

New ways of working - enabling patient access through reliance or regional review models

28-29th February 2024
Sao Paulo Airport Marriott Hotel,
Sao Paulo, Brazil

WORKSHOP REPORT



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Report details

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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' mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and health technology assessment (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. 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 and grants.

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Section 1: Executive Summary

Background to the workshop

Faced with increasingly complex technologies and novel evidence generation techniques, regulatory agencies are being challenged to work in new ways. There is pressure on them to be agile and effective in their processes and more efficient with their resources. Risk-based approaches – including collaborative reviews, work sharing and reliance - are now considered an important part of the regulatory toolkit to facilitate timely patient access to medicines.

While risk-based approaches are well-developed concepts for agencies, how to implement these in practice is not always clear. Companies can also face challenges when taking up risk-based pathways, such as difficulties obtaining unredacted assessment reports from reference agencies and a lack of global alignment on the definition of product 'sameness'.

Several collaborative review initiatives are being piloted or implemented by regulatory agencies around the world. The Caribbean Community (CARICOM) and the Central American Mechanism for the Joint Evaluation of Medicines are collaborative processes in Latin America, though the Caribbean regional process faces notable challenges, and the Central American Mechanism is still in early stages. Learning from the experiences of these processes, initiatives such as the ACCESS Consortium and Project Orbis, and regional reliance models, e.g., in Africa, could help to identify best collaborative practices globally, as well as to advance more collaborative models across Latin America.

In this workshop, CIRS brought together senior representatives from regulatory agencies, pharmaceutical companies and academia from 18 countries across the Americas, Africa, Asia and Europe, to examine risk-based approaches in more detail. The aim was to identify what is needed for risk-based approaches to work effectively and efficiently, incorporating lessons learned from the various models being implemented around the world.

Workshop sessions

This multi-stakeholder workshop consisted of a series of presentation sessions, panels and three parallel breakout discussions. Presentations explored the current global landscape of risk-based models, learnings from unilateral reliance models, implementing good reliance practices, leveraging information from reference agencies, facing internal barriers to reliance, and learnings from regional and trans-regional risk-based models.

The breakout groups were asked to discuss and develop recommendations on three topics:

- **Regional collaboration** – What are the key considerations or frameworks that enable the construction and delivery of an efficient and effective regional/trans-regional model?
- **Changing mindsets** – How can this best be achieved within companies and agencies to enable reliance and collaborative models?
- **Good collaborative practices** – What needs to be in place in companies and agencies to move from principle to implementation?

Venue/format

The workshop was held in person in Sao Paulo over two days, 28th and 29th February 2024.

Key points from presentations and open-floor discussions

Agencies are implementing different risk-based models

CIRS is undertaking research studies, providing tools and enabling dialogue to support agencies and companies in moving from concept to practical implementation of risk-based approaches. A CIRS survey of regulatory agencies in [2022](#) showed that many agencies around the world are implementing these approaches as part of their toolkit, and often, they have more than one risk-based model as 'one size does not fit all'. Another CIRS study that characterised company experiences when using reliance pathways in Latin America found heterogeneity in the way that agencies in the region apply reliance. Certain agencies appeared to be leading the way in terms of transparency and consistency, so there may be an opportunity for cross-regional learning of best practices.

Unilateral reliance approaches, where an agency relies on a reference agency assessment, have been implemented in many countries, including Brazil and South Africa. Both countries were faced with backlogs of applications, increasing numbers of submissions and capacity challenges. Unilateral reliance has helped to alleviate the backlogs for certain types of applications and reduce assessment times in comparison to full reviews. Lessons learned include the need for continued monitoring of the review process and timelines with metrics, implementation of good review and reliance practices, as well as conducting pilot studies and receiving feedback from companies on their experience with the reliance pathway.

Going beyond good principles to good practice

The [World Health Organization \(WHO\) Good Reliance Practices](#) are strongly linked to the [WHO Global Benchmarking Tool \(GBT\)](#) that evaluates regulatory systems. Therefore, understanding and adhering to GBT standards including regulatory harmonisation, competence and continual improvement are key to implementing reliance.

In Malaysia, various forms of regulatory reliance have been used for over 20 years, but it was not until 2019 that the first formal facilitated pathway using a full reliance and risk-based approach was implemented. Since then, the Malaysian agency has established tools and practices to facilitate risk-based approaches, such as a dossier checklist for applicants to communicate the similarity of submitted datasets, internal standard operating procedures and report templates, internal training, dialogue meetings with external stakeholders and strengthening post-market activities. These activities have helped the agency to learn how other agencies deal with certain issues and to build trust in other agencies' reports.

Steps are being taken towards the application of unilateral reliance in several countries of Latin America, including Ecuador and Peru. However, there are still significant areas for advancing regional collaboration. Opportunities include formalising agreements between agencies to enable information exchange, contributing to the updating of Pan American Health Organisation (PAHO) documents and periodic training of staff. Management staff in particular need to be actively supportive of applying reliance at the regional level.

Overcoming internal barriers

Agencies often face resistance to reliance internally, which may be linked to cultural issues, such as perceptions that professional skills are being undermined and jobs could be lost. In the Australian experience, support for reliance was increased internally by implementing both top-down and bottom-up approaches. From the top, it was emphasised that reliance is a formal government policy, debated and passed in Parliament, and is about improving public health rather than reducing resources. Reliance 'champions' were introduced to emphasise the benefits to patients and regulators, and opportunities were given to build confidence in other regulators such as joint meetings and secondments.

Companies also face internal barriers to reliance, which can relate to systems and digitalisation; capacity and capability; enterprise strategy and cultural aspects. For example, there can be issues with resource allocation to support additional documentation provision and coordination linked to reliance. Capacity building and education are needed to align expectations and change mindsets within companies. External factors such as lack of alignment on the definition of product sameness, multiplicity of market-specific requirements and difficulties obtaining and sharing unredacted assessment reports, also cause internal issues for companies.

Assessment reports have value, but a common template is needed

CIRS has been working with agencies and companies to facilitate the implementation of reliance by assessing the [use of assessment reports and documents](#). Studies have highlighted that public assessment reports (PARs) contain a high proportion of reliance-relevant information, however, they do not seem to be used by relying agencies. Non-public documents are often required to demonstrate the sameness of the product and understand the decision made, but are not easily obtained. Challenges around the availability, clarity, format and completeness of assessment reports remain. Potential solutions include improved communication channels and information-sharing platforms; harmonised definitions and assessment report templates; and mindset change through training.

In addition to being used for reliance, assessment reports have a role in helping to build capacity and capability within a relying agency, as they allow assessors to learn best practices from reference agencies. Building capacity and enhancing regulatory practices are important steps for agencies looking to one day become a reference agency themselves.

Regional approaches to risk-based evaluation

There are several types of risk-based approaches being implemented on a regional level. The success of the European Medicines Agency (EMA) Centralised Procedure is based on the political and economic framework of the European Union (EU), as well as the advancement of regulatory harmonisation, transparency and trust between Member States over the last 60 years. The African Union is also considered a success factor in the regional harmonisation initiatives that facilitate reliance and work sharing between agencies in each African regional economic community. However, for these efforts to remain sustainable, the regional initiatives need resources such as reference materials and workforce strengthening. Work is ongoing to develop a continental reliance framework for the African Medicines Agency (AMA), which will make recommendations to countries that have ratified the AMA Treaty.

Looking beyond regions, Project Orbis is a collaborative review procedure spearheaded by the US Food and Drug Administration (FDA) Oncology Center of Excellence that allows concurrent submission and review of oncology products among eight agency partners. Project Orbis has demonstrated many tangible benefits, a key one being earlier product approvals for patients; however, this has presented challenges for the partnering agencies, such as keeping up with the short review timelines. Some companies have also experienced difficulties coordinating questions and requests from several different Project Orbis partners.

The ACCESS Consortium offers a work sharing process, where participating agencies review different parts of the dossier but make their own independent decisions on the application. There are several advantages of such a procedure, including increased agency efficiency and a shorter submission gap, although it can be challenging to build trust and coordinate between agencies. The ACCESS process is thought to be successful because it is a collaborative effort of like-minded agencies, based on a foundation of respect, transparency, flexibility and equality, and the premise that each agency has something to offer to the other members.

A digital future

From a company perspective, the future of collaborative review lies in building a dynamic Cloud-based ecosystem where one product, from multiple manufacturing sites, can be submitted and shared for review by multiple agencies, upholding data security and protection. Information would be available in real time so agencies can see the progress of review processes and make an approval very quickly once there is reference country approval.

Learnings and next steps for Latin America

Unlike Africa and Europe, Latin America has no overall political or economic union. This means there is an additional hurdle to bringing all countries together as a common market attractive to industry. Nevertheless, several initiatives could lead to partial collaborative processes, including the Pacific Alliance (Chile, Colombia, Mexico and Peru), Southern Cone (Brazil, Argentina, Chile, Uruguay and Paraguay) and the Andean Pact (Colombia, Ecuador, Peru and Bolivia). There are examples of like-minded agencies working together and building collaborative initiatives without political union, such as the ZaZiBoNa initiative in the South African Development Community (SADC) and the ACCESS Consortium. Perhaps by identifying other like-minded agencies, who may not necessarily be geographically close, agencies in Latin America could start to formalise regional and trans-regional collaborations for implementing risk-based approaches.

It is important that agencies remain interested in regulatory harmonisation and convergence. For example, the Brazilian Health Regulatory Agency (ANVISA) has put a lot of effort into adopting guidance from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and is now preparing for WHO GBT assessment. Smaller, less mature agencies, however, may need more resources to work towards harmonisation and convergence, as well as more opportunities to learn from more mature agencies. Defining the maturity level of different agencies in Latin America is an important step to understanding what an integrated regional collaboration may look like.

While backlogs are often blamed on agencies, companies also contribute to the issue in some Latin American countries where there is a tendency to 'join the queue', by submitting an incomplete dossier. This needs to be avoided, and as with any region, companies must work with good submission practices in mind, communicate clearly and be transparent.

For some Latin American agencies, the lack of financial and technical independence from their governments may be a barrier to implementing risk-based approaches. Strong leadership from agency heads, improving internal processes and gaining government support could help Latin American agencies to adopt such approaches.

Recommendations from breakout discussions

Regional collaboration

Recommendations for further work to enable the construction and delivery of an efficient and effective regional/trans-regional model include:

- Define criteria for determining 'like-mindedness' and measure this across agencies.
- Characterise the strengths needed for agencies to collaborate with each other.
- Conduct a landscaping exercise to better understand how agencies are using Memoranda of Understandings (MoUs) to facilitate collaboration.
- Investigate a shared risk-benefit model.

- Map out the capabilities of different agencies based on information from the WHO GBT and List of WHO-Listed Authorities.
- Conduct research studies comparing target vs actual timelines for work sharing and regional review pathways.
- Measure local timelines for work sharing, priority and standard pathways.

Changing mindsets

Recommendations for further work to enable mindset changes in companies and agencies to support the use of reliance and collaborative/workshare models include:

- Develop an overarching roadmap for reliance based on previous CIRS workshops and research, including steps on how to change mindsets.
- Expand the WHO Good Reliance Practices document to include guidelines for implementing reliance for both relying and reference agencies, with support from ICH.
- Develop a database of reliance and work-sharing resources.
- Establish a data-sharing platform between regulators and sponsors.
- Examine the 'sameness' concept in more detail to facilitate alignment on the definition of sameness. For example, if the full dossier is not available, in which instances could certain information be accepted based on the product's degree of identity? Which sections of PARs can allow verification of product sameness?
- Compare PARs and unredacted reports - is the additional information sufficient for agency decision making or not?
- Standardise PARs from reference agencies.
- Agencies should offer a pre-submission process/meeting to help clarify if companies have the right information to submit via a reliance route.
- Reference agencies should become aware of the extent that other agencies are relying on their decisions and offer training and access to the required documentation to enable good reliance practices.

Good collaborative practices

Recommendations for further work to facilitate the implementation of good collaborative practices in companies and agencies include:

- Examine how assessment reports are developed, who is using them and how they are being used.
- Harmonise assessment reports to facilitate review across agencies.
- Develop a framework that shows reviewers how they should undertake reliance.
- Improve agencies' transparency on the reasons for accepting or rejecting reliance requests.
- Conduct research comparing life cycle management products that have undergone reliance vs non-reliance pathways.
- Develop an IT tool/data-sharing platform that is secure and easy to use.
- Survey how agencies are implementing good review practices, including which requirements are being addressed, and develop a document outlining best collaborative practices.
- Conduct a study on the barriers that impede the entry of products into the market – what are the causes? Is it a matter of pricing or access?
- Agencies with established reliance processes should facilitate training for agencies with less experience.
- Companies should provide unredacted assessment reports and Q&A documents to facilitate review.

Workshop Programme

Please note, affiliations are stated as they were at the time of the meeting, 28th and 29th February 2024.

