CIRS R&D Briefing 91

Approaches to Implementing Regulatory Reliance – Considerations for Agencies

CIRS Centre for Innovation in Regulatory Science

Emphasising the indispensable role of regulatory reliance, this briefing highlights its importance as a strategic necessity for regulatory agencies seeking to ensure the efficient review of medicines.

Regulatory Risk-Based Review Routes in ASEAN countries, Saudi Arabia, and Australia

By examining agency regulations and guidelines, various strengths associated with the implementation of risk-based review routes within ASEAN countries and other key jurisdictions have been identified. Many challenges presented by the implementation of these pathways have also been highlighted, as have numerous enablers of their use.

Measuring the Impact of Reliance on Timelines, Efficiency, and Effectiveness

Risk-based reviews (reliance) can accelerate medicine availability and help to ensure resource usage is optimised. Examples and case studies demonstrate its efficiency and effectiveness in regulatory processes.

Key Considerations for a Roadmap to Implementing Regulatory Reliance

CIRS' roadmap and ten practical steps for agencies considering how to implement reliance into their frameworks. Successful implementation requires strategic planning, with a focus on internal alignment, external collaboration, and transparent practices.

Risk-based routes can augment the regulatory process and facilitate timely patient access to medicines. Flexible, scalable, and transparent reliance practices within regulatory frameworks are key to achieving this.

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Introduction

This briefing, developed by the Centre for Innovation in Regulatory Science (CIRS), delves into the increasingly pivotal role of regulatory reliance in the global pharmaceutical landscape. Reliance is defined by World Health Organization (WHO) as the act whereby the regulatory authority in one jurisdiction considers and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible, and accountable for the decisions taken, even when it relies on the decisions, assessments, and information of others (WHO, 2021).

Reliance is recognised as a crucial 21st-century tool in the timely approval of medicines, no longer a matter of choice but a strategic necessity for regulatory agencies worldwide. Based on CIRS' recent survey of agencies, 94% have unilateral reliance in place (32 across Africa, Asia, Latin America, and the Middle East). The benefits of reliance include optimisation of agency resource, accelerated review processes, more timely access to medicines, and enhanced capacity building, ultimately leading to more effective and efficient public health outcomes (CIRS, 2022).

CIRS has developed this briefing to support agencies in developing guidelines and implementing reliance. The findings are based on the experience and knowledge gathered through CIRS' global collaborations, multi-stakeholder workshops, and research. CIRS focuses on the approaches to implementing regulatory reliance together with the considerations for agencies, and aims to provide a comprehensive understanding of the following aspects:

- A comparative analysis of the approaches to reliance in five ASEAN countries (Singapore, Malaysia, Thailand, Indonesia, the Philippines), Australia and Saudi Arabia. The application of reliance in the aforementioned countries, detailing the criteria and characteristics of their respective models, highlighting similarities, differences, and potential strengths and weaknesses.
- Methods for assessing the impact of reliance, ensuring it contributes to timely, efficient, and effective processes in medicine availability.
- Strategic considerations and proposed methodologies for effectively implementing reliance, with a view towards future opportunities.
- Tailored commentary and recommendations for agencies, drawing from the broader findings to support initiatives in developing and implementing reliance guidelines.

Regulatory Risk-Based Review Routes in ASEAN, Saudi Arabia, and Australia: Strengths, Challenges, and Enablers

Background

National Regulatory Authorities (NRAs) within the Association of Southeast Asian Nations (ASEAN) have sought to embrace the concept of risk-based review to enhance their regulatory processes and facilitate timely access to high-quality, safe, and effective medicinal products. The 'Agency Comparison Tables for Abridged & Verification Review Pathways' (Appendix 1) provides a summary of the existing abridged and verification risk-based review routes in five ASEAN countries that have produced guidance or regulations for these pathways (Philippines, Indonesia, Thailand, Malaysia, and Singapore), and in two additional countries that conduct risk-based reviews and/or have regional significance (Saudi Arabia and Australia). An abridged review requires the product to have been registered by a Reference Regulatory Authority (RRA) and then a scientific assessment is carried out in relation to its use under local conditions and regulatory requirements, whereas a verification review, whilst also requiring registration by RRA(s), looks to validate the status of the product and ensure that the product to be marketed locally conforms to that authorised by the RRA. By summarising the risk-based review routes, including regulations, guidelines, target times, eligibility criteria, recognised RRAs, and documentation requirements, this analysis aims to provide a picture of the current regulatory risk-based review environment within these seven countries. Agency utilisation or participation for the WHO Collaborative Review Procedure (CRP) and the ASEAN Joint Assessment (JA) Procedure are also noted. Insight into common practices and the key elements of effective regulations and guidelines can assist agencies considering the implementation of these review types.

Method

To compile the summary tables, CIRS undertook a comprehensive review of publicly available information. This included an in-depth analysis of regulations and guidelines available on the agencies' websites. In addition, CIRS considered various publications, reports, briefings, and presentations (e.g., from CIRS, WHO) on risk-based reviews to ensure a broader understanding of the practical application and nuances of risked-based review routes. CIRS's proprietary regulatory review time databases were also used, where possible, to provide an indication of the routes' efficiency (timelines). The method was designed to produce a comprehensive overview of the formal risked-based review mechanisms in the selected countries, by focusing on the formal regulatory frameworks, and also by highlighting strengths, challenges, and enablers for the use of those pathways, based on the publicly available information. Understanding each country's approach to risk-based review can provide valuable insights to stakeholders concerned with the implementation of these routes.

