples are shared below:

Example 1: Health Canada, Canada

2003–2005 – Evaluation of the process and timelines using **CIRS Country Report and Metric tool** in comparison with other major NRAs to identify process limitations and understand where time is spent (Hirako et al., 2007). This led to the introduction of a project management system by the agency (modelled on FDA and EMA) and an updated fee structure that resulted in a 99% reduction of backlog.

2010 – Health Canada participates in the development and validation of the **Quality Scorecards** (Good Review and Submission Practices). The structured and detailed feedback provided by industry and Health Canada enabled dialogue and resulted in recommendations for optimising the quality of regulatory submissions and review in Canada (Salek et al., 2012).

2008–2013 – Health Canada, together with other major NRAs, forms a benefit-risk consortium facilitated by CIRS (McAuslane et al., 2017). The collaboration results in the development of the **UMBRA benefit-risk framework and template** which was utilised by the NRAs to modify their clinical assessment templates to ensure alignment and facilitation of shared and joint reviews.

> "Participating in the CIRS benchmarking activities has been one element of the strategy that has allowed us to respond to the Canadian governments direction to improve performance (…). An important outcome has been **the ability to give factual information that allows for identification of improvements that are resource dependent in order to make a stronger case for additional resource."**
>
> Dr Robert Peterson; Former Director General, Health Canada

2018 – Health Canada pre- and post-marketing reviewers participate in **QoDOS decision-making studies**, demonstrating good incorporation of quality decision-making practices within the agency framework and reviewer practices, and similar approaches to decision-making compared to other major NRAs (CIRS, 2019).

2014–2022 – Health Canada utilises the **CIRS Metric tool** to enable annual publication of its review times based on information from the public domain and the agency's public assessment report. Most recently, a CIRS analysis showed a 34% and 36% reduction in median time from first-world submission to approval at Health Canada for new active substances approved via Access Consortium and Project Orbis respectively (CIRS, 2022).

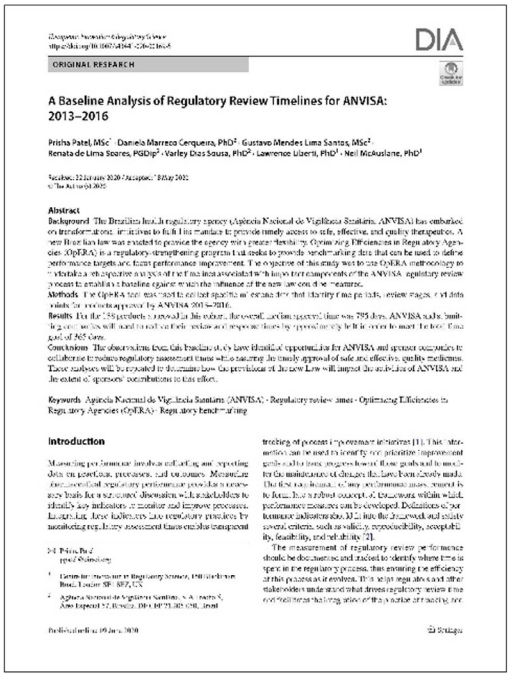
Example 2: Brazil, ANVISA

2004 – ANVISA regulatory review **Metrics** are assessed through the CIRS Growth and Emerging Markets industry benchmarking study (CIRS, 2019b).

2013 – CIRS applies the **Quality Scorecards** to evaluate company perception on the quality of the review in ANVISA and other NRAs in the region. This builds a picture of areas in which an NRA works well and areas for improvement (CIRS, 2015).

2013–2017 – ANVISA participates in OpERA where a number of CIRS tools are applied (CIRS, 2019c) to evaluate processes and enable further efficiency and effectiveness:

- Assessment of the agency's processes to identify opportunities and challenges using the **Country report**
- The agency provides review data directly to CIRS using the **Metrics tool** (Patel et al., 2020), establishing a baseline against which the influence of a new law could be measured
- Application of the **GRevP Embeddedness survey** to facilitate implementation of Good Review Practices by the agency



DIA

ORIGINAL RESEARCH

A Baseline Analysis of Regulatory Review Timelines for ANVISA: 2013–2016

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Abstract

Introduction

- Agency reviewers complete case studies using the **UMBRA benefit-risk framework and template** to enable a structured approach to benefit-risk

- Agency and its reviewers assess their implementation of quality decision-making using **QoDOS** to identify generally favorable practices

2016 – ANVISA accepted as a New Regulatory Member of the ICH. The implementation and adherence to ICH Guidelines by ANVISA is evaluated in a study facilitated by CIRS (ICH, 2021).