Day 1: 28th February 2024

Session 1: Embedding a unilateral risk-based model as part of the modern agency's regulatory toolkit – moving from concept to implementation to best practice	
09:00	<p>Co Chair's welcome and introduction Dr Lawrence Liberti, Director of the D.K. Kim International Center for Regulatory Science and Associate Professor of the Department of Regulatory and Quality Sciences, University of Southern California</p> <p>Balbiana Sampaio, Chief Advisor, Agência Nacional de Vigilância Sanitária (ANVISA), Brazil</p>
09:05	<p>Country welcome and introduction Balbiana Sampaio, Chief Advisor, ANVISA, Brazil</p>
	<p>Current implementation of risk-based models of review - insight into the changing regulatory landscape <i>Overview of outputs from CIRS surveys and research studies focusing on reliance, its implementation and ways of measuring the impact.</i> Dr Neil McAuslane, Director, CIRS</p>
09:25	Discussion
	<p>Risk-based approaches to the evaluation of new medicines: utilisation of a unilateral model of review – what are the challenges and lessons learned? <i>What are the underlying principles, policy tools and support needed for an agency to implement unilateral reliance? What have been the challenges, solutions, opportunities and main learnings moving from concept to practice? What still needs to evolve and what could be considered good practice?</i></p>
09:30	<p>Case Studies Brazil – Dr Fabrício Carneiro de Oliveira, Head of Biological Products, ANVISA, Brazil</p>
09:45	<p>South Africa - Dr Boitumelo (Tumi) Semete, Chief Executive Officer, South African Health Products Regulatory Authority (SAHPRA)</p>
	<p>Companies' internal considerations and challenges when utilising a unilateral model of reliance: what do companies see as good practice?</p>
10:00	<p>Dr Daniela Bravo, Executive Manager Regulatory Policy and Intelligence Latam, AbbVie, Brazil</p>
10:15	Discussion
10:45	Break
Session 2: Going beyond good reliance principles to good practice - what needs to be considered when implementing or using reliance models?	
11:15	<p>Good Reliance Management and Assessment Practices – what are the critical components to enable agencies to implement a risk-based review process that meets GBT standards?</p> <p>Dr Samvel Azatyan*, Team Lead, Regulatory Convergence and Networks [RCN], World Health Organisation (WHO)</p>

*Presented via recording

11:30	<p>Tools, practices and agency activities that can facilitate risk-based approaches</p> <p>Dr Noraisyah Mohd Sani, Senior Principal Assistant Director, Centre of Product & Cosmetics Evaluation, National Pharmaceutical Regulatory Agency (NPRA), Malaysia</p>
11:45	<p>Internal barriers, cultural and process changes – what needs to be overcome within an agency when embarking on implementing or utilising a reliance model?</p> <p>Regulatory perspective – Prof John Skerritt, Enterprise Professor in Health Research Impact at the University of Melbourne, Australia</p>
12:00	<p>Internal barriers, cultural and process changes – what needs to be overcome within a company when deciding to utilising a reliance model?</p> <p>Daniela Ulbricht, Pharma Portfolio Strategy Director, Emerging Markets, GlaxoSmithKline, Brazil</p>
12:15	<p>Implementation of reliance in Ecuador</p> <p>Daniel Antonio Sanchez Procel, Executive Director, National Agency for Health Regulation, Control and Surveillance (Agencia Nacional de Regulación, Control y Vigilancia Sanitaria – ARCSA)</p>
<p>Session 3: Leveraging Information from reference agencies on their assessment – What is needed and how best can this be facilitated?</p>	
14:00	<p>Chair’s introduction</p> <p>Prof John Skerritt, Enterprise Professor in Health Research Impact, University of Melbourne, Australia</p>
14:10	<p>Utility of public and non-public assessment reports from reference agencies – what is being utilised and for what reason?</p> <p>Dr Magda Bujar, Senior Manager, Regulatory Programme and Strategic Partnerships, CIRS</p>
14:30	<p>Discussion</p>
14:35	<p>Panel Discussion</p> <p>Stakeholder perspectives: What information should agencies utilise for risk-based approaches and how could stakeholders enable the process?</p> <p><i>What types of documents are requested from reference agencies? How are they being used for risk-based decision making? Do non-public documents help agencies? If so, what are the main ways? Would information be missing from public documents that could be of value if provided?</i></p> <p>5 - 7 minutes’ viewpoint followed by panel discussion and reflections from the floor</p> <p>A country implementing a reliance pathway - El Salvador Luis Alejandro Rivera, Gerente de Administración y Desarrollo Institucional, El Salvador</p> <p>A country implementing a reliance pathway – Egypt Dalia Abouhusein, QA General Manager, Egypt Drug Authority</p> <p>Company perspective</p> <p>Leonardo Semprún, Senior Director, Global Regulatory Policy Lead, LATAM, MSD, USA</p>
15:30	<p>Break</p>

Session 4: What are the frameworks that agencies have implemented to practically use regional/trans regional models and what are the learnings?

	Case studies
	Regional approaches to risk-based evaluation – What needs to be in place for these to operate effectively? What are advantages and barriers for regional alignment review models? Do these aid patient access to medicines?
16:00	Regional reliance models - Prof Steffen Thstrup , Chief Medical Officer, European Medicines Agency
16:15	Regional reliance models – Jackson Kiberenge , Drug Registration Officer, Tanzania Medicines and Medical Devices Authority, Tanzania
16:30	Discussion
16:35	Orbis– A collaborative model with sharing assessment as it occurs Sophie Sommerer , Director General, Biologics and Radiopharmaceuticals Drugs Directorate (BRDD), Health Canada
16:50	ACCESS workshare – could this concept be utilised as a model for other regions? Dr Claus Bolte , Chief Medical Officer, Swissmedic
17:05	What do companies see as the advantages and barriers for regional review or collaborative review models? Priti Shah , Executive Director, International Regulatory Affairs, AstraZeneca, UK
17:20	Discussion
17:45	Introduction to Roundtable Discussions
18:00	End Day one
19:00	Reception
19:30	Dinner

Day 2: 29th February 2024

Session 5: Roundtable Discussions

08:30

Roundtable A: Regional collaboration – what are the key considerations or framework that enable the construction and delivery of an efficient and effective regional/trans regional model?

English Speaking

Chair: Prof Steffen Thirstrup, Chief Medical Officer, European Medicines Agency

Rapporteur: Marite Prieto, South Latam Cluster Lead, Pfizer, Brazil

Roundtable B: Changing mindset – How can this best be achieved within companies and agencies to enable reliance and collaborative models?

English Speaking

Chair: Dr Boitumelo (Tumi) Semete, Chief Executive Officer, SAHPRA

Rapporteur: Sheila Inada, Regulatory Affairs Manager, AstraZeneca, Brazil

Spanish Speaking

Chair: Patricio Enrique Reyes Sepúlveda, Head of New Product Registration Section, Institute of Public Health, Chile

Rapporteur: Ana Gabriela Trejos Vásquez, Regulatory Affairs Lead, Caribbean, Central America and Venezuela, Roche, Costa Rica

Roundtable C: Good Reliance/collaborative practices for companies and agencies – what needs to be in place to move from principle to implementation?

English Speaking

Chair: Cynthia Ban, Global Head, Regulatory CMC, Vaccines, Sanofi, Canada

Rapporteur: Luciana Carla Duran, Senior Regulatory Affairs Manager/ Regional Regulatory Affairs Lead, Novo Nordisk, Brazil

Spanish Speaking

Chair: Maria Antonieta Román, Regional Regulatory Policy Lead, Emerging Markets - Latam, Novartis

Rapporteur: Heloísa Fávoro, Regulatory Affairs Director, AbbVie, Brazil

12:30

End of roundtable discussions and Lunch

Session 6: Next steps for risk-based evaluations	
14:00	Chair's Introduction Prof Steffen Thirstrup , Chief Medical Officer, European Medicines Agency
14:05	Feedback by roundtable rapporteurs and discussion.
15:05	Moving from regional to continental reliance – What is the approach for Africa and why is it important? Alex Juma Ismail , Program Officer, Regulatory Systems Strengthening, AUDA NEPAD
15.20	Discussion
15:25	Panel Discussion – What are the next steps in the implementation of risk-based evaluations? <i>What's next for jurisdictional and regional models? Is continental convergence part of the plan? What are the opportunities and challenges? How can regional or national reliance models underpin continental models?</i> Alex Juma Ismail , Program Officer, Regulatory Systems Strengthening, AUDA NEPAD Dr Claus Bolte , Chief Medical Officer, Swissmedic Balbiana Verazez Sampaio Oliveira , Chief Advisor, ANVISA, Brazil María Antonieta Román , Head of Regulatory Policy in Latin America, Novartis Dr Lawrence Liberti , Director of the D.K. Kim International Center for Regulatory Science and Associate Professor of the Department of Regulatory and Quality Sciences, University of Southern California
16:25	Chairman's summary
16:30	Close of Workshop

Section 2: Presentations

Please note that the following presentation summaries represent the views of the individual presenters and do not necessarily represent the position of the organisation they are affiliated with.

The slide featured in each of the following summaries is attributed to the individual presenter and has been reproduced with their permission.

Affiliations are stated as they were at the time of the meetings, 28th and 29th February 2024.

Session 1: Embedding a unilateral risk-based model as part of the modern agency's regulatory toolkit – moving from concept to implementation to best practice

Current implementation of risk-based models of review - insight into the changing regulatory landscape

Dr Neil McAuslane, Director, CIRS

Importance of reliance approaches and different models as part of the regulatory toolkit

For more than a decade, CIRS has been exploring reliance models from an evidence-based perspective, with several current projects in this area (including the Latin American Systems to Enable Reliance [LASER-2] project, reliance workshops, and publications).

Regulatory systems, irrespective of maturity and resources, can be more effective if they are willing to leverage decisions made by other regulatory authorities; this is not a new idea. When CIRS conducted a survey of 32 agencies from Africa, Latin America, and the Middle East ([2022](#)), to ascertain the type of reliance models in place, results showed several ways of undertaking a risk-based approach. The majority of responding agencies (94%) had a unilateral model in place, whereby one agency relies upon a reference agency. A further 56% were using a collaborative review model (e.g., Project Orbis), while others were using work-sharing arrangements (e.g., ACCESS). There were also regional and centralised reliance models in place (e.g., CARPHA, in the Caribbean).

When asked about the key benefits of these models, agencies said, first and foremost, effective and efficient use of resources, then faster availability of medicines for patients. In addition, leveraging information from reference agencies helps build regulatory capacity through improved knowledge and experience. However, CIRS found that few agencies were incorporating measures to see whether or not these benefits were actually being observed.

Measuring the impact of different reliance models

Agencies are open to the idea of risk-based approaches, but it is important to measure the benefits of such models, looking at good practices and how to make them more efficient, while recognising that one model does not fit all. Not only do we know that “what gets measured gets done,” but also that a feedback loop is needed to identify what is not working.

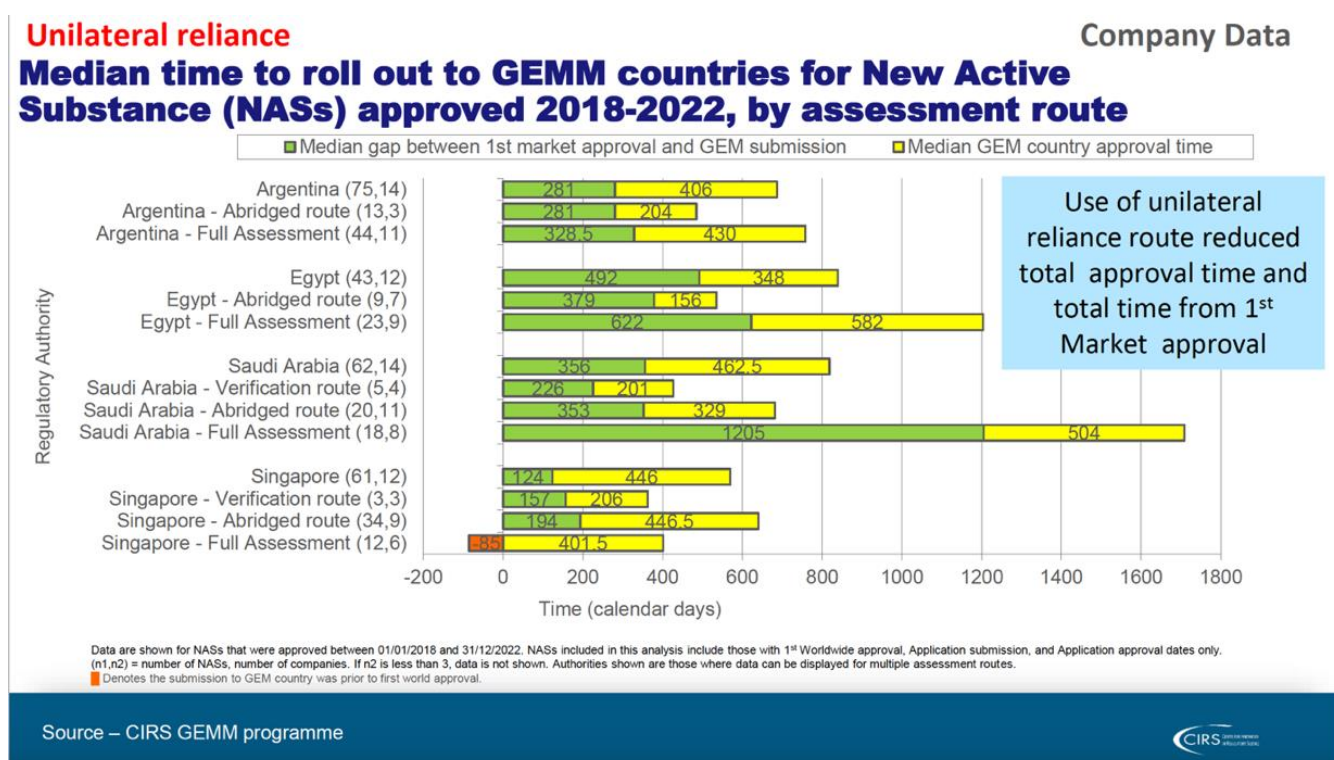
How can the benefits be measured?

- Availability of medicines – looking at the throughput of medicines and how long they take to become available.

- Agency resource or workload – numbers of products approved with same resource pool, backlog of applications, cost of time spent on review, etc.
- Mindset change and critical thinking – knowledge and capabilities of reviewers resulting in better quality review; number of questions asked; cycles of questions and quality of review.
- International collaboration – degree of alignment and uptake of international standards, access to external expertise, etc.
- Stakeholder feedback – there is a need to build trust.

Examples: Availability of medicines

1. For example, utilising data from the CIRS [Growth and Emerging Markets Metrics](#) (GEMM) Programme, improvement can be seen in the median time for medicines to become available for those going through unilateral reliance compared to full assessment (see slide below). Looking at the median gap between the first market approval and submission to the GEMM country (green bar), and the median approval time in that country (yellow bar), the use of unilateral reliance reduces the total rollout time (green + yellow) and often reduces the GEMM country approval time (yellow).



2. In another example using a collaborative approach (Project Orbis), NAS products approved by Project Orbis were submitted earlier than non-Orbis NASs, resulting in faster approval and total rollout time in each participating country (see CIRS [R&D Briefing 88](#)).

The LASER-2 project

CIRS' LASER-2 project was focused on promoting regulatory reliance in Latin America and the Caribbean. The objectives of the project were to get feedback from companies utilising reliance mechanisms across Latin America, characterise their experiences, identify barriers and best practices, and in turn, support and optimise the use of reliance through agency interactions in the region.

CIRS looked at data quantifying the time it takes to go through these reliance processes within countries in Latin America, as well as companies' perceptions of:

- How well the reliance process worked
- The level of knowledge and expertise within the agency
- The return on investment for the company
- Consistency of guidelines
- Transparency of decision making.