Table 1 – Summary of Abridged Risk-Based Review Routes

Agency:	FDA	NADFC	TFDA	NPRA	HSA	SFDA	TGA	
Country:	Philippines	Indonesia	Thailand	Malaysia	Singapore	Saudi Arabia	Australia	
Route Name	Abridged	120WD	Abridged Evaluation	Abbreviated	Abridged	Abridged	COR-A	COR-B
Assessment Type	Abridged	Abridged	Abridged	Abridged	Abridged	Abridged	Abridged	Abridged
Target Time (Agency Time in Working Days)	45 wd	120 wd	New drugs: 180 wd Biologics: 200 wd Vaccines: 250 wd *	120 wd	180 wd	60 wd	120 wd	175 wd
Eligibility – New Chemicals	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Eligibility –Biologics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Number of RRAs	14	6	7	2	Not specified	2	7	7
RRAs‡	AUS; BEL; CAN; CHE; DEU; EU; FRA; ITA; JPN; NLD; SGP; GBR; USA	AUS; CAN; EU; JPN; GBR; USA	AUS; CAN; CHE; EU; JPN; GBR; USA	EU; USA	†	EU; USA	CAN; CHE; EU; JPN; GBR; SGP; USA	CAN; CHE; EU; JPN; GBR; SGP; USA

wd, – working days
RRA – Reference Regulatory Authority
*Priority review – New drugs: 150 wd; Biologics: 180 wd; Vaccines: 180 wd priority
†A competent drug regulatory agency, defined as "a national regulatory authority participating in WHO's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, and listed as such on WHO's website."
‡ISO 3166 three-letter codes (alpha-3)

Strengths

The implementation of formalised risk-based review practices across Indonesia, the Philippines, Malaysia, Singapore, Thailand, Saudi Arabia, and Australia strengthens the regulatory toolboxes of these countries, with benefits to patients, industry, and other key stakeholders (WHO, 2021). Each of these countries studied have defined target times and product eligibility criteria (Table 1). Whilst Malaysia, Singapore, Saudi Arabia, and Australia generally provide robust documentation requirements, those elsewhere could be considered less well-defined (Appendix 1 – Tables 4 & 5).

Challenges

Despite the aforementioned strengths, there are several noted challenges across the countries as well as divergences between them. Although divergences in regulatory frameworks and pathways are not an issue *per se* – as these are often justified by variances in local populations or conditions – differences between the pathways and requirements, and consequently the lack of harmonisation across agencies, present a challenge to applicants looking to submit a single dossier globally (CIRS, 2021). Consequently, it may be helpful for agencies to seek greater convergence and utilise a common set of definitions as well as best practices when implementing a reliance approach.

A key difference identified was a lack of certain risk-based review pathways. For example, the absence of a verification review process in countries such as Indonesia and Thailand – a route which could be considered a potential opportunity for resource optimisation – presents a divergence from the three other ASEAN countries studied, which all had a verification route in place. Data from CIRS' Growth & Emerging Markets Metrics Programme indicates a median review time for the verification route in Singapore that is 241 calendar days shorter than that of the abridged route, demonstrating that verification route could further expedite the approval of medicines compared to abridged.

Limited transparency on the scope of the review (i.e., the practical steps involved in reviewing the reference documentation and/or submission) particularly in countries such as Indonesia, Thailand, and Saudi Arabia, was also noted as a potential challenge for stakeholders, particularly applicants and patients seeking to understand how a decision was made (Appendix 1 – Table 7). Across the other countries studied, it was noted that information on the scope of the review was generally described at a high level only (e.g., Singapore – Abridged Review (Appendix 1 – Table 7)). WHO's Good Reliance Practices (GRelP) guidance highlights transparency and predictability in the practise of reliance as important in ensuring the principle of consistency is upheld by regulatory authorities (WHO, 2021).

Variability in the maximum number of years from RRA approval also existed between the countries. Notable differences may influence industry submission strategies. Narrow

windows between RRA approval and submission to the local market can encourage timely submission of new medicines, whilst also ensuring that product data in the information package has not changed, although it may present industry with resource challenges if different requirements exist across agencies.

Whilst there are many considerations that determine the RRAs accepted in each country, it can be seen as an area where divergence is common. Malaysia and Saudi Arabia, for example, are countries where the US FDA and EMA are the only accepted RRAs. By contrast, Thailand, and Australia each list seven acceptable RRAs. Although having fewer acceptable RRAs is not a weakness in and of itself – as a smaller pool could serve to increase the consistency of the review process – there may be instances where limited RRAs are a barrier to submission. The existence of agreements and processes to ensure that the relying agency is able to obtain the necessary information from RRAs is also a factor in the number that can be considered.

Requirements for unredacted assessment reports and full Questions &Answers (Q&A) document, although common and aimed at ensuring transparency and thoroughness, could also, at times, be a barrier to submission, particularly where access to these reports is problematic due to the confidential nature of information. WHO recommends that NRAs use Public Assessment Reports (PARs) as the primary sources of information for risk-based assessments. However, in practice, PARs are often stated as insufficient within the guidelines of the agencies studied, however it is noted that there are examples where an authority may consider accepting these reports if accompanied by redacted information and Q&A, and if the applicant has shown proof and effort to obtain unredacted versions (e.g., NPRA in Malaysia). Other authorities, such as SFDA, may accept redacted or edited reports if the redactions are unrelated to the quality, safety, or efficacy of the product. Guidelines stating that trade secrets, confidential commercial and financial information can be excluded from the submission (e.g., SFDA guidance) may help to alleviate intellectual property concerns when unredacted assessment reports are required.