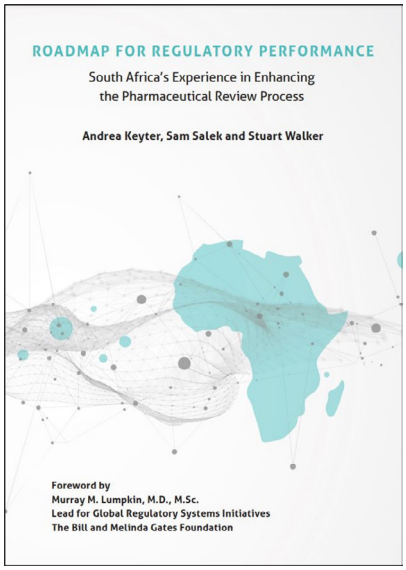
2017 – CIRS organises a Workshop for global regulators in Sao Paulo: "Facilitating the review of new medicines through risk-based evaluations: How can a stratification process be utilised to achieve an effective use of resources?" (CIRS, 2017).

2020 – ANVISA publishes data on its website regarding medicine approval, public assessment reports, and approval analytics (ANVISA, 2022).

2022 – CIRS collects data on ANVISA using its **Metrics tool** to collect information from the public domain. The initial analysis published by CIRS focuses on Orbis approvals showing the reduction in time to market (CIRS, 2022). CIRS initiates validation of the public data together with ANVISA, where the preliminary results show a reduction in median approval time for new active substances by 33% from 2017 to 2021.

Example 3: South Africa, SAHPRA

2004 – South Africa MCC regulators review **Metrics** initially assessed through CIRS Growth and Emerging Markets industry benchmarking study.



2016 – South Africa becomes an observer of ICH. The agency's implementation and adherence to Guidelines are evaluated through a study facilitated by CIRS (ICH 2021).

2018 – CIRS organises a Workshop for global regulators in Johannesburg: "Practical implementation of reliance models: What are the barriers and facilitators to the successful application of these models for innovative medicines, generics and variations?" (CIRS, 2018).

2019 – CIRS **Country report** and **Metrics Tool** are used to evaluate the South African review process. The tools offer recommendations for improved patient access to new medicines through timely registration (Keyter et al., 2019; 2020).

2020 – CIRS **Country Report** utilised to evaluate the SAHPRA processes for reliance and recommendations for the implementation of an abridged review process. Stakeholders develop a framework for reliance with a view to optimise regulatory review processes in South Africa (Keyter et al., 2020a).

2020 – CIRS **Metric tool** applied to evaluate overall approval timelines for new chemical entities and generic products registered by SAHPRA. The analyses showed a reduction of approval timelines by 68% for applications in the backlog that apply reliance models (Keyter et al., 2021).

2020 – Recommendations made to improve SAHPRA communication of BR decisions, using the **UMBRA Framework and Template** as a guidance for benefit-risk assessment and the basis of the South Africa public assessment report format.

2020 – CIRS supported PhD student Andrea Keyter publishes a **Roadmap** for regulatory performance in South Africa (Keyter et al., 2020b).

2021 – Agency reviewers complete case studies using the **UMBRA benefit-risk framework and template** to facilitate implementation of a structured approach to benefit-risk assessment.

2022 – South Africa attains WHO ML-3 for vaccine regulation and the agency implementation of Guidelines is evaluated in an ICH study undertaken by CIRS (ICH, 2021).

2022 – Comparison of ZaZiBoNa using the **Country Report** (Sithole et al.,2021a), followed by industry evaluation of the efficiency and effectiveness of ZaZiBoNa. Parallel evaluation by NRAs including SAHPRA using the **PEER questionnaire** (Sithole et al. 2022a, b) enabled an improved understanding of the performance of the ZaZiBoNa initiative and recommendations for the way forward.

Conclusion and next steps for interested organisations

The CIRS OpERA programme is focused on understanding and optimising the core activities an NRA undertakes as part of its medicines review process. On the other hand, the GBT is critically important in evaluating national regulatory systems of medical products. Therefore, OpERA tools help to identify or support practices in line with the WHO GBT.

Each of the OpERA tools described in this Briefing has been shown to support the goals of the WHO GBT as they specifically relate to the review process. The OpERA tools not only offer simple approaches that support regulatory system strengthening, they help build a culture of transparency and ongoing evidence-based process optimisation for which every NRA strives.

NRAs wishing to learn more about the OpERA tools, which are available at no charge to agencies, or would like to receive training or further support from CIRS on their completion, can contact CIRS, Dr Magda Bujar, mbujar@cirsci.org.

Confidentiality

We recognise that much of the data collected via CIRS OpERA tools will be highly confidential. CIRS has more than 30 years of experience in handling data provided by agencies. No country-identifiable or product-specific data or reports will go into the public domain or be shared with other authorities without the written permission of an NRA. Therefore:

- All information collected from individual agencies will be kept strictly confidential.
- No data that will identify an individual NRA will be reported or made available to any third party unless specifically agreed to in writing by the providing NRA.
- External reports or presentations of the data will include only anonymised information.

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About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. CIRS provides an international forum for industry, regulators, Health Technology Assessment (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 pharmaceutical products. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, special projects and grants.

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