Results

In summary, there is heterogeneity in the way agencies apply reliance across Latin America, which is unsurprising for a large area with different types of agencies. Certain drivers facilitate authorisation, including the use of formal reliance pathways, or a focus only on overviews and summaries instead of detailed elements of the Common Technical Document (CTD). Certain activities could be barriers, including misuse of the Certificate of Pharmaceutical Product (CPP) and requesting information exceeding international norms. A number of countries have good practices in place concerning review, consistency and transparency of guidelines. The hope is that these observations will allow the identification of best practices that can be used to encourage agencies to optimise their reliance approaches.

Summary

Agencies are actively implementing different risk-based approaches, but one size does not fit all. Risk-based approaches must have measurable benefits and models, practices, and processes need to be transparent. Best practices need to be developed and implemented to ensure trust from all stakeholders, including patients. CIRS is continuing to undertake research and enable dialogue to ensure the conversation around risk-based models is evidence-based.

Risk-based approaches to the evaluation of new medicines: utilisation of a unilateral model of review

Case Study: ANVISA

Dr Fabrício Carneiro de Oliveira, Head of Biological Products, ANVISA, Brazil

Increasing efficiency without compromising safety

ANVISA's mission is to protect and promote the health of the Brazilian population, and provide access to new drugs. Due to increasing submission numbers for synthetic and biological drugs, ANVISA needed to find a new way of working that would increase efficiency without compromising patient safety – in order to ensure that a backlog of assessments would not impact its mission.

What could ANVISA do to improve efficiency without compromising safety?

- Improve internal procedures to avoid duplication of efforts during the assessment process.
- Work smart, e.g., introducing a new optimised assessment process online for post-approval changes.
- Reduce bureaucracy and increase the number of immediately implementable submissions, especially for post-approval changes – bearing in mind that this would increase risk level.
- Increase participation in joint assessment programmes, such as Project Orbis or EMA Open.

Reliance considerations

For ANVISA, the main goal of using reliance is to strengthen regulatory capacity to make a better use of limited resources, especially human resources. It is important that relying agencies consider their goals and necessities, the level of reliance to use (e.g. full acceptance, verification, abridged review) and which reference agencies to rely upon (see slide below for the list of reference authorities used by ANVISA under the [Normative Instruction #289/2024](#) that was published on 25th March 2024).

AREE (Normative Instruction proposal)*

- I - European Medicines Agency EMA (centralized analysis processes), applicable to medicines and biological products;
- II - Health Canada, applicable to medicines and biological products;
- III - World Health Organization - WHO, applicable to API, medicines and biological products;
- IV - European Directorate for the Quality of Medicines & HealthCare - EDQM, applicable for API;
- V - Swiss Agency for Therapeutic Products - Swissmedic, applicable to medicines and Biologicals;
- VI - Medicines and Healthcare products Regulatory Agency – MHRA, United Kingdom: applicable to medicines and biological products;
- VII - US Food and Drug Administration - FDA: applicable to medicines and biological products.
- VIII - Therapeutic Goods Administration (TGA) – Australia: applicable to medicines and biological products

* Others may be included if established criteria are fulfilled.



List of reference authorities used by ANVISA under the [Normative Instruction #289/2024](#).

First, regulatory convergence is needed to achieve the goal of reliance. A formal relationship needs to be established between agencies to exchange documentation and information; some agencies will answer questions quickly, while others will be slower. The language of documentation is also an important consideration for ANVISA (e.g., must be Portuguese, Spanish, or English) to reduce translation time. Active participation in joint assessment programmes, where there is already trust between agencies, creates and increases confidence in using reliance procedures. Maintaining the sovereignty of reviewers' decisions can help to increase their confidence in the reliance procedure.

Metrics are key to understanding the impact of reliance. Relying agencies must establish reasonable metrics that take into consideration the complexity of the assessment.

Lessons learned

For both biologic and new synthetic drugs, a substantial reduction in assessment time was observed by ANVISA when its reliance pathway was chosen. For synthetic drugs, reliance pathway assessment took approximately 20% of the time required for the regular pathway; for biologics, reduction in assessment time ranged from 30% to 50% compared with the regular assessment route.

Moreover, some dossiers submitted through the reliance pathway were granted marketing authorisation without the need for clarifications or additional information requests. Even when there were questions, they were much simpler than questions received in an ordinary assessment procedure.

Next steps

Now that ANVISA has a well-established reliance procedure, the next steps will be to:

- Create trusting relationships with new authorities.
- Continue monitoring the reliance process and timelines.
- Request feedback from companies using the reliance pathway to understand what can be improved.

Summary

ANVISA needed to find new ways of working to increase efficiency without compromising patient safety, to ensure that a backlog of assessments would not impact its mission to protect and promote the health of the Brazilian population. Implementation of the now well-established reliance pathway has seen a reduction in assessment time compared with the regular assessment pathway for both biological drugs and synthetic drugs, with most dossiers submitted through the reliance pathway being granted marketing authorisation without the need for clarifications or additional information requests. ANVISA wishes to update its list of reference authorities, while continuing to monitor whether the reliance procedure is reducing assessment time.

Case Study: SAHPRA

Dr Boitumelo (Tumi) Semete, Chief Executive Officer, SAHPRA

In 2016, SAHPRA had a backlog of 7902 medicinal product applications in its system; by 2018, this escalated to 8220. Of these, around 95% were generics. There were also around 7780 variations in the backlog, making the total backlog around 16,000 applications. In addition, a median approval time of 1622 calendar days was reported between 2015 and 2018. Since SAHPRA is resource-constrained, it was essential to clear this backlog.

Review pathways utilised by SAHPRA

Review pathways utilised by SAHPRA are as follows:

- Full review: complete scientific review for safety, quality, efficacy, Good Manufacturing Practices (GMP).
- Abridged review: to assess specific, pre-agreed areas within the dossier of substantive interest to SAHPRA, e.g., regional requirements.
- Verified review: to validate that applications conform to that of the reference agency and provide required information; SAHPRA looks at sameness of the product.
- Risk-based assessment: focusing on Critical Quality Attributes per product (see table below).
- SAHPRA does not currently have a recognition mechanism.

Challenges with using the reliance approach, particularly for generic applications

The reliance pathway was introduced in 2019, as a means to assist in reducing the backlog. While SAHPRA's throughput increased, reliance could be only applied to about 30% of applications received. It had been expected that use of reliance for most generic applications would substantially reduce the backlog, since these products have typically been authorised by reference agencies. However, the situation was far more complex.

Part of the challenge was obtaining unredacted reports and final assessment reports, which were often either delayed or not sent at all. Even if SAHPRA received these reports, some were outdated because of the extent of variations introduced in the meantime. A major delay was assessment of the quality and bioequivalence aspects of generics, which constitute a large portion of the information to be reviewed for approval of medicines.

Of the total backlog, approximately 20% were eligible for the reliance pathway, while the rest had to be subject to full review, due to the above challenges. This necessitated an alternative intervention for these types of applications.

Risk-based assessments

SAHPRA developed a risk-based approach pathway to alleviate the backlog and improve efficiencies, intended for well-known generic applications that did not qualify for reliance review. Only experienced evaluators were involved in the risk-based assessment process. The process included:

- A risk classification applied before assessment to determine whether the product should receive full review – essentially a 'triage' system.
- Optimisation of the overall registration process – identifying operational inefficiencies.
- Improved use of evaluation tools and documentation of this process for iterative learnings.

- An amended peer review process, whereby a team would conduct the peer review at standing weekly peer review sessions.

Key differences compared with full review were as follows:

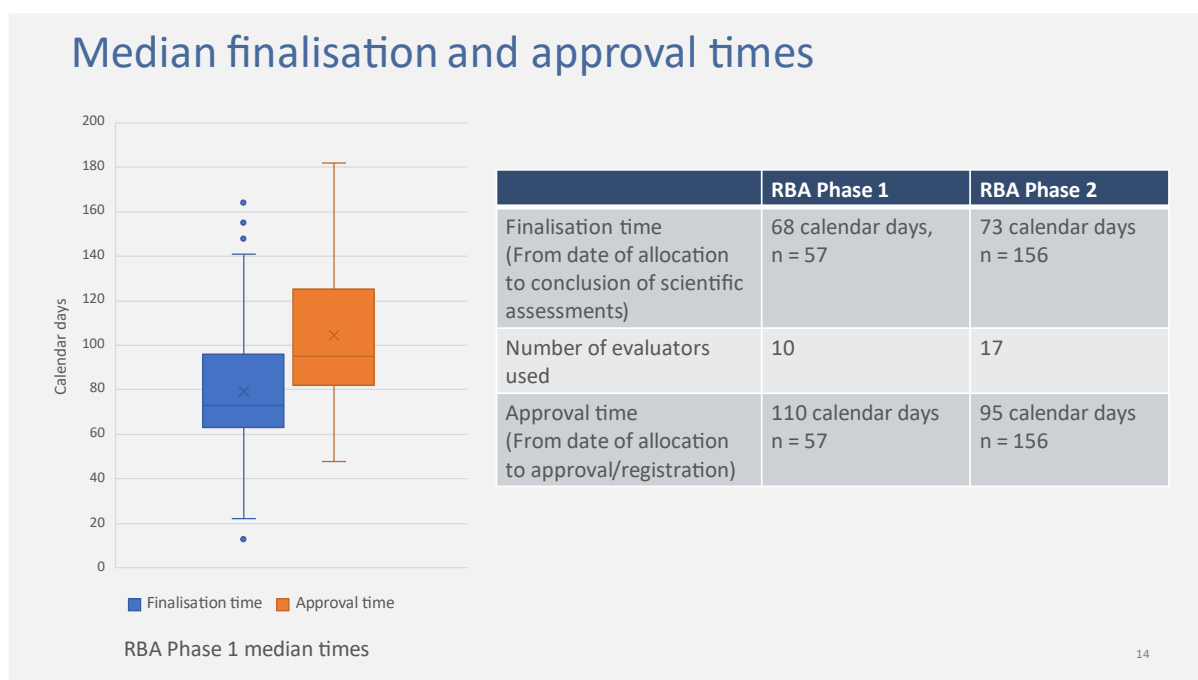
Full review	Risk-based assessment
Umbrella approach utilised for all types of medicines	Risk-classification incorporated at screening stage with medicines classified according to risk – all high-risk products undergo full review
Random allocation of dossiers, longer timelines	Dossier allocated in batches, tighter timelines
Assessment of all sections of the dossier	Evaluation and reporting of Critical Quality Attributes in the dossier that affect product quality Critical sections identified for low- and high-risk applications Continuous compilation of reports for peer review meetings
Need to await availability of peer reviewer, with allocation based on their availability	Standing weekly peer review sessions – reports placed online and collaboratively reviewed by eight to twelve evaluators One application peer-reviewed by three to six evaluators before the session and by ~twelve during the session
Peer review can take up to a month, due to awaiting availability of peer reviewers	Peer review took 8 days per three applications allocated to one evaluator
Final decision taken by the Quality Assurer	Final decision taken during peer review session
Additional Quality Assurer step taken before signing off the query letter to the applicant	Quality Assurance is built into peer review meetings
Additional days are taken for signing off the query stage	Signing off query letters happens on the day of the peer review session – no additional time required for final decision
Response times maintained at 30 working days – extension requests granted without a valid justification requested	Response time reduced from 30 to 15 working days – if not received in time applicant immediately contacted for justification Extension requests carefully evaluated before approval
Responses evaluated and peer-reviewed when there is availability of evaluators	Responses evaluated within 24 hours of receipt, and immediately compiled for weekly peer-review meetings

Parameters used to determine risk classification

SAHPRA used the following parameters to determine whether the product was high or low risk:

- Availability of a valid Certification of Suitability (CEP) or Confirmation of Active Pharmaceutical Ingredient Prequalification document (CPQ).
- Pharmacopoeial status of the Active Pharmaceutical Ingredients (API).
- BCS classification of the API.
- Solid-state properties of the product.
- The concentration of the API in the Finished Pharmaceutical Product (FPP).
- Pharmacopoeial status of the FPP.
- Type of dosage form.
- Complexity of the manufacturing process.
- Excipients.
- Container closure system.
- Reference product used for bioequivalence / comparative dissolution.

Piloting this risk-based assessment programme for the product backlog reduced median finalisation and approval times (see slide below).



Lessons learned

The following are learnings from the risk-based assessment pilot studies:

- The allocation stage required gathering multiple details about the application (e.g., API, API manufacturer, FPP, FPP manufacturer, contract research organisation, bioequivalence study number, etc), necessitating a centralised database containing all relevant information on each application.
- Careful monitoring was required to ensure portfolio coordinators sent queries out to applicants in accordance with set timelines.
- Employing the weekly peer review meeting approach led to efficiencies.

- Use of multiple senior evaluators led to assurance of thorough review of all Critical Quality Attributes, guaranteeing that only products of quality, safety and efficacy were approved.

Summary

Faced with a substantial backlog of medical product applications, SAHPRA introduced the reliance mechanism in 2019, but was able to use this for fewer applications than anticipated. A new approach was needed to alleviate the backlog. A risk-based assessment approach was piloted, with a risk classification stage whereby products were stratified as high or low risk, before being allocated to full review or risk-based assessment. The risk-based assessment process enabled SAHPRA to optimise its operations, with less time wasted waiting for assessors, batch allocations and joint weekly peer review mechanisms.

Companies' internal considerations and challenges when utilising a unilateral model of reliance: what do companies see as good practice?

Dr Daniela Bravo, Executive Manager Regulatory Policy and Intelligence Latam, AbbVie, Brazil

Reliance is already a reality around the world, with many practical examples in place and few doubts about its benefits for industry, regulators, and patients. Still, there are outstanding opportunities to ensure reliance reaches its full potential. Some questions remain, for example: the best way to implement reliance to attain the needs of a specific jurisdiction, which vary from one to another.

Unilateral reliance and recognition, as defined by WHO, is when a country chooses to rely on or formally recognise an assessment from another country unilaterally and without reciprocity. This may be the simplest reliance model to implement, and it is the most prevalent around the world.

Regulatory strategy – is it worth using reliance?

When companies are discussing their regulatory strategy, they assess which countries will benefit from use of reliance as part of the submission plan. The main objective is to identify opportunities to bring products to patients more quickly. For example, if the country is a 'Wave 1' country, use of unilateral reliance may not make sense.