Language barriers, while a common challenge when reviewing documentation and more generally in international correspondence, can also present a challenge for industry and the reviewers in utilising PARs. This factor, while not an obvious weakness in the countries studied, merits consideration when implementing risk-based reviews, due to the potential costs and challenges associated with translating documents into local languages.

Enablers

Clear, transparent, and up-to-date guidelines, with limited local requirements, and metrics are key enablers of risk-based reviews (CIRS, 2021). International collaboration and capacity building are also key enablers. Whilst conducting risk-based reviews does not reduce the need for regulatory capabilities, these can be enhanced via exposure to RRAs reviews and decisions, and also through exchanges and staff visits (WHO, 2021). The implementation of formal reliance routes does not mandate an all-or-nothing approach to their use.

Transparent metrics on the time taken for risk-based reviews versus full reviews are crucial for understanding the efficiency of these regulatory process, and then highlighting or improving their effectiveness. Acquiring metrics that separate agency from sponsor time in the review process, in order to compare an agency's time to their stated target, is a worthwhile albeit more ambitious goal.

The use of PARs, in line with WHO GRelP, can be another important enabler (CIRS, 2021). WHO advises NRAs aspiring to serve as RRAs to publish their PARs in a widely understood language, in order to document their regulatory decisions more clearly (WHO, 2021).

Finally, case studies could also serve as enablers by helping to build confidence across all stakeholders and by highlighting the practical benefits of these assessment routes for sponsors, regulators, and patients. Respondents to CIRS' agency survey on risk-based approaches to medicines registration, presented at CIRS' 2022 'Collaborative models for regionalisation, work and information sharing' workshop, indicated a desire to understand how these reviews are conducted in practice – particularly by authorities with strong regulations – and for agencies to share their experiences of implementation (CIRS, 2022).

Measuring Impact of Reliance on Timelines, Efficiency, and Effectiveness

Background

WHO encourages NRAs which have implemented risk-based pathways to measure the impact of reliance by establishing metrics related to regulatory decision-making (WHO, 2021). These metrics can include review times, the number of products reaching the market, costs saved, and redirection of resources to areas of higher regulatory risk. While the idea of monitoring the effects and benefits of reliance is important, such analyses are not generally undertaken by agencies (McAuslane et al., 2023). However, quantitative, or qualitative metrics may be helpful to agencies to determine the extent to which these pathways are beneficial, thereby enabling agencies to measure success when implementing reliance. Such information could provide support for identifying areas where reliance may be most applicable and assist agencies in amending, and subsequently optimising, their risk-based processes as they move forward.

Although a set of formalised measures for evaluating the impact of reliance currently does not exist, a number of measures have been identified (Figure 1) based on outcomes from CIRS' research and multi-stakeholder workshops. These metrics have been applied within agencies, as demonstrated by the examples and case studies below. It should be noted that the relevance of such measures will depend on the type of reliance pathway used by an agency and what the goal of the pathway is. In addition, quantifying the impact of regulatory reliance on public health, economic health, agency efficiency, and resource utilisation is currently limited (Liberti et al., 2023), however it would help to further strengthen the case for implementing reliance and demonstrate the value of this regulatory approach to the wider community.

1. Availability of medicines

- Regulatory review time
- Submission time to market
- Overall time to availability
- Response time to health emergencies
- Public health, life expectancy

2. Agency resource and workload

- Number of products approved with same resource pool
- Workload and resource availability
- Backlog of applications
- Reviewer cost (time spent on review vs cost to train reviewers)
- Operational cost of NRA (e.g. facility, HR)

3. Agency critical thinking

- Knowledge and capabilities of reviewers internally resulting in a better quality of review
- Number of questions, number of cycles of questions and quality of review

4. International collaboration

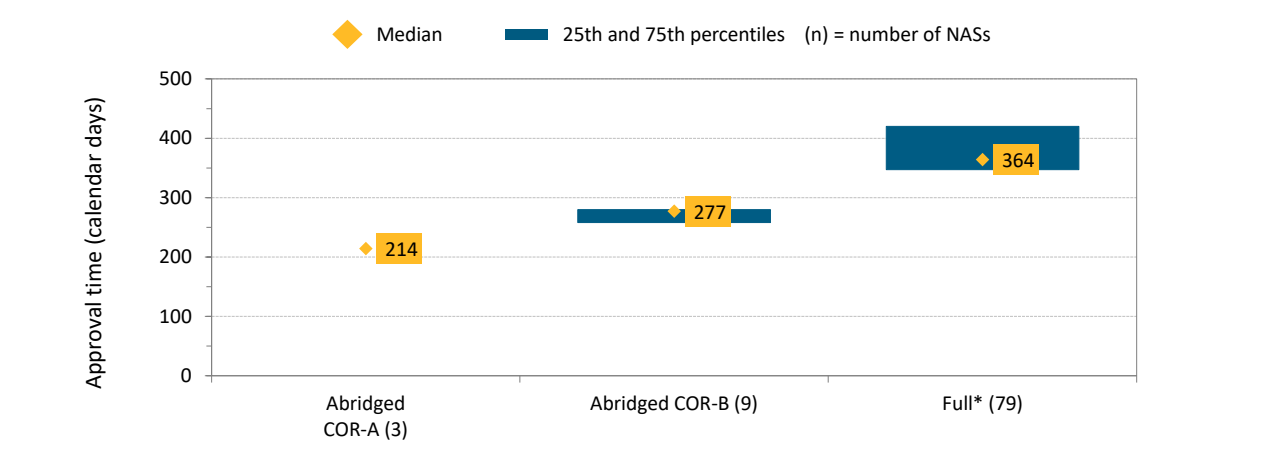
- Access to external expertise (academic, commercial, other agencies)
- Degree of alignment/uptake of international standards
- Surveillance – degree of reliance on inspections for clinical/manufacturing
- Number of partnerships established through MOUs etc. with other agencies