The company considers if other documentation required by the relying authority will be available at the time of submission, or if it will be possible to add documentation before the completion of the assessment. The company also considers timelines to approval. Finally, the company considers the sameness of the products. Products can change rapidly during their lifecycle, and post-approval changes can be approved by the reference authority even before the submission of the marketing authorisation application to the relying authority.

Practical experience using a unilateral reliance model

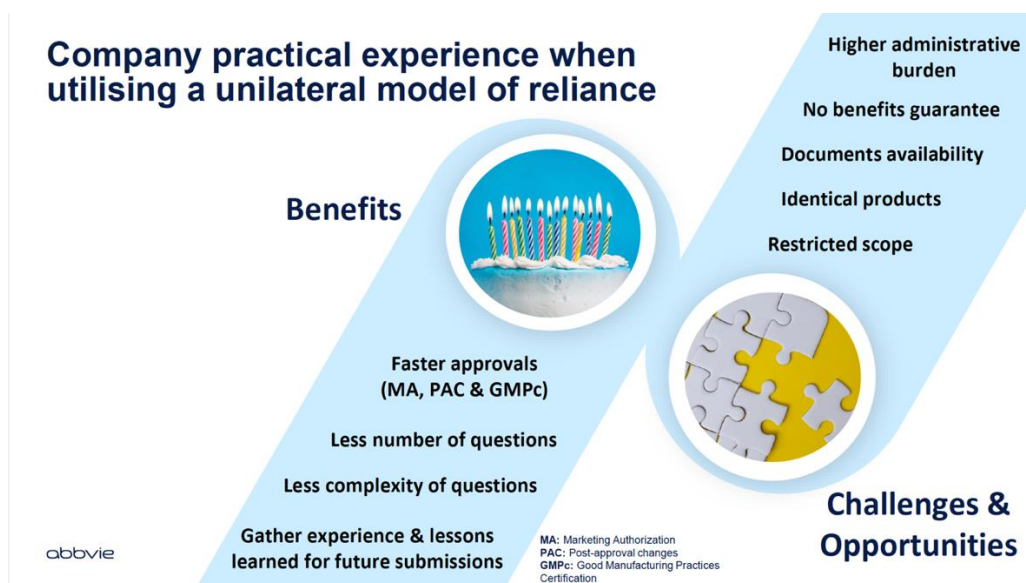
Benefits

The efficiency of the health authority as a whole is optimised so the benefits are broad:

- Faster approvals of products for marketing authorisation, post-approval changes, and GMP certifications.
- Fewer questions asked and a lower complexity of questions.
- Many lessons learned for future submissions.

Challenges and opportunities

- Higher administrative burden – mainly due to redundant or additional documentation requested.
 - For example, there can be a requirement to provide a complete comparison between the information submitted to the relying authority and the reference authority. A shorter document where the company states the differences would be much more efficient for both the company and the relying authority.
- Reliance regulations do not always assure a benefit in the timeline to the approval.
- Documentation not always available – for example, unredacted assessment reports.
- Reliance regulations ask for the products to be identical.
 - From an industry perspective, products can still be considered for reliance (even partial reliance) if there are differences in their documentation, e.g., in the manufacturing sites or suppliers, or indications or conditions of use.
- Restricted scope – there are more opportunities for the use of reliance, especially in Latin American countries.



Good practice from an industry perspective

Process

The more complex and unpredictable the process, the less likely companies are to adhere to reliance models. A robust process for reliance implementation should be in place, which means having:

- legal provisions, supported by guidelines that clarify the process.
- appropriate governance and resources.
- clear and simplified procedures, with a list of reference authorities and documentation required.
- faster and more predictable timelines.
- flexibility and a broad scope, including for post-approval changes, GMP certifications, pharmacovigilance, etc.

Documentation

Optimisation of industry resources for reliance encourages its use and will speed up access to innovative therapies. Best practices are as follows:

- The relying authority should use PARs as the primary source of information for unilateral reliance. The CPP can be used as a unique tool for reliance in the context of unilateral recognition or verification.
- The reference authority should provide timely and complete information available on their website through the product lifecycle.
- The relying authority should avoid redundant requirements and internationally align dossier content.

Transparency

The availability and content of documentation provided by the reference authority has a high impact on industry adherence to the unilateral reliance model. Early dialogue between the company and relying authority can improve understanding of the product and the rationale for the reference authority decision making. Best practices are as follows:

- Reference authorities should make PARs as complete and consistent as possible, with mechanisms for providing additional confidential information to the relying authority if necessary.
- The relying authority should make public that reliance was used to support the decision.

Trust

Trust is the fundamental basis for reliance. This is not only between health authorities, but also between the relying authority and industry. It is important that:

- relying authorities implement mechanisms to monitor efficiency, and gather industry feedback on what is working well and what is not working
- relying authorities prepare to use multilateral reliance pathways in the future.

Summary

The unilateral reliance model has challenges that make its implementation complex, but there are also many opportunities to be explored, which could benefit authorities, industry, and patients. Conducting pilots and keeping an open dialogue between authorities and industry are both key to the success of unilateral reliance models.

Session 2: Going beyond good reliance principles to good practice - what needs to be considered when implementing or using reliance models?

Good Reliance Management and Assessment Practices

What are the critical components to enable agencies to implement a risk-based review process that meets GBT standards?

Dr Samvel Azatyan*, Team Lead, Regulatory Convergence and Networks [RCN], WHO

Empowering global health

Strong regulatory capacity is an essential component of a well-functioning healthcare system, but globally, more than 70% of countries have weak national regulatory systems, preventing them from implementing key regulatory functions. At present, only 59 countries (~30%) have regulatory systems at WHO GBT maturity levels three or four.

WHO's regulatory systems strengthening programme aims to address this challenge by:

- objectively identifying the gaps and strengths in the regulatory systems
- providing capacity-building based on identified gaps, and,
- promoting smart regulation (good regulatory and reliance practices).

WHO addresses the above issues in four different ways:

- Promoting good governance and transparency in the medical product sector through good regulatory practices.
- Promoting and facilitating different processes to help build strong national regulatory systems.
- Developing a global regulatory curriculum and global competency framework to ensure an appropriately skilled and educated workforce.
- Promoting regulatory cooperation, convergence, and harmonisation, based on reliance on the work of trusted regulatory authorities.

Reliance in medical product regulation

In 2021, WHO proposed the definition of reliance as the “act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own national regulatory decision”.

Reliance has many important benefits. Facilitating efficient global regulatory oversight reduces timelines for important medical products to reach patients, as well as broadening patients' access via simultaneous approval of medical products across different regions. Reliance helps allocate resources to value-added regulatory functions and facilitates capacity-building in national regulatory authorities (NRAs) that are involved in reliance activities, helping them make higher quality, evidence-based decisions.

Reliance also increases the efficiency of regulatory systems and facilitates access to quality-assured, effective and safe medical products for all. Finally, and critically, it supports regulatory preparedness and response in the case of public health emergencies.

* Presented via recording

Good Reliance Practices and the WHO GBT

The [WHO 'Good Reliance Practices'](#) document, developed in 2021, is wide in its scope. It addresses reliance activities related to all types of regulated medical products, including medicines, vaccines, blood and blood products, and medical devices, including *in vitro* diagnostics.

It also addresses all regulatory functions that are outlined in the WHO GBT, throughout the life cycle of a medical product. This high-level document will be complemented by a repository of case studies, practice guides and examples to help regulatory authorities interested in implementing reliance.

Initiating reliance mechanisms

For reliance to be properly implemented and managed, its critical components must be understood. That means, first and foremost, adherence to the WHO GBT, which sets a common standard for regulatory practices across authorities, including key elements as outlined on the slide below.

Critical Components of Good Reliance Management

Adherence to Global Benchmarking Tool (GBT) Standards

A. Understanding GBT Standards

- GBT serves as a tool for benchmarking regulatory systems globally.
- Setting a common standard for regulatory practices and fostering consistency.

B. Key Elements of GBT Standards

- Harmonization: Ensuring alignment with international regulatory norms.
- Competence: Demonstrating the capability to meet global standards.
- Continual Improvement: Commitment to evolving and adapting to best practices.



7

Some regulatory authorities are interested in implementing reliance but do not know where to start. Key principles for starting to implement reliance are as follows:

- Foster trust amongst regulatory authorities, since you cannot initiate reliance without trust.
 - This will be achieved by sharing information, working together and understanding each other's processes
- Initiate applications for lower-risk medical products first
- Define reliance models that are appropriate in the country context based on a needs and risk-based approach.
 - The risk-based approach considers the type of product, source, resources, available expertise, identified public health needs, and existing opportunities for implementation of reliance.

There are different levels of assessment to be considered by regulatory authorities interested in implementing reliance, as follows:

- Work sharing through joint assessments, joint activities, and sharing of activities to accomplish specific regulatory objectives.

- The abridged regulatory pathway, where regulatory decisions in the country are based on reliance, helping to save resources, whilst maintaining sovereignty and oversight standards.
- Regional reliance mechanisms, based on central assessment of medical products within the centralised body or regional regulatory system, which generate binding decisions or recommendations for their member states.
- Unilateral or mutual recognition arrangements, which assume acceptance of regulatory decisions from other trusted regulators or institutions in their own national decision making.

'Implanting' reliance in facilitated regulatory pathways

Reliance has been successfully 'implanted' in a number of facilitated regulatory pathways supported by WHO. First, by way of the WHO pre-qualification collaborative registration procedure, which was instrumental for a number of medicines and vaccines, and now *in vitro* diagnostics and vector control products, based on the outcomes of WHO pre-qualification.

Another option is the stringent regulation authority (SRA) collaborative registration procedure, which is based on approvals by named SRAs. This concept is currently under revision, and will soon be replaced by the concept of 'WHO Listed Authorities', but has been effectively implemented to date. There are also several regional regulatory organisation initiatives and networks.

It is vital that reliance authorities remain fully independent and accountable of their own decisions, even if these decisions based on reliance.

Key components of informed reliance

Trusted regulatory bodies

Informed reliance relies on the recognition and acceptance of regulatory decisions made by trusted bodies with rigorous evaluation processes. Therefore, trust is a key component of reliance, since a pool of trusted regulatory bodies must be willing and able to share their information with others, who are in turn willing to use this to inform their national decision-making processes. These trusted bodies often have established expertise, robust regulatory frameworks, and well-defined guidelines for evaluating medical products.

Regulatory collaboration and harmonisation

Regulatory collaboration and harmonisation are also critically important for informed reliance, which involves sharing information, aligning regulatory requirements, and establishing various types of mutual recognition provisions and agreements to ensure the acceptance of regulatory decisions generated by trusted bodies.

Patient centricity

The patient-centric approach should be central to the regulation of medical products. All stakeholders will benefit from reliance, including national governments, manufacturers, NRAs and even donor communities, but patients are the most important beneficiaries.

Summary

Reliance promotes a more efficient approach to regulatory oversight, thus, improving access to quality assured and effective safe medical products for all patients over the entire life cycle of medical products. The WHO Good Reliance Practices are strongly linked to the WHO GBT that evaluates regulatory systems. Therefore, understanding and adhering to GBT standards including regulatory harmonisation, competence and continual improvement are key to implementing reliance. Only by embracing collaboration, networking and applying reliance can access to medical products be accelerated globally and global health resilience be strengthened, and ultimately, improve lives of people around the world.

Tools, practices and agency activities that can facilitate risk-based approaches

NPRA's perspective

Dr Noraisyah Mohd Sani, Senior Principal Assistant Director, Centre of Product & Cosmetics Evaluation, National Pharmaceutical Regulatory Agency (NPRA), Malaysia

All regulatory agencies are under pressure to expedite the regulatory review process. With increasing workloads and limited resources to consider, risk-based and reliance approaches are seen as efficient ways to ensure increasing patient accessibility to medicinal products in a timely manner.

NPRA has been using reliance partially in various forms for >20 years for certain aspects of pre- and post-marketing assessment. Recently, NPRA has transitioned to a full reliance and risk-based approach, focusing on what is locally critical.

Potential benefits of a reliance and risk-based approach have been clearly mandated to staff; that is, to ensure that medicines will be accessible in a timely manner; to reduce duplication of work, especially for products that have been approved by an SRA; and to drive focus toward risk-based evaluations, focusing on what is locally critical versus what can be leveraged from decisions made by SRAs.

Facilitated registration pathway

NPRA facilitate approval of marketing authorisations in Malaysia via a number of different pathways, including the facilitated registration pathway (using a reliance and risk-based approach).

Pathway guideline

NPRA introduced a clear and transparent guideline for the facilitated registration pathway in 2019. At this time, the scope was limited to new drug products, including new chemical entities and biologics, including biosimilars. Reference agencies included the US FDA, EMA and WHO pre-qualification products covered by the alternative listing procedure approved by FDA and EMA.

There were two routes on the facilitated registration pathway:

- Abbreviated review: for products approved by at least one reference agency (either EMA or FDA), with a timeline of 120 working days.
- Verification review: for products approved by two reference agencies, with a timeline of 90 working days.
 - The submission for the product should be within two years from the date of approval by the chosen reference agencies.

Between 2019 and 2023, few products were submitted via this pathway, possibly due to the limited scope of products and reference agencies. Therefore, NPRA expanded the guideline to include more products and reference agencies, as well as clearly defining 'abbreviated' and 'verification' review. In addition, the time limit of two years from date of approval was extended to three years, with timelines also revised. The guideline is available in English on [NPRA's website](#).

Details of revised guideline:

- Products: Now includes generic medicines, and cell and gene therapy products.
 - Products must be approved or reviewed by a full evaluation process, with submission within three years from date of approval by chosen reference agencies.
 - Other criteria: Must be a Pharmaceutical Inspection Co-operation Scheme (PIC/S) inspected manufacturing site; drug master file must be the same as approved by the chosen referral

agencies; proposed indication in term of dosing patient group / directions of use should be the most stringent amongst agencies that have approved the product (need to consider in the local context); proposed package insert and package information leaflet should be the same as what had been approved by the reference agencies.