Figure 1 – Potential measures to evaluate the impact of regulatory reliance

Measures – Examples & Case Studies

1. Availability of medicines

An analysis of the two abridged reliance review pathways from the Australian TGA (Figure 2), based on data obtained from the public domain, demonstrates that the two pathways, COR-A and COR-B are associated with faster review timelines compared to the full review pathway, as demonstrated by the median review timelines. In line with the agency target guidelines, the COR-A pathway was faster compared to COR-B when comparing new active substances approved 2018–2022. The review timelines for the abridged pathway were also more predictable compared to the full review pathway, based on the variance shown by the 25th and 75th percentiles. All in all, this analysis shows that a reliance review can speed up the regulatory review, thereby ensuring an efficient process and thereby increasing the timely availability of medicines.



Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. For COR A no variance (25–75th percentiles) are shown as there are <5 NASs

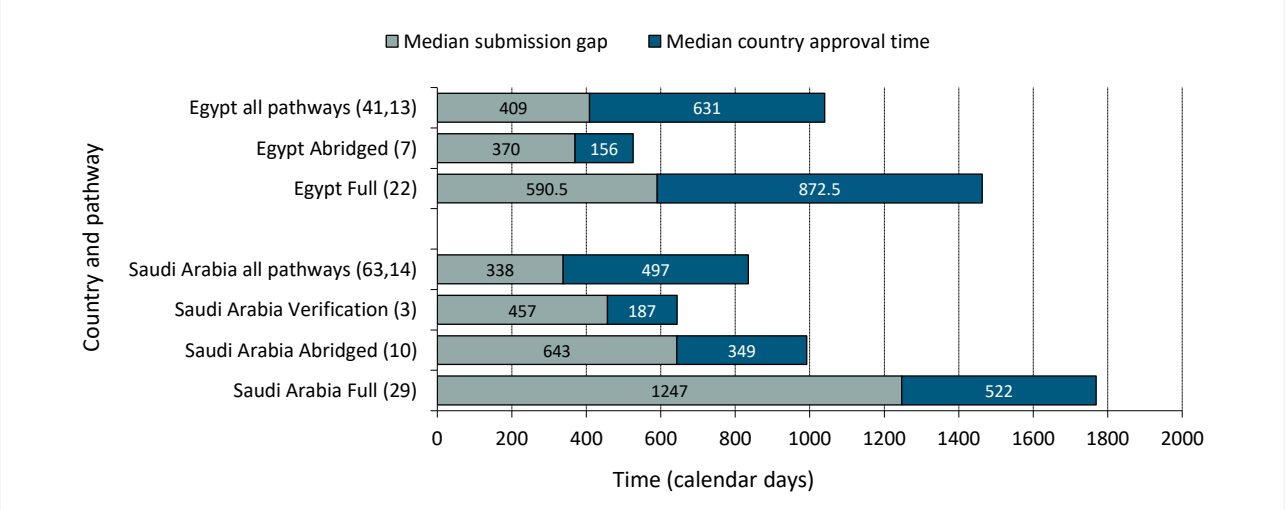
**Standard = non-COR-A or COR-B approvals*

Source: CIRS 6 agency Briefing 88; data obtained from the public domain

Figure 2 – Australia (TGA) – approval time for new active substances approved 2018–2022 – COR-A and COR-B versus full review

An evaluation of reliance review pathways from Egypt and Saudi Arabia (Figure 3), based on data obtained from the industry (CIRS Growth and Emerging Markets Metrics Programme; CIRS, 2023a), similarly demonstrated the positive impact of reliance on the regulatory review timelines for the two agencies based on the median times shown for the abridged and abridged/verification procedures respectively. In addition, reliance was also associated with a shorter submission gap from first world submission. This may be explained by a number of reasons: the requirement from the agency that there is a maximum number of years from reference agency approval, alignment in requirements between reference and relying agency enabling a more efficient submission process, or company strategy.

The final example is the South African regulatory authority, which has implemented reliance in order to tackle the agency's backlog of applications (Figure 4). This was enabled through a revised legislation that ruled reliance and work-sharing practices permissible. By December 2022, the inherited application backlog had been successfully cleared by the agency. The timelines evaluated demonstrate that the median scientific review time was shorter for clinical data assessed in an abridged manner through reliance compared with that via the full review pathway for new chemical entities approved 2019–2022. In addition, the timelines for approval of applications in the backlog stream were 68% quicker for both new chemical entities and generics, using facilitated regulatory pathways, such as abridged and verification review models (Keyter et al., 2021). Consequently, this has enabled a timelier availability of medicines in South Africa through the resolution of backlog.



Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. Submission gap is calculated from date of first market approval to date of submission to the country (Egypt/Saudi Arabia)

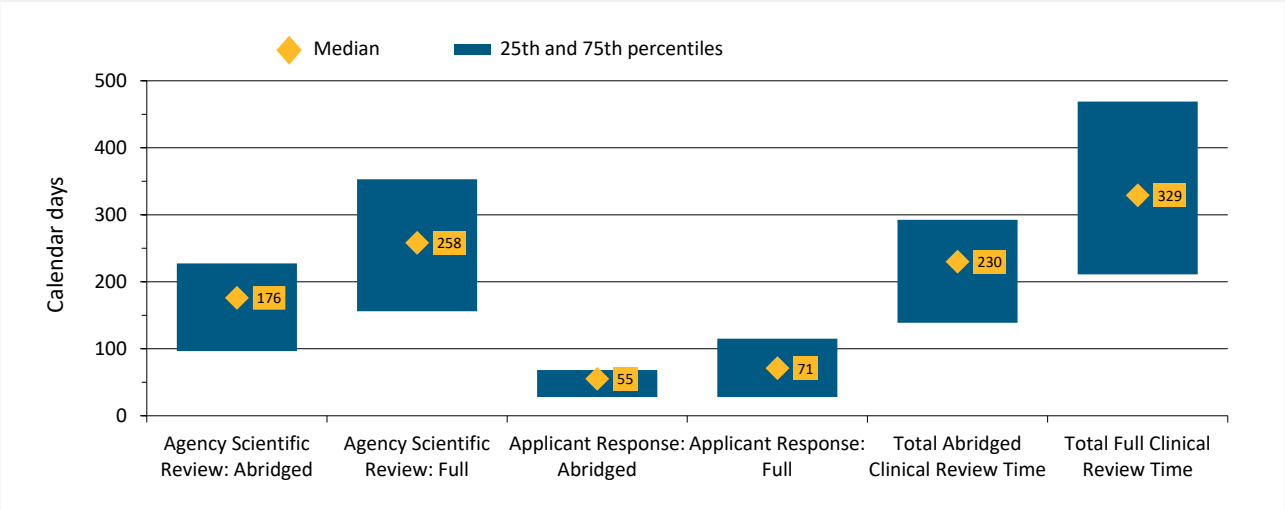
n in bar = median number of days; (n1,n2) = number of NASs, number of companies

NASs included in this analysis include those with first world submission, first world approval, application submission and application approval dates only. If n1 is less than 5 or if n2 is less than 3, data is not shown.

All pathways = abridged + full

Source: CIRS Growth and Emerging Markets (Industry) Metrics Programme

Figure 3 – Egypt and Saudi Arabia – time to roll out for New Active Substance (NASs) approved 2017-2021 – all pathways, versus abridged/verification and full



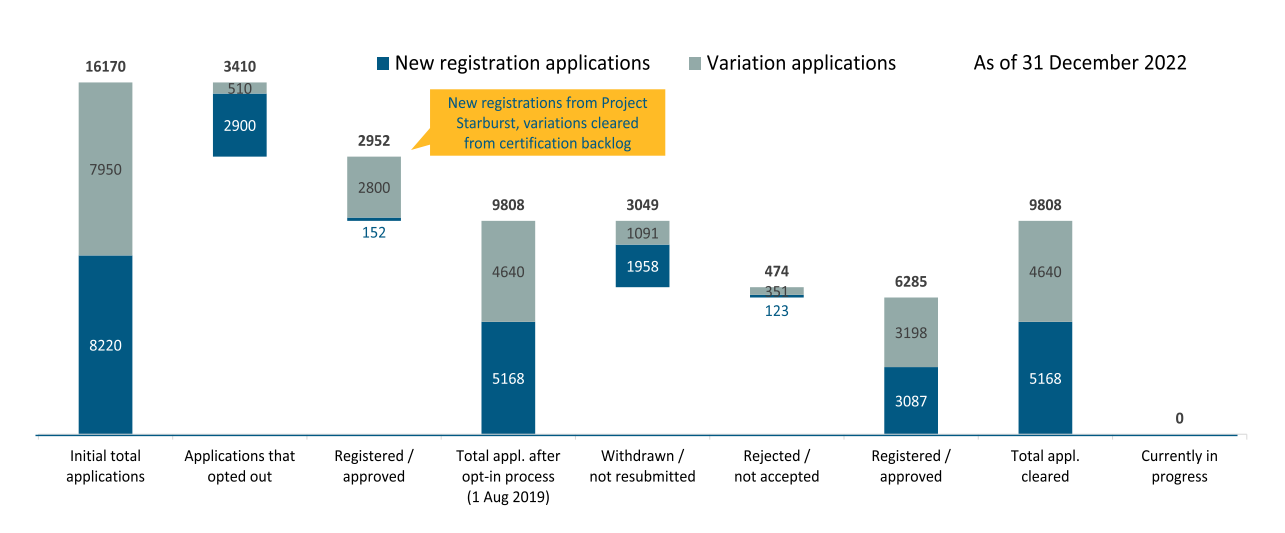
Source: https://cirsci.org/publications/posters/evaluation-of-the-impact-of-reliance-on-the-regulatory-performance-in-the-south-african-health-products-regulatory-authority/

Figure 4 – South Africa: clinical review times (agency and applicant time) for new chemical entities approved August 2019 to December 2022 – abridged versus full review

Finally, it should be noted that CIRS has been benchmarking NRAs since 2002 using a methodology developed with agencies (Hirako et al., 2007). The CIRS Metrics tool, which is available to agencies, 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 (CIRS, 2023b).