- References agencies: Five have been added [Health Canada; Pharmaceuticals and Medical Devices Agency (PMDA), Japan; Swiss Agency for Therapeutic Products (Swissmedic), the Australian Therapeutic Goods Administration (TGA), and UK Medicines and Healthcare products Regulatory Agency (MHRA), as well as incorporating ASEAN Joint Assessment (JA) (see below)].
- Abbreviated review: includes products that have been approved by any of the review agencies or approved by the WHO Collaborative Registration Procedure (CRP), with a 90 working days timeline.
- Verification review: applies to products approved via the [ASEAN Joint Assessment Procedure](#), with a timeline of 30 working days.

Documents required for the facilitated registration pathway

- Full dossier: Complete CTD (stability study should comply with ASEAN stability guidelines, where relevant).
- Complete assessment reports from chosen reference agencies with Q&A documents, and any documents pertaining to post-approval variations.
- Proof of approval from reference agencies, plus declaration letters and statements to say that the information submitted is true and authentic.
 - Applicants must declare that all aspects of product quality and the intended direction for use are identical to those currently approved by the reference agencies.
 - NB: A different type of the container closure and pack size may be proposed to meet ASEAN stability requirements (if applicable); a different manufacturing site may be allowed if clearly justified.

Other tools included to facilitate risk-based evaluation are:

- a dossier checklist for the applicant to highlight the similarity (or otherwise) of the data set
- a flow chart showing the process for each pathway
- a written Standard Operating Procedure (SOP) for the assessor and a standard template for the assessment report, and
- a frequently asked questions document.

Practices to further facilitate risk-based approaches

Verification of sameness

NPRA must verify product sameness, referring to the aforementioned checklist, and cross-checking with the submitted assessment report. NPRA also look at critical information including the indication, dosage, route of administration, the dosage formulation, manufacturing process, and control, leveraging most of what has been assessed by reference agencies, except for differences highlighted by the applicant.

Risk-based, focusing on locally critical

NPRA look into the applicability of the reference agency assessment in the Malaysian context, particularly in terms of indication, target population, epidemiology, clinical relevancy of endpoints, etc. In terms of quality, NPRA focus on differences within quality parameters, especially in relation to product stability and climate condition. There is also a need to look into country-specific information, such as on the package insert and labelling. Furthermore, there is a need to look through the post-approval changes document to ensure that the dossier submitted to NPRA has the most recent approval by the reference agency. Lastly, for the risk management plan, NPRA must evaluate whether the risk minimisation measures can be implemented in Malaysia.

Preparation of assessment report

NPRA then prepare the assessment report, for which there is a template provided.

Other activities to facilitate risk-based approaches

Agency activities

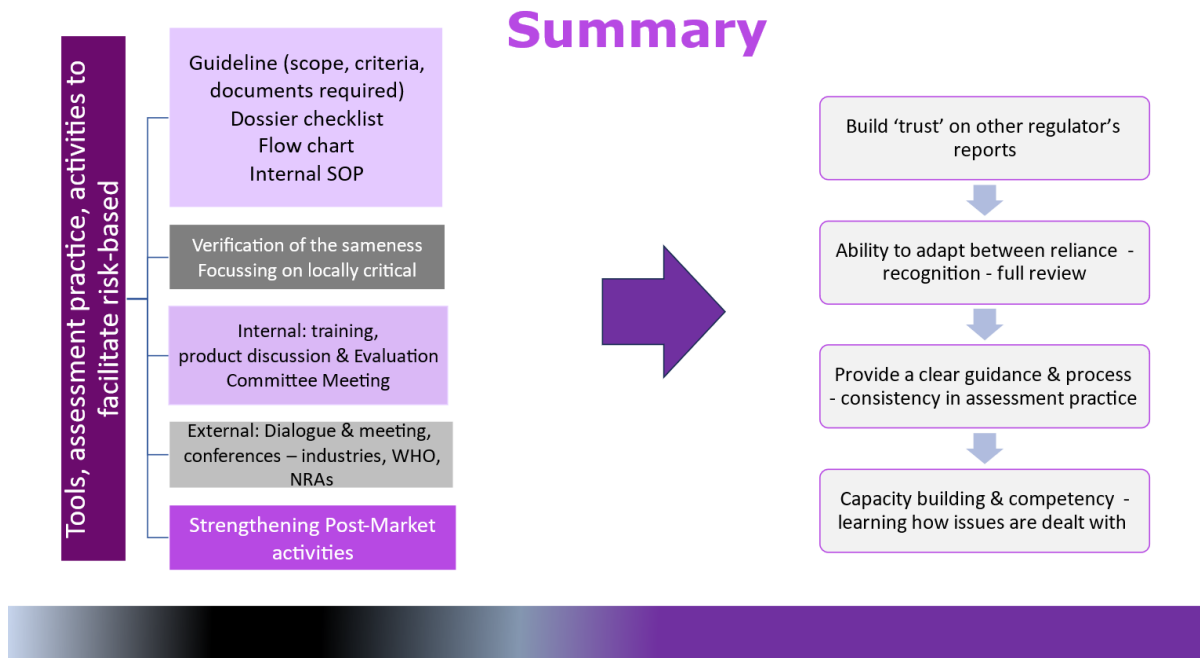
- Internal: training for reviewers, product discussion and product evaluation committee meetings.
- External: regular conversations / meetings with stakeholders to facilitate discussion on problems faced with applications made via the facilitated registration pathway.

Regulatory strengthening

- Post-market surveillance: taking a risk-based approach.
- Intensified pharmacovigilance activities, including monitoring the risk minimisation measures that have been approved for Malaysia, and doing pharmacovigilance inspections.

Summary

The most important tool to facilitate the risk-based and reliance approach is a transparent and clear guideline outlining scope, eligibility criteria, and documents required. The guideline for the Malaysian facilitated registration pathway also includes a dosage checklist and flow charts. An internal SOP for reviewers is also crucial to guide the reviewers, enabling them to focus on what is locally critical. The hope is that this provides clear guidance on the process, leading to consistency in assessment practice, as well as fostering capacity building and competency, especially amongst reviewers.



Internal barriers, cultural and process changes – what needs to be overcome within an agency when embarking on implementing or utilising a reliance model?

Regulatory perspective

Prof John Skerritt, Enterprise Professor in Health Research Impact, University of Melbourne, Australia

The challenge and the opportunity

There are several cultural barriers to the implementation of regulatory reliance, which are often understated. It is one thing to develop rules, regulations, processes and procedures to enable reliance, but in order for them to work, it is critical to convince staff they are a good idea and to actually implement processes. This kind of change takes time to build confidence among evaluators. In Australia, the TGA started confidence-building activities with other regulators back in 2011, seven years ahead of regulatory reliance actually commencing.

Regulatory reliance is now firmly accepted in Australia, but this was not always the case. Until 2017, TGA always undertook a full independent review of all data. Although timeframes were very predictable, taking around 220 to 230 working days, the approach was not efficient or responsive to the priorities of healthcare professionals, industry, or patients in addressing unmet medical need.

In 2017/18, reliance pathways were introduced in Australia and, importantly, were codified in law, following widespread support from a public consultation. Some patient groups expressed concern that medicines would be approved without adequate TGA review. They were reassured that TGA would have access to all relevant data and full unredacted evaluation reports. Healthcare professionals and industry were strongly supportive, so two reliance (abridged review) pathways were initiated:

- COR-A – Approved overseas <1 year, identical medicine, supply chain, dossier.
- COR-B – Identical medicine and supply chain but additional data allowed (e.g., post-approval variations, updated stability and manufacturing data, clinical data updates).

In total, by the end of 2023, 42 medicines had been approved by TGA under these pathways.

Reasons for reluctance to embrace reliance

While the implementation of reliance was a great initiative, it was initially met with varying levels of support and resistance from different parties within TGA:

- Clinical evaluators and toxicologists were most resistant, although both groups described themselves as “the most over-worked parts of the organisation”.
- Reasonable support for reliance was received from Chemistry Manufacturing and Controls (CMC) / quality evaluators, as they were used to using European Directorate for the Quality of Medicines and Healthcare (EDQM) quality evaluations for APIs, etc.
- Laboratory staff also sometimes used EU batch release for vaccines, so they were used to working internationally. They were therefore reasonably comfortable with reliance, as long as they could access the protocols.
- GMP inspectors were very supportive, as their system of clearances and long-established PIC/S partnerships made it easy for them to implement and accept reliance.

There were several broader reasons for reluctance to accept reliance:

- Evaluators felt they could not always access the information they needed – some reports initially received were heavily redacted, technical emphasis differed across regulators, and they sometimes faced difficulty asking questions of evaluators from other regulators.

- Sponsors sometimes struggled to get hold of necessary reports from regulators or from other parts of their own companies. Occasionally, TGA helped them, but the legal responsibility to access reports was with the sponsors.
- 'Sameness' of product was sometimes hard to verify given the complexity of global supply chains. TGA developed an SOP to verify sameness to the extent it is possible to do so.
- It was difficult to share commercially confidential information in some cases given the lack of secure IT systems.
- There were sometimes differences in product characterisation or review processes in different countries. For example, vaccines are medicines in Australia, whereas they are considered biologics in many other countries.
- Importantly, staff internal cultural issues were also prevalent.

Cultural issues

There was a general perception, especially amongst clinical evaluators and toxicologists, that their professional skills may be undermined. They were worried they would lose their jobs, although TGA actually increased their staff numbers during the period of implementation of reliance processes.

In the early days, there was no clear sense of the benefit-risk paradigms used by other regulators, and the expertise and qualifications of evaluators in other countries was unknown. Some also wrongly believed that they might be personally legally responsible if the medicine later had serious safety or efficacy concerns.

Other barriers

There were perceived threats to sovereignty of decision making (e.g., the view that the decision is already made) – although the final market authorisation decision is always made by TGA. There were concerns that reliance would actually increase workload. Staff turnover was also a concern, since international cooperation strongly depends on the establishment and maintenance of interpersonal relationships.

There was a lack of information available about which agencies undertake reliance, recognition and variants thereof, and a lack of databases of manufacturers, especially of API manufacturers, making it hard to confirm CMC information received and, in some cases, avoiding duplicate GMP inspections. Finally, the decision by other agencies to rely on TGA as a reference agency was often unilateral and made with little or no consultation.

Winning support for reliance

Top-down approaches

The TGA leadership took several approaches to win support for reliance from reluctant staff members:

- Explained that reliance is now the law, set in both legislation and regulation.
- Invested in training staff and developing SOPs for reliance processes.
- Emphasised that reliance was not about reducing resources, but rather evaluators being able to focus on areas of higher public health risk.
- Ensured senior staff were part of the process, e.g., participating in meetings and ensuring a shared voice between senior regulators (ACCESS, ICMRA, bilateral relationships).

Bottom-down approaches

TGA also employed several bottom-up approaches to win support from reluctant staff members:

- Fostered internal champions, emphasising the benefits to patients and regulators.
- Provided evidence of support from industry and other regulators.

- Implemented confidence-building initiatives, including face-to-face meetings and secondments, improving familiarity with other countries' regulatory systems, and providing personal contact points.
- Development internal SOPs for using evaluation reports from other regulators.
- Developed metrics for documenting the success of reliance.

Moreover, TGA provided clarity on when reliance should not be used, including secondary reliance (e.g., reliance on a report from another regulator that had itself been prepared through reliance), or situations of high uncertainty (e.g., conditional approval, emergency use authorisation). TGA also emphasised the importance of reconsidering drug indications locally if the reference agency changes the indications for the original approval.

What did different stakeholders think of reliance?

Industry saw many benefits of reliance, including: faster market authorisation, with fewer duplicated questions from regulators; timely launch of new products within a small Australian market; maintaining Australia as a top-tier regulator; fostering regulatory approvals in Asian markets; streamlining management of submissions and improving predictability of approvals; and the ability to stimulate international regulatory alignment.

Patient and consumer groups are largely unaware of the use of reliance. They may not see this as relevant to them at first but are likely to if it gives them the benefit of faster access to medicines. Regulators could work more to emphasise the public health benefits of reliance.

Advice for implementing reliance

It is important that agencies implementing reliance 'keep it simple'. Mutual Recognition Agreements are not always necessary and there may be too many additional requirements for reliance and recognition that undermine its purpose (see slide below).

Try to keep reliance and recognition simple !

Mutual Recognition Agreements MRAs are usually not necessary

- Often tied to Trade Agreements, can require Cabinet approval
- More a tool for recognition than reliance and to underpin mutual trade
- Can commit partners to undertake activities e.g. GMP inspections they may not otherwise have planned
- Countries often unilaterally decide to choose particular reference agencies anyway

Too many additional requirements for reliance/recognition undermine purpose

- Environmental risk data ?
- Single arm studies or Real World Evidence not permitted in clinical data ?
- Exclusion of ATMPs/ cell and tissue products or of novel technologies ?
- Exclusion of first in class new active substance ?
- Narrow definition of product sameness ?



Other potential concerns

Even if the aforementioned cultural issues are addressed, there are some ongoing challenges for implementing reliance:

- There is no standardised format or single platform between international regulators for assessment report sharing.
- Regulators often do not document levels of uncertainty for individual product approvals.
- There is no single list (endorsed by regulators) of countries using reliance and reference countries.
- Redaction of evaluation reports (especially from US FDA, and particularly of CMC data) is a concern.
- Reliance opportunities in other areas need further development, such as Good Clinical Practice inspections, post-approval variations, pharmacovigilance, range of products.
- More evaluation of reliance and its impact on performance is needed.

Summary

While there are ongoing challenges, there are many reasons to be optimistic about the future of reliance. Many countries have implemented regulatory reliance, and now there is a need to ensure it runs as smoothly as possible. It is particularly important to ensure that cultural issues, and other potential barriers to implementation, are not forgotten within agencies.

Internal barriers, cultural and process changes – what needs to be overcome within a company when deciding to use a reliance model?

Company perspective

Daniela Ulbricht, Pharma Portfolio Strategy Director, Emerging Markets, GlaxoSmithKline, Brazil

Barriers from a company perspective

Companies face several barriers when deciding to use a reliance model, which can be either internal barriers within the company or external barriers that create difficulties internally within the company. These barriers may be divided under the following headings:

- Lack of aligned concepts
- Unclear ways of working
- System and digitisation concerns
- Need for capacity building
- Enterprise strategy aspects
- Cultural aspects.

Alignment and ways of working (external)

Although the need to verify sameness of products and requests for documentation from reference agencies are not internal barriers, they do cause difficulties internally.