2. Agency resource and workload

The new re-engineered regulatory processes, now including a reliance pathway, contributed significantly to the full clearance of the backlog of product registrations at the South African agency (Figure 5), both for variations and new product registrations. These approaches have already been deployed in other core business areas within SAHPRA since then. The reliance pathway allowed the agency to avoid duplication of regulatory effort and to conserve limited resources by not needing to conduct a full review of the data submitted to support the application for market authorisation.



Source: https://www.sahpra.org.za/wp-content/uploads/2022/12/MEDIA-RELEASE-Backlog-Clearance-02-December-2022.pdf

Figure 5 – SAHPRA backlog resolution – application backlog reduced by 100% to date

In the cases of verification and abridged reviews, SAHPRA necessitated that applicants obtain consent from the reference NRA to allow SAHPRA access to full un-redacted assessment report for the registered product. A redacted version, from publicly available sources, would be obtained when the un-redacted report was unobtainable. The redacted report would be deemed acceptable provided it contained the scientific data essential for informed regulatory decision-making (Keyter et al., 2021).

Agency approach (SAHPRA, 2022)

> *"The South African Agency appointed a total of 113 assessors to review applications for market authorization, of whom 57 were allocated to review applications for business-as-usual (BAU) only. The primary scientific assessment was followed by a peer-review, conducted by a second assessor. Expert committees were used in the review process in an advisory capacity. The clinical and quality expert committees were engaged in the BAU review process while only the clinical expert committee participated in the BL review."*
>
> *"The learnings from the Backlog Clearance Project have been shared not only within the South African regulatory agency, but further afield in Africa, where numerous NRAs are battling their own application backlogs. Expedited, streamlined regulatory processes and outcomes translate into improved access to quality, safe and effective medicines, which is ultimately the mandate of every NRA."*

The review of assessment reports will dictate the resource needed for the review, depending on to what extent the agency will check for completeness, review the reference agency information, or undertake their own critical review. The WHO recommends that NRAs use PARs as the primary sources of information for risk-based assessments. However, relying agencies are often challenged by the redacted nature of PARs regarding safety, quality or efficacy. In addition, it should be noted that in addition to PARs, other documents are important to support reliance decision making, such as the marketing authorisation application (MAA) dossier provided by the applicant, the Certificate of Pharmaceutical Product (CPPs), and/or the unredacted assessment reports (UARs) from the reference agency. This additional documentation can be utilised by the relying agency to refer for any clarifications to further understand the information that was considered by the reference agency.

3. Agency critical thinking

Respondents to a 2022 CIRS agency survey on risk-based approaches to medicines registration (CIRS, 2022) – where 32 agencies participated from Africa, Latin America, Asia, and the Middle East – indicated that the top perceived incentive/benefit for agencies to undertake a unilateral reliance review was efficient/effective use of resources (79% agencies), as well as faster availability of medicines (79%) highlighting the importance of the two measures described above. In addition, 59% of the agencies believed that reliance built regulatory capacity through improved agency knowledge and experience, demonstrating the importance of measuring any changes in agency critical thinking as a result of implementing reliance and collaborating with more experienced agencies. The improvement in agency critical thinking could also be measured by assessing the quality of the review as well as decision making of the reviewers before and after the implementation of reliance.

This could be evaluated through a number of metrics e.g., by assessing the number of rounds of questions throughout the review; the quality of the questions; the transparency and consistency of the review; the quality of the communication between the agency and the sponsor during the review; the quality of agency decision making. CIRS tools (CIRS, 2023b), such as quality scorecards as well as quality decision-making practices, could be utilised for this purpose.

4. International collaboration

International collaboration is both seen as an enabler and an outcome of regulatory reliance. This has been highlighted by the Brazilian regulatory agency, which has recently implemented reliance but also became a Regulatory Member of ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) and PIC/S (Pharmaceutical Inspection Co-operation Scheme) (DIA, 2023):

> *"ANVISA has also realized the benefits of increased engagement in international regulatory cooperation and convergence processes. By participating in forums like ICH and PIC/S, ANVISA has become experienced and familiar with the best practices of more mature regulators. This not only facilitated adoption of some of these practices in Brazil but also increased ANVISA's trust in other regulatory organizations, enabling the agency to recognize the value of reliance as a tool to strengthen regulatory practices that can also be applied to different regulated products."*

Conclusion

Assessing the impact of reliance is key to ensuring it is working efficiently and effectively. Metrics have been identified – e.g., availability of medicines, workload, resource, critical thinking, collaboration – and their application in regulatory agencies has demonstrated the positive effect of reliance on these outcomes. Development of additional measures as well as case studies, for example focusing on the economic impact of reliance, will be key to further strengthen the case for implementation of reliance by agencies. Additional resources, which can be used to support the evaluation of reliance impact or implementation of reliance, have been summarised in the next section.

Example Resources for Agencies Implementing Reliance

WHO's Good Reliance Practices (GRelP) Guidance – This document by the World Health Organization offers guidance on the principles and practices of regulatory reliance, emphasising transparency, predictability, and consistency in agencies' processes.

CIRS R&D Briefing 82 – Regulatory reliance pathways: what are the opportunities and barriers? – This briefing explores the various aspects of regulatory reliance, including its application across different stages of the medical product lifecycle. It offers insights into how NRAs can use reliance to conserve resources, build expertise, and enhance the quality of regulatory decisions. The briefing also discusses the return on investment for using reliance pathways and identifies potential barriers and areas for improvement.

South African Regulatory Authority: The Impact of Reliance on the Review Process Leading to Improved Patient Access: This paper provides a detailed case study on how the South African Health Products Regulatory Authority (SAHPRA) has implemented reliance in its review process, demonstrating the practical benefits and challenges of such an approach.

Reliance-Based Regulatory Pathways–The Key to Smart(er) Regulation?: This article discusses the use of reliance pathways, including the exchange of inspection reports and joint assessment programs like Project Orbis. It emphasises that reliance is not outsourcing decision-making but a tool for informed decision-making, highlighting its benefits for regulatory agencies and applicants.

Webinar: Enabling the use of regulatory reliance in the Americas: This webinar was held by the Pan American Health Organization (PAHO) to promote the exchange of information and experiences towards greater regulatory convergence in the Americas. It was organised by the Pan American Network for Drug Regulatory Harmonization (PANDRH), and aimed to identify opportunities, discuss the key outstanding obstacles, and recommend a path forward to expand the use of reliance.

Regulatory Reliance Principles: Concept Note and Recommendations (Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH): The paper's primary objective is to present essential examples and principles of regulatory reliance. It continues discussions from the 2016 Pan American Network for Drug Regulatory Harmonization (PANDRH) Conference and addresses a recommendation from that same conference for PAHO to create a concept paper on reliance. The paper incorporates global perspectives, including recent inputs from the World Health Organization (WHO). Its overarching aim is to enhance understanding among PANDRH stakeholders about reliance, to improve the application of this concept.

DIA Europe 2023 Pre-Conference Workshop Report: This report summarises the outcomes of a workshop focusing on regulatory system innovation through collaboration and reliance.

It highlights how the COVID-19 pandemic has spurred increasing cooperation among regulators and discusses the harmonisation of requirements towards global standards. The workshop also addressed key issues that are important enablers for regulatory reliance, such as global dossier submission, management of post-approval changes, and ensuring product sameness.

Relianomics: A proposed framework for the assessment of the societal, economic and efficiency impacts of regulatory reliance pathways: This paper, and the analysis within, seek to lays the groundwork for 'relianomics', a proposed concept defined as "a structured framework for the assessment of the impact of regulatory reliance pathways on regulatory, economic, societal, and other systems".

Key Considerations for a Roadmap to Implementing Regulatory Reliance

Background

The principles for good reliance have already been identified by the WHO (WHO, 2021), however, it may not be clear to agencies still how to practically implement reliance, what may be some of the considerations as well as a possible steps in this process.

Based on findings from CIRS Workshops, work with agencies as well as research, CIRS has developed the following roadmap and ten practical steps (Figure 6) that may be helpful to agencies when considering how to implement reliance into their frameworks.

It should be noted that the roadmap's steps are not exhaustive – other documents and steps require consideration to ensure an effective and efficient process is in place.

Comments Regarding the Roadmap

Importantly, before beginning the process of implementing reliance, the regulatory agency has to determine if its current law needs to be modified to ensure that reliance can be implemented. This may need to be modified before reliance can be enacted.

Steps 1–3: Describe the importance of ensuring internal alignment and education, as well as external collaboration with agencies, and ensuring trust-building activities during the process of implementing reliance.

Steps 4–7: Outline the necessary steps to put in place a process for reliance – here WHO good reliance practices (WHO, 2021), good review practices as well as implementation of other structured frameworks (e.g., benefit risk) will be key to ensuring best practice. For the criteria/requirements for reliance (e.g., reference agency selection, documentation requirements, depth of review) – consider those outlined in the comparative tables (in Appendix 1 and described in the first section of this report).

Steps 8–10: Describe considerations once a reliance process has been implemented, e.g., for training and measuring the impact of reliance through metrics, to ensure reliance is working efficiently and effectively. The measures outlined in the previous section of this document could be applied for the purpose of evaluating how well reliance is working. Feedback from stakeholders and reviewers is important to ensure input and iteration on best practice.

Finally, it should be noted that documentation by the agency of these various implementation process steps will be key to ensure transparency and to support a feedback loop to ensure improvements to the process can be made.