In most cases, time has passed since the original approval and the dossier and/or information relating to the product is not the same. However, it is the responsibility of the company to prove sameness to the health authority. A strict interpretation of sameness may potentially prevent reliance. A flexible and risk-based approach allows the evaluator to rely on the part of the file where there are no differences and to use an abridged independent review for differences of importance in the national context. The use of reliance for post-approval changes should be encouraged as a way of improving efficiency, streamlining planning and critically, reducing supply disruption.

Another barrier is the multiplicity of documentation required, which varies by country, with some health authorities requesting many market-specific documents plus additional documentation for comparison. Meeting such documentation requests can be a huge amount of work for companies.

Ideally, required documents should be minimised with the intent to verify sameness. There must be an aligned understanding on the meaning of documents to avoid duplication of information, with clear requirements based on a scientific and risk-based approach. Flexibility around timelines to submit documents is also needed.

Finally, it can be difficult to obtain complete unredacted assessment reports and non-public information for SRAs. Not all SRAs publish assessment reports in English or give permission to share them.

Systems and digitisation (external)

IT system development is a huge opportunity for industry growth and for connecting health authorities. There is a need to find ways to bring disparate systems together into a single platform to make information easily accessible. Reliance pathways should seek to drive harmonisation and digitisation using the electronic CTD (eCTD) format for dossier submission, through cloud-based platforms, with documentation provided in electronic format. There is a need for accepting other means to check authenticity and revisiting the

requirements for legalisation and notarisation of documents. This would foster smarter and optimised submission processes.

Capacity building (internal)

Pharmaceutical companies are large organisations representing many different therapeutic groups. If groups are required to support reliance processes without any background, it is possible that each would have different ways of working, and different agilities in responding to health authorities, mainly in cases where the requirements are not aligned or pre-defined. There is a need to properly allocate resources for global and local teams to consolidate all documentation health authorities ask for.

In addition, cross-fertilisation and education is needed to leverage understanding and change internal mindsets on reliance. Reliance 'champions' assigned to talk about reliance across therapeutic groups and different areas across the company can help to increase internal understanding.

Enterprise strategy (internal)

Reliance should be considered and discussed as a corporate way of working at the earliest stages of enterprise strategy, to embed the risk-based approach within strategic decision making and to allow for early engagements with the national health authorities. This can help with resource allocation, alignment of expectations and intelligence on local requirements, which will help companies to be more successful.

Cultural aspects (internal)

There are still some uncertainties about the required capabilities for reliance and reluctance to use reliance due to a perceived lack of experience. There is a need to leverage change management skills to optimise critical thinking in this regard. Trust is also critical. There is an opportunity to foster transparency and information sharing amongst agencies and companies.

Summary

In conclusion, several approaches are needed to overcome barriers to reliance from the company perspective. Capacity-building and education are needed to align expectations inside the company, with early and continuous dialogue and experience sharing with national health authorities. Moreover, a shift must be made at the health authority level, from the current practice of revising the entire documentation to value-added assessment according to local needs, based on the reliance concept. Proper resource allocation is required, while NRA sovereignty must remain absolute.

Reliance is not a loss of sovereignty as the relying agency remains always independent in its decision and can decide whether the assessment carried out by another agency is accepted fully or partially. Reliance is not an 'all or nothing' but allows the relying agency to focus on potential gaps and differences justified by science.

Internal Barriers from a Company Perspective

- Aligned concepts

- Ways of Working

- Systems & Digitalization

- Capacity and Capabilities Building

- Enterprise strategy

- Cultural aspects

- Reliance and Sameness concept not globally aligned
- Uncertainties about LCM and maintenance of dossier sameness
- Multiplicity of required documents & Market specific requirements – need to clarify terminology and purpose of each document requested
- Assessment reports not shared by all Stringent Regulatory Authority
- IT platforms & Digitalization – limited acceptance & external development
- Required resource allocation for PSM, specific documentation, as comparison assessments and reliance templates
- No clear understanding of reliance definition and mechanisms – need capability development & education
- Need earlier planning within enterprise strategic decision boards in early stages, embedding risk approach & engagement with NRAs
- Strategy driven by medical need and commercial prioritization and less consideration on regulatory complexity
- Trade offs - losing flexibilities e.g., indication (GDS vs EU SmPC)
- Need to encourage the use of reliance embedded in a trust agenda

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Implementation of reliance in Ecuador

Daniel Antonio Sanchez Procel, Executive Director, National Agency for Health Regulation, Control and Surveillance, Agencia Nacional de Regulación, Control y Vigilancia Sanitaria (ARCSA)

There is a need to establish inter-institutional cooperation mechanisms that guarantee safety, quality and efficacy of medical products registered at the local level. In Ecuador, work has been undertaken to develop good regulatory practices, build regulatory trust and improve working efficiency, in order to optimise resource use and improve access to medicines.

Regulatory framework of Ecuador supporting the implementation of reliance

Internationally Ecuador's regulatory policy has been framed by the International Regulatory Framework defined by the Andean Medicines Policy signed in 2009 by the Ministers of Health of Colombia, Ecuador, Peru, Bolivia and Chile with the objective of guaranteeing access to safe, efficacious and high quality medicines to the population of the region and the commitment to establishing guidelines for the harmonisation of policies, health registries, pharmacological quality control and some technical elements for international trade.

At the national level, Ecuador has the National Medicines Policy 2017-2021, the Ministerial Agreements 586 and 385 as well as Resolution ARCSA of 008-2018-JCGO, to guarantee the availability and quality of medicines.

Reliance-based reviews for chemically synthesised medicines or biological products

ARCSA has specific technical instruction manuals for the approval of chemically synthesised medicines and biological products using a reliance-based review. The process of approval is clearly defined: submission of the application; review of the information; complying with additional information; payment of a fee; a technical-chemical review of safety and effectiveness; responding to deficiencies, if the product requires it again; and finally, issuance of the health product registration.

There is no time limit is specified for the approval process, it is estimated that it should take no more than 60 days, as long as applicants provide additional information quickly. For biological products, there is a more exhaustive review (stability studies are incorporated).

The requirements for approval of chemically synthesised medicines and biological products using a reliance-based review include authorisation from the owner of the product, approval by a reference authority, certificate of the pharmaceutical product, label proposals, user leaflet, analytical methodology and proof of payment.

Points that are critical to note are as follows:

- To access the reliance pathway, medicines must be within the National List of Basic Medicines, a requirement established by the Ministry of Public Health.
- There is limited exchange of information by some reference regulatory agencies. In some cases, the links on agency websites to verify published information do not work.
- There is no time limit for approval defined through formal regulation.
- Requirements that authorisation of clinical and non-clinical studies must comply with Ecuadorean regulations.

High surveillance agencies according to Ecuadorean Regulations

 <p>National Regulatory designated by the Pan American Health Organization / World Health Organization as Regional Reference agencies because of their regulatory and oversight capacity and functionality</p>	 <p>WHO stringent regulatory agencies;</p>
 <p>Ministry of Food and Drug Safety of South Korea; and</p>	 <p>European Medicines Agency (EMA).</p>

Agencia Nacional de Regulación, Control y Vigilancia Sanitaria 

Note: The above slide is an English translation of the original slide that was presented in Spanish.

Opportunities for improvement

In Ecuador

Opportunities for improvement of national regulations have been identified as follows:

- Inclusion of public assessment reports in the regulatory framework for biological products, to expedite the review process
- Specifying a time limit of three months for approvals, without taking into account time to solve deficiencies
- Requirement that the Ministry of Health has to authorise access to the homologation process for products not included in the National Medicines List
- Recognition of a summarised production and control protocol, in accordance with formats established by reference authorities
- Elimination of the requirement for non-clinical or clinical studies for the registry of biological products
- Recognition of the lot release certificate issued by the national regulatory authority of the product's country of origin.

Between regulatory agencies

Opportunities for international improvement have been identified as follows:

- Formalise agreements between agencies to establish strategies and contact points, enabling exchange of information and reliance implementation
- Active participation in collaboration and updating of documents issued within the scope of the Pan American Network for the Harmonisation of Pharmaceutical Regulation, with documents issued being binding under each country's regulations
- Periodic training of regulatory agency personnel from management to technical levels.

Summary

There is a need to establish inter-institutional cooperation mechanisms to guarantee safety, quality and efficacy of medical products registered at the local level. For implementing reliance, it is important that there is involvement at the management level, regional level and from the political decision-makers' perspective. Steps have been taken in Ecuador in recent years to develop good regulatory practices, improve working efficiency and implement reliance-based review.

Session 3: Leveraging Information from reference agencies on their assessment – What is needed and how best can this be facilitated?

Utility of public and non-public assessment reports from reference agencies – what is being utilised and for what reason?

Dr Magda Bujar, Senior Manager, Regulatory Programme and Strategic Partnerships, CIRS

Public assessment reports (PARs) are critical to implementing reliance, but accessing them is a challenge, as highlighted in a recent survey undertaken by CIRS across global regulatory agencies. In the WHO [Good Reliance Practices](#) document, it is stated that regulatory agencies are encouraged to produce PARs, and that relying regulatory agencies should use these as the primary source of information for assessments. This is key to demonstrating sameness of the product, as stated by the International Pharmaceutical Regulators Programme [Q&A on reliance](#).

CIRS has undertaken a number of studies in this area, seeking to answer several questions:

- Are PARs useful for reliance purposes?
- What information can be found in reference agency PARs?
- Why do agencies require non-public documents?
- Is the terminology “unredacted” appropriate, or is better terminology needed (given there is always a requirement for some level of reduction)?
- What are the challenges and solutions for the using public and non-PARs?

This presentation covered two studies: a desk-based research study looking at PARs; and a perception study on reference agency documents and assessment reports (industry and agencies).[†]

Study 1: Evaluation of agency PARs

Goal: Appraise the utility of PARs as tools to guide regulatory decision making by health agencies that use the documentation for reliance purposes.

Approach: PARs were compared against information that is generally required by relying agencies to enable a risk-based decision. CIRS looked at 33 PARs developed by seven major agencies (FDA, EMA, Health Canada, Swissmedic, TGA, ANVISA, and MHRA), regarding the scientific assessment for marketing authorisation of six new active substances.

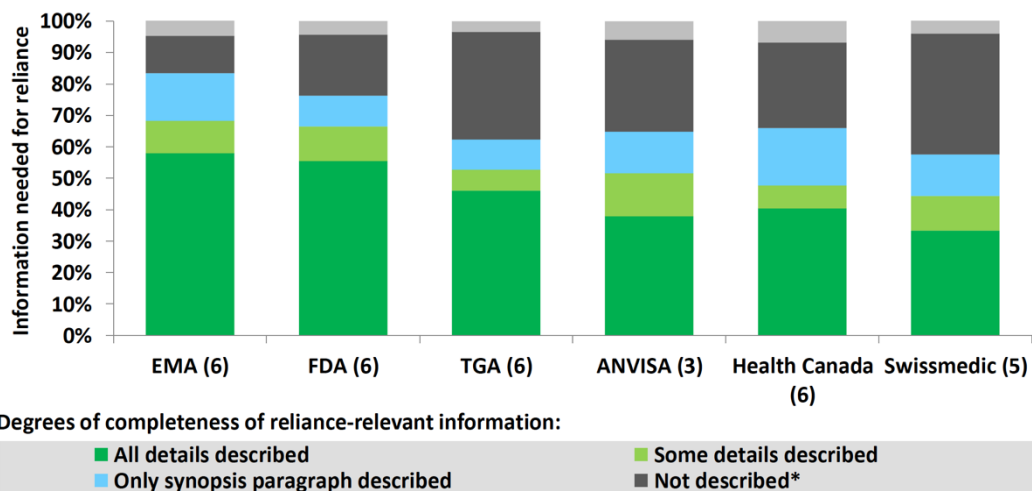
Main stages of the study:

1. Literature review: Since different agencies require different information for reliance, CIRS undertook a literature review to collate a generic non-agency-specific list of information that agencies require for reliance.
2. Consolidation: This list was consolidated into five sections according to sections of a PAR, e.g., regulatory background, clinical, non-clinical, CMC, benefit-risk assessment.
3. Comparison: CIRS compared the agency PARs for specific products versus the list of information generally required by relying agencies to undertake reliance.

[†] Post-meeting note: These studies have since been published as CIRS R&D Briefings [92](#) and [94](#).

Results

Overall summary: Inclusion of reliance-relevant information in PARs, by agency



Degrees of completeness of reliance-relevant information:



(n): Number of Public Assessment reports (PARs) for approved NAsS assessed in this study.
 *: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective UAR)



NB: Slide shows the degree of completeness of reliance-relevant information in the PAR. It is important to note that PARs are not the only source of reliance-relevant information; such information may be found in documents other than the PAR e.g. the MAA, CPP.

Results show that a lot of information needed for reliance is described within PARs, but this varies according to the agency. When analysing according to section, there was a comparatively low degree of completeness of reliance-relevant information in the CMC section. However, for other sections, there was a higher degree of completeness of information.

Recommendations

CIRS has developed a number of recommendations based on this study:

- Reference agencies – a mindset change is needed
 - Review PAR content/format with relying agencies in mind – align with best practice and other agencies
 - Establish communication channels and platforms with agencies to share non-public information
 - Ensure that PARs are published for different applications including extension of indication
- Relying agencies
 - Understand the decision-making approach and context of the PAR
 - Utilise PARs as sources of information
 - Request non-public information from the sponsor or reference agency – Memorandums of Understandings (MoUs) may be needed
 - Apply caution to work-sharing products – ensuring all PARs are considered
- Sponsors
 - Ensure availability of communication channels and platforms for sharing additional reliance-relevant information with the relying agency.

Study 2: Industry and agency perception of reference agency documents and assessment reports

Goal: To better understand the provision of regulatory review documents and reports, including what type of documents are requested, how often, and how they are being used for risk-based decision making. The emphasis was on non-public documents.

The study was split into two surveys (focusing on the abridged procedure):

- Company survey: Responses were received from 11 major multinational companies
- Agency survey: Responses were received from 10 agencies (in Latin America, Asia, the Middle East, Africa, and Europe)

The results of the agency survey were presented.

Documentation - what documents do agencies require to undertake an abridged reliance procedure?

All agencies who responded to the survey require a full dossier and non-public documents. Just under half also require publicly available documents, such as PARs.

Use of PARs – do agencies utilise only PARs to undertake an abridged reliance procedure?

Very few responding agencies utilise only public PARs for reliance review. There are several criteria for only using PARs (e.g., PARs that contain high quality, complete information; for products with low risk; when non-public information cannot be shared). The agencies that only utilised PARs felt that PARs provide all information relevant for decision making and provide information relevant to benefit-risk, as well as sameness of product.

Challenges and solutions to using PARs for reliance

Certain challenges and solutions were raised by responding agencies with regards to using PARs for reliance:

- Limited access to and availability of PARs – solutions suggested:
 - Ensure PARs are posted on a platform by the reference agency in a short timeframe following approval.
 - Ensure PARs are published for different application types including, e.g., variations.
 - Enable better communication between regulators through confidentiality agreements and MOUs in case unredacted information is needed.
- Quality of reports and completeness of reliance-related information - solutions suggested:
 - Advocate for a standardised PAR template and best practices.
 - Develop clear and comprehensive criteria for accepting public documents for reliance review.
 - Determine if certain important technical information like detailed specifications could be added to a PAR.
- Authenticity of PARs – solution suggested:
 - Enable a mechanism for document verification and authentication.
- Clarity on how to use PARs – solution suggested:
 - Develop a SOP on how to utilise a PAR for the purpose of reliance.

Provision of non-public documents for reliance – are non-public documents a regulatory or legal requirement, or are they requested on an ad hoc basis? What kind of non-public documents are required for reliance?

Out of nine responding agencies, the provision of non-public documents was a regulatory requirement for five agencies, a legal requirement for four, and requested ad hoc by three. Most agencies required a large range of documents. The non-public documents required by the majority (>50%) were: interim and final collated Q&A; interim and final assessment reports; risk management plans; list of outstanding issues; post-marketing

commitment; and updated CTD sections. Information was generally required to be submitted as unredacted and provided by the applicant.

Agency use of non-public documents – what is the rationale for requesting non-public documents?

All responding agencies agreed that first and foremost, the purpose of requesting non-public documents is to confirm sameness of the product and to understand the reference agency's decision making. Building trust was also mentioned as a key component, although this is not the true purpose of the assessment report; there may also need to be other mechanisms to build trust.

Challenges and solutions to using non-public documents for reliance

Certain challenges and solutions were raised by responding agencies with regards to using non-public documents for reliance:

- Difficulty obtaining relevant non-public documents in a timely manner – solutions suggested:
 - To implement an efficient process for submission and retrieval of documents.
 - Authority should request documents early in the review process.
 - Applicant to authorise reference agency to share reports with the authority.
 - Agency to establish MoUs with reference authorities.
 - To enable direct access to reference reports or have the sponsor provide them by default with submission.
- Lack of communication to enable secure sharing of confidential non-public information – solutions suggested:
 - Develop secure platforms and protocols for handling and sharing non-public documents.
 - Increase dialogue among regulators.
- Lack of clear and harmonised standards, templates and criteria for accepting non-public documents – solutions suggested:
 - Introduce a common template for reference agency review reports.
 - Define clear and standardised criteria for accepting non-public documents.
- Differences in product, e.g., post-approval changes / in the dossier – solutions suggested:
 - Ensure the dossier is similar.
 - Any differences in dossier or product to be clearly stated and justified.
- Lack of clarity on the process for becoming a reference agency – solutions suggested:
 - Regulatory system strengthening to build capacity.
 - Clarify the criteria for becoming a reference agency.

Other challenges and solutions for reliance implementation

When asked about other major challenges in addition to the availability of assessment reports, most responding agencies specified changing the mindset of reviewers to understand the differences between reliance and a full review. The next most selected challenge was having the resource to put reliance in place.

Responding agencies suggested the following solutions:

- Encouraging a cultural transformation at the agency level through training and capacity building.
- Increasing collaboration, particularly around information sharing between relying and reference agencies, as well as applicants.
- Building better platforms for sharing information and communication.
- Having clear, consistent criteria for utilising different assessment reports.
- Convergence in terms of reliance practices and definitions.

Summary

The implementation of reliance is challenged by the lack of availability of PARs. CIRS undertook several studies to assess the use of assessment reports and documentation for reliance. A key finding was that, while PARs contain a high proportion of reliance-relevant information, they do not seem to be utilised by regulators for the purpose of reliance. Unredacted assessment reports and non-public documents are seen as key for demonstrating sameness of product and the decision made, but their availability is a challenge.

There were several common challenges across both public and non-public documents, around availability, completeness, communication channels and having clear definitions in place. Potential solutions include: advocating for standardised reports; having clear, complete documents; having them available in a timely manner; and most importantly, changing the mindset of reviewers in terms of how those documents are being currently utilised.

Post-meeting note: The studies presented have since been published as CIRS R&D Briefings [92](#) and [94](#).

Panel Discussion

Stakeholder perspectives: what information should agencies utilise for risk-based approaches and how could stakeholders enable the process?

Each panellist was asked to provide their thoughts on:

- What types of documents are requested from reference agencies?
- Do non-public documents help agencies and if so, what are the main ways?
- Would information be missing from public documents that could be of value if provided?
 - To confirm sameness of the product
 - To understand reference agency decision making
 - For information/record keeping (e.g., if there is an issue)
 - To reduce delays in the approval process
 - To increase knowledge/building capacity of regulators;
 - To build trust with the reference agency.
- How are they being used for risk-based decision making?

El Salvador agency perspective

Luis Alejandro Rivera, Administration and Institutional Development Manager, National Directorate of Medicines (DNM), El Salvador

- DNM uses national reference agencies that have four qualities: transparency, reliability, competency and consistency. DNM tries to apply reliance across the whole life cycle of regulation and uses GMP certificates from other countries to recognise the registration of medicines.
- DNM has signed MoUs with other agencies so it can share information or take actions that are needed to improve its reliance pathway. DNM is also part of a committee of Central America agency directors, which helps to gain and develop regulatory trust.
- DNM does not directly ask for documentation from reference agencies. Instead, the agency accesses publicly available documents, often obtained via official websites or other public resources. It is important for relying agencies to know where to find this information.
- Having access to assessment reports would be a key element to better understanding the decision-making process of reference agencies and increasing trust. This could be a way to reach mutual agreement for facilitating exchange of information.
- To guarantee uniformity of product, it is required that manufacturers present the same documentation in their application to DNM as in their applications to other NRAs.
- Non-public documents can be of great value because they contain detailed and specific information, e.g., about irregularities in technical information, demonstrated benefits and possible risks. These documents give a holistic understanding of the product.
- Public documents often omit valuable or even essential information for agencies applying reliance, including specific details about the product's formulation, detailed clinical trial data and information about previous quality concerns.
- DNM has faced some challenges in its pathway to reliance, including promoting the importance of trust; increasing credibility as a regulatory agency; promoting strategic alliances between agencies and the health industry; modernising technology for transparent exchange of health information; establishing reasonable requirements and having controls in place to ensure proper application of reliance; application of the same criteria to all types of medical products, and introduction of standardised processes.

Egypt agency perspective

Dalia Abouhusein, QA General Manager, Egypt Drug Authority

- The Egyptian Drug Authority was established as an independent authority in 2019, after the issuance of the Egyptian Drug Authority Establishment Law. This is an independent authority reporting directly to the Egyptian Prime Minister. Before this, medical products were regulated through three different institutions working collaboratively under the umbrella of the Ministry of Health.
- In Egypt, reliance practices have been used for many years, although not using the term 'reliance'. Quality guidelines referenced reliance as a tool to implement risk-based approaches within the Egyptian Drug Authority. The agency now has new guidelines for reliance for several processes (e.g., market authorisation, resonance, lot release, lab testing, etc).
- The Egyptian Drug Authority requests several documents to ensure sameness of product: the full CTD file, the assessment report, the CPP, and other documents.
- The Egyptian Drug Authority also has a pathway if the assessment report is not available, as is often the case. However, it is useful to have the assessment report as it is not only used to ensure sameness, but also to enhance and build capacity of assessors through best practice learnings.
- The Egyptian Drug Authority shares work activities with other NRAs and some NRAs are relying on the Egyptian agency's decisions and activity. It is a requirement as a reference and relying agency to have a policy in place to share information, which is a very important activity.
- The goal of the Egyptian Drug Authority is to build capacity and enhance organisational practices to one day be a WHO-listed authority or reference country to other NRAs.

Company perspective

Leonardo Semprún, Senior Director, Global Regulatory Policy Lead, LATAM, MSD, USA

- The regulatory landscape in Latin America is very complex, with varying levels of agency maturity and implementation of reliance; and diverse levels of progress in international initiatives for cooperation, collaboration, and convergence. Legal landscapes and international agreements are also variable.
- Documentation plays a key role in enabling reliance. It is used for regulatory decision making, to accelerate approvals, and to enhance trust and capacity across regulators. While both public and the non-public documents contribute to risk-based decision making, there are questions about the utility and accessibility of non-public documents.
- Use of a harmonised dossier for global submissions enhances efficiency and reduces filing time. To ensure product sameness and enable risk-based review, clear guidelines are necessary. A signed declaration of product sameness, along with justification of any potential differences, should be provided to the regulatory agency; it is also crucial for relying agencies to receive the same product documentation assessed by the reference agency to ensure global patient access to high-quality products.
- The PAR should be made available as it provides information for regulatory decision making, but completeness and usability can vary across agencies. Additional information such as unredacted assessment reports, the marketing authorisation application dossiers, or the CPP may be used by relying agencies to make an informed decision. This will vary depending on the agency maturity.
- Clear guidance on expected information in unredacted assessment reports is crucial for industry stakeholders.

- In terms of recommendations, stakeholders must focus on continuous dialogue, clarity and making purposeful requests for documentation. Communication channels should be established for sharing reliance-relevant information. PARs should be aligned across agencies, with science-based reliance practices being promoted.
- Harmonisation and alignment of technical documents is critical to improving the review process. In turn, trust and efficiency can be enhanced in regulatory decision making.
- The ultimate vision is to create a cloud-based system where one product, from multiple manufacturing sites, can be submitted and shared for review by multiple regulatory authorities, upholding data security and protection.

Session 4: What are the frameworks that agencies have implemented to practically use regional/trans regional models and what are the learnings?

Regional approaches to risk-based evaluation – What needs to be in place for these to operate effectively? What are advantages and barriers for regional alignment review models? Do these aid patient access to medicines?

Regional reliance models – EU perspective

Prof Steffen Thirstrup, Chief Medical Officer, EMA

The European system

The EU is a political union bringing together 27 countries and cultures, with 453 million citizens and 24 languages. As such, the same legislation relating to medicines can be brought in across all Member States, layering national legislation on top (e.g., for pricing and reimbursement).

The EMA works closely with the NRAs of the European Economic Area, which includes the 27 EU Member States, Iceland, Norway, and Liechtenstein. The scope of the EMA is the regulation of medicines: products that are intended to diagnose, treat, and cure diseases in both humans and animals. Medical devices are out of scope, apart from drug-device combinations, where EMA looks at the drug component, as are tobacco, food, alcohol bureaus, and so forth.

The EU uses English as its official business language, circumventing concerns regarding language used in assessment reports and other official documents. All consumer and healthcare-professional-facing documents, including the product label, Summary of Product Characteristics (SmPC), and insert leaflets are translated into each Member State language. This can be challenging; if there is an update to the SmPC, there will be an update into all 24 Member States' languages, with an English document kept as the master version. As an example of harmonisation, EMA is currently working on an electronic Patient Information Leaflet (e-PIL) for patients, so they can access medicines' insert leaflets in different languages.

Procedures in place

In Europe, the harmonised legislative framework dates back to 1965. At that time, the centralised procedure was established together with the EMA in 1995. The centralised procedure is for new active substances (both chemical and biologicals), advanced therapy medicinal products (ATMPs), vaccines, and several other product types falling under its mandatory scope. This is the only way an applicant can bring many products to the European market, including all biotech, cancer, cardiovascular, or HIV products.

At the other end of the scale is the national procedure, where the applicant applies for a national marketing authorisation with every member state.

There are also two further procedures, which are work sharing and reliance models: the mutual recognition procedure and the decentralised procedure (see slide below). Fundamentally, these work in a similar way to one another: the applicant applies for marketing authorisation in one country and that assessment report is then used in all 'concerned Member States'.

The mutual recognition procedure is a two-step process; the applicant gets a national authorisation and uses that to link up and add in more countries. Whereas, with the decentralised procedure, the applicant selects countries, and then moves forward. These two procedures are mainly used for generics, because they do not necessarily need a marketing authorisation in all 27 Member States.

The marketing authorisation for the centralised procedure is issued by the European Commission, the only body that can enforce a legal act on all 27 Member States. Products using the mutual recognition or decentralised procedure option obtain national marketing authorisations.



Classified as public by the European Medicines Agency

What is needed for reliance to operate effectively?

Regulatory harmonisation

On top of the legal framework, there is one set of harmonised European guidelines for industry. It is not easier to get a product licensed in one country versus another; the guidance is the same, with the same scientific and regulatory principles applied across the board. Should Member States disagree about product approvals, the Committee for Medicinal Products for Human Use (CHMP) is the arbitrating body.

Although there may be a wait for a time slot when using the national procedure, approval timelines are the same – the clock starts when the assessment starts. All Member States use the same eCTD dossier form. The EMA is spending a lot of time and money on harmonisation of IT systems, review tools, and cloud-based storage. There is one repository where companies upload their application, and the different Member States can download what they need at the appropriate time.

There is also a Pan-European benchmarking and auditing system in place, so individual Member States' systems can be benchmarked and reviewed, including the EMA itself.

Transparency and trust

Transparency and trust are also important. For the collaborative dossier assessment, one Member State will do the full assessment; or for the centralised procedure, there will be typically two national expert groups. In order to involve all Member States, transnational assessment teams were created; for example, there may be a Lithuanian non-clinical assessor, a Polish clinical assessor, and a Danish rapporteur.

The National Assessors Network Training Center now provides training and assessment to newcomers within different agencies, assuring the same standard, the same level of understanding, and the same approach to assessment is taken across the board.

Experts can also get to know one another by being involved in working parties and expert communities at the EMA. For example, there is a non-clinical work party, and an expert community for cardiovascular diseases, which are staffed with experts from all 27 Member States. These act as pools of experts, where individuals can work together and exchange views, and in doing so obtain a mutual understanding of how each other works.