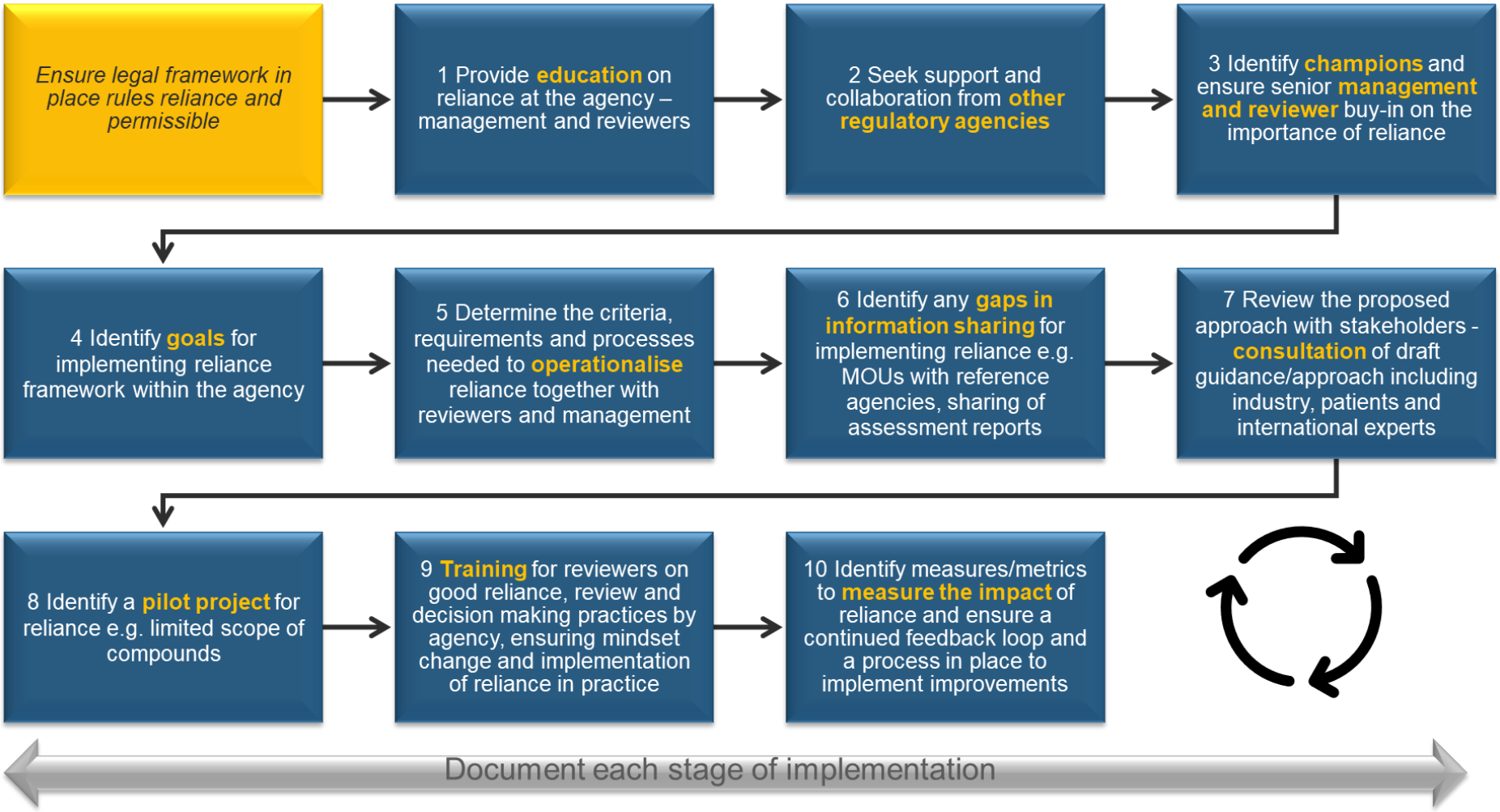


Figure 6 – Key Considerations for a Roadmap to Implementing Regulatory Reliance

Conclusion

Agencies around the world, regardless of their maturity level, have been actively implementing reliance approaches as part of their toolkit. Reliance should be regarded as a regulatory enabler as it helps facilitate timely access to important medicines, enables optimal use of available resources regardless of the application type and frees up capacity to focus on value-add activities. Importantly, it should be noted that reliance preserves sovereignty of decision making by the agency and does not compromise safety, efficacy, or quality of products.

The implementation of formal reliance routes does not mandate an all-or-nothing approach to their use. Even modest levels of reliance can deliver resource savings, while also allowing agencies to experiment, learn, and adjust accordingly their processes to find a balance that suits their needs and capabilities. Reliance should be scalable and adaptable, allowing agencies to start small and increase its use. Agencies should look to adapt and improve their process as they become more comfortable and proficient in the use of risk-based reviews. This flexible approach recognises that a degree of reliance, even if limited, is preferrable to an agency conducting non-value-added review activities.

Agencies looking to implement reliance should consider findings from this report, particularly the roadmap proposed. Furthermore, CIRS can support agencies in implementing reliance with educational seminars and by providing regulatory and performance measurement tools. The tools can be used to define and measure regulatory practices and processes for the review of medicines.

Sovereignty dictates that each NRA must define their own strategy for an appropriate risk-based approach for reliance, as they are ultimately responsible for their own decisions irrespective of the depth of reliance used. In addition, when implementing a reliance approach, agencies should look to collaborate and build trust with other agencies in the region, as well as with more experienced agencies. Agencies should consider reviewing and adopting WHO Good Reliance Practices, implementing training, and ensuring participation in international regulatory harmonisation and convergence initiatives such as ICH.

It is important for the agencies to also ensure that reliance practices and processes are transparent and measurable, by setting up appropriate internal metrics and getting feedback from internal and external stakeholders. This can help ensure that reliance is supporting the efficiency and effectiveness of regulatory review processes and enabling timely availability of medicines globally.

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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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