Full transparency is required on many levels. All assessors and employees of the European system have their declarations of interest published. This means assessors may be excluded from particular procedures because they have either an established or perceived conflict of interest. Assessment reports on the EMA website are redacted as little as possible (almost only commercial confidential information in the CMC section and the names of assessors, due to data protection European laws).

EMA has re-started (post-COVID) publishing clinical trial results submitted as part of a dossier, as well as starting to publish protocols for clinical trials getting approval in Europe. The aim is to move towards greater levels of transparency.

Summary

Regulation is designed to protect patients and bring products to the market with a positive benefit-risk, not to be a barrier to innovation and patient access. Collaboration and reliance have multiple benefits, for regulatory authorities, developers and patients worldwide. Reliance should be considered by all agencies, independent of their capacity or maturity, for the whole product life cycle. Building trust will take time and requires collaboration and common understanding.

Regional approaches to risk-based evaluation – What needs to be in place for these to operate effectively? What are advantages and barriers for regional alignment review models? Do these aid patient access to medicines?

Regional reliance models – African perspective

Jackson Kiberenge, Drug Registration Officer, Tanzania Medicines and Medical Devices Authority (TMDA), Tanzania

The TMDA is an organisation under the Ministry of Health for the Tanzanian Mainland and is responsible for regulating medicines and medical devices. TMDA's mission is to protect public health by ensuring access to quality-assured medical products. To support this mission, TMDA participates in two regional medicines regulatory harmonisation initiatives (MRH), for the East African Community (EAC) and for the SADC. TMDA relies on the final recommendations received from these two initiatives.

Types of risk-based approaches used

Work sharing

The mode of reliance for the EAC-MRH and SADC-MRH initiatives is work sharing:

- Joint assessment is conducted with one country as rapporteur and another country as a peer reviewer.
- The final report is jointly reviewed in sessions that take place on a quarterly basis (for both the EAC and SADC).
- Each country adopts the recommendation, which includes a common list of questions, compiled by each country and sent to the applicant.
- If the product is recommended for registration / approval, each participating country finalises the recommendation for approval within 90 days.

Unilateral reliance pathway

Another risk-based approach used by TMDA is unilateral reliance. With the unilateral reliance pathway, TMDA does abridged assessments for products that have already been prequalified using the WHO-CRP procedure. TMDA also relies on SRA-approved products, based on the availability of the full or unredacted evaluation report.

Reliance based on signed agreement

Another risk-based approach TMDA uses is based on signed agreements between member state countries within the EAC or SADC, whereby one NRA relies on decisions made by another NRA. For example, there is a signed MoU between Rwanda FDA and TMDA, where Rwanda FDA relies on TMDA decisions. Currently, TMDA has MoUs in place with Namibia, Burundi, Botswana, South Sudan and Zanzibar for various regulatory functions, including marketing authorisation.

Advantages for regional alignment review models

The advantages of using regional alignment review models include:

- Shorter timeline for approval of the product - at the national level in Tanzania, it previously took 280 days to approve a product. Using the risk-based approach based on work sharing, TMDA approves products in around 90 working days.
- Opportunity to train other NRAs that have limited capacity in terms of assessor expertise.
- Use of regional harmonised guidelines and procedures.

- Increased access to generic medicines and broader, more rapid access to vaccines and other therapies.
- Optimised use of resources and reduced replication of work.
- Promotes Regional Centres of Regulatory Excellence and mutual recognition agreements, such as signed MoUs.

Barriers for regional alignment review models

The barriers associated with regional alignment review models include:

- Varied capacity amongst NRAs: some are mature in regulatory capacity, others less so.
- Limited expertise and experience in reviewing complex formulations. For example, advanced therapy medicinal products and new chemical entities.
- Lack of an information-sharing platform, which impacts the availability of the final report.
- Limited access to the full evaluation report from SRA countries.

Summary

TMDA utilises several risk-based approaches, with benefits including shorter timelines for product approval and increased access to medicines. Several things are needed to ensure regional risk-based approaches can operate effectively (see slide below). For sustainability, regional collaborative initiatives need resources, including both reference materials and a dedicated workforce. TMDA would like to promote stakeholder engagement and engage with academic institutions to offer programmes to increase the educated workforce. There is also a need to develop an effective information-sharing platform to ensure reference materials are easily available.

WHAT NEEDS TO BE IN PLACE FOR THESE TO OPERATE EFFECTIVELY

- For sustainability, the regional collaborative initiatives need resources such as reference materials (USP, BP/Phar. Eur.,) and workforce.
- Expanded product scope to be considered for regional review
- Promote stakeholder engagement
- Engagement of academic institutions to offer post graduate courses in Regulatory Science
- Development of effective Information sharing platform (website, data repositories, portals)
- Development of strong policies that promote work sharing, unilateral reliance, information sharing and collaborative review

Project Orbis – A collaborative model with sharing assessment as it occurs

Health Canada perspective on collaborative assessments

Sophie Sommerer, Director General, Biologics and Radiopharmaceuticals Drugs Directorate (BRDD), Health Canada

Project Orbis

Project Orbis is an FDA Oncology Center of Excellence initiative for oncology products, which provides a framework for parallel submission review and information sharing among international partners. Project Orbis aims to give patients faster access to promising cancer treatments across the globe. Health Canada has been a partner in Project Orbis since its inception in 2019, and now there is a growing list of partners including:

- TGA of Australia
- ANVISA of Brazil
- Health Products and Food Branch (HPFB) of Health Canada, Canada
- Ministry of Health (IMoH) Pharmaceutical Administration of Israel
- Health Sciences Authority (HSA) of Singapore
- Swissmedic of Switzerland
- MHRA of the UK.

Project Orbis has three different types of collaborative review:

- Type A, the simultaneous review, when a submission comes into one of the Project Orbis partners very close to the time that it is submitted at the US FDA
- Type B, when the application is made within more than 1 month of the FDA submission
- Type C, when the application is made any time after the FDA submission.

In all of these cases, Project Orbis has provided regulatory agencies like Health Canada with the opportunity to get access to reviews from the FDA, and various levels of collaboration, depending on which type of review has been initiated. Sponsors can select which Project Orbis partners they would like to be involved and regulators have the opportunity to discuss their own capacity to engage on these files as well.

Project Orbis at Health Canada

At Health Canada, Project Orbis has been used for new active substances and supplements for indications for approved products. Health Canada has two expedited review pathways: either a priority review pathway, or products can be considered for advanced consideration for a notice of compliance with conditions, which has an expedited timeline.

Project metrics

For the first couple of years of Project Orbis, momentum was building, and by 2021 the number of submissions was increasing, for both new active substances and supplements to new drug submissions (see slide below). There was a fairly even split across Type A, B, and C submissions. Health Canada has been involved in 59 completed submission reviews between 2019 and 2023. Health Canada is completing these reviews ahead of schedule compared with regulatory timelines, particularly for new indications for existing products.

Project Orbis at Health Canada: Project Stats

Approved NDS & SNDS by PO Type (2019-2023)

- Completed submission review by Health Canada between 2019 – 2023 = 59 submissions:
 - Type A (19), Type B (19), Type C (21)

NDS					SNDS				
YEAR	TYPE A	TYPE B	TYPE C	TOTAL	YEAR	TYPE A	TYPE B	TYPE C	TOTAL
2019	0	0	0	0	2019	3	0	0	3
2020	3	0	0	3	2020	4	1	0	5
2021	4	2	7	13	2021	2	6	0	8
2022	0	2	4	6	2022	4	6	4	14
2023	0	0	2	2	2023	2	1	2	5
Total	7	4	13	24	Total	15	14	6	35

NDS = New Drug Submission

SNDS= Supplement to a New Drug Submission

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Project experience

Health Canada has seen a marked difference between Project Orbis submissions and submissions not going through the Orbis pathway – first, in terms of shorter timelines to approval, but also in terms of the submission gap (see [CIRS R&D Briefing 88](#)). In the past, there has often been a delay in filing with smaller jurisdictions, with Europe and the US tending to be the first targets. With Project Orbis, there has been a change in filing behaviour, with submissions now coming earlier to Health Canada and other partners.

In Health Canada’s experience, each application has been unique, although has always required some agility. Health Canada has continued to refine internal processes and implement lessons learned, e.g., use of a multi-disciplinary assessment aid.

There has been opportunity for information exchange, which has been particularly valuable, offering the chance for evaluators within Health Canada to talk to like-minded individuals who are looking at the same information. This has helped in building confidence in each other and in Health Canada’s own assessments.

Increased openness and transparency amongst partners have also been a benefit of Project Orbis. There have been many collaborative discussions, including with regulators that have comparatively more capacity, which has helped strengthen the quality of Health Canada’s reviews.

Challenges

Timelines are short for Type A & B submissions, so pressure is felt in continually trying to condense timelines. Health Canada has limited resources and trying to work more quickly is not always easy. It can be challenging to align timelines with partners in light of high workloads and resource constraints.

Downstream healthcare system impact is another challenge, e.g., pressure on funding bodies. The regulatory authorisation step is just one part of getting a product to market. Health Canada has to consider what this means for health technology assessors and payers, for example.

Communication with sponsors when working on these Project Orbis submissions could also be improved, for example, in terms of understanding the status of a Project Orbis application.

Potential for improvement

There could be a reduction in duplication of questions if Health Canada could access responses to questions from other regulators who are ahead in the process. This would help in removing the wait time for a response, while sponsors would not need to respond to the same question multiple times.

What's next for Project Orbis?

Project Orbis partners would like to keep an open dialogue with applicants, and are encouraging industry to think about pipeline submissions, to aid preparation for future submissions, e.g., workload management and planning.

Health Canada is continuing to build interagency collaboration, investing in aligning regulatory and policy approaches where possible. Within Project Orbis, there is a push to be more intentional with reducing duplication, taking into consideration each agency's national requirements and policies. In addition, there is a desire to expand Project Orbis to include more regulatory jurisdictions, at the discretion of the FDA.

Finally, Health Canada continues to look for opportunities to facilitate information exchange and to build upon, refine and apply best practices and the learnings of its experiences.

Summary

Project Orbis provides a framework for parallel submission review and information sharing among international partners. Health Canada has seen a large difference between Project Orbis submissions and submissions not going through the Project Orbis pathway, both in terms of shorter timelines to approval and submission gaps. Challenges remain, including the pressure from short timelines and the potential downstream healthcare system impact. Looking to the future, there is a desire to expand Project Orbis to include more regulatory jurisdictions, encourage forward planning from industry and improve information sharing.

ACCESS work sharing – could this be utilised as a model for other regions?

Dr Claus Bolte, Chief Medical Officer, Swissmedic, Switzerland

ACCESS overview

ACCESS is based on respect, transparency, openness and flexibility, with the premise that each country has something to offer to the other members. For new drug applications and line extensions, the workload is simply split by CTD modules. Members have equal status in terms of engagement and decision making and can opt out when it comes to limited capacity or capabilities.

The [ACCESS Consortium](#) operating model is systematic, repeatable and reliant on formal processes and expertise, which are needed in addition to shared methodologies and international standards. Applicants (sponsors) can choose from two to five jurisdictions (Australia's TGA, Health Canada, Singapore's HSA, Swissmedic and the UK MHRA). All five jurisdictions have a collective population base of ~160 million.

The ACCESS charter lays out relevant processes as well as conveying the above principles related to culture and attitudes, and resource equity. It goes beyond evaluating modules of a marketing authorisation application, extending into post-marketing and inspection activities, spanning from small to large molecules, and more recently, also covering ATMPs.

The [Swissmedic website](#) provides more details, the number and names of products already approved, as well as different types of recent activities. It also shows the [strategic plan for ACCESS](#), which was published in 2021, and has been revised every year to accommodate new technical and regulatory developments.

Work-sharing opportunities and challenges

Companies have shared that they submit a lot earlier when using an ACCESS pathway. ACCESS enables a more efficient use of scarce resources, for both regulator and industry, resulting in better review quality as a result of cooperation. Pertinent metrics published in [CIRS R&D Briefing 88](#) confirm reduced submission gaps, as well as competitive approval times.

The key challenge is conducting a peer review based on something another agency has assessed. Trust must be built between parties, while consolidated work-sharing procedures are needed, and these take time to develop. Increased coordination efforts are also needed, particularly working across several time zones.

Worksharing: Pros (Opportunities) & Cons (Challenges)

Opportunities	Challenges
Efficiency: Reduced workload due to splitting review / modules between agencies	Building trust
Sharing of resources and expanding expertise across jurisdictions	Increased coordination effort including working across several time zones
1st-wave -agency positioning with a large population	Creating consolidated work-sharing procedures
Faster assessment time and shorter submission gap	Peer review based on « foreign » assessment report

Summary

The ACCESS Consortium offers a work-sharing model where participating agencies review different modules of the dossier but make their own independent decisions in the end. Shorter submission gaps, more efficient use of scarce resources and competitive approval times clearly outweigh coordination efforts between agencies.

What do companies see as the advantages and barriers for regional review or collaborative review models?

Priti Shah, Executive Director, International Regulatory Affairs, AstraZeneca, UK

Every regulatory authority is looking at regional work sharing and collaborative pathways to facilitate faster access to life-saving medicines and innovation. The main reason for this is to save resources: there is no single country that has the resources or capability on their own, particularly as products are becoming increasingly complex.

Global collaboration is urgently needed. Working together allows patients earlier access to medicines, which is both an industry objective and a regulator's objective.

This is a time of great regulatory change. Science is developing faster than guidelines can keep up; there are new modalities and therapeutics, and many different regulatory pathways. Patients have a bigger voice in regulatory decision making. Artificial intelligence and digital health are changing how things are done. The types of data reviewed are very different.

There is a need to future-proof processes to prepare for these changes that are on the horizon.

Where we live makes a difference to medicine availability

The industry vision is for patients to have simultaneous access to medicines globally. However, for emerging markets, there is often a delay in registration. According to data from the CIRS 2022 Emerging Markets Metrics Programme, median time from first global approval to submission in some countries is close to 300 days, with median time to approval of 800 days. Some authorities are taking 500 days to approve even with a global reference approval. This delay may be due to reliance on a reference country, company strategy, or a lack of optimised processes and longer review times. For example, availability of the right information to make decisions is often repeated as a challenge.

Learnings from the pandemic

With the AstraZeneca COVID vaccine, the same dossier was submitted to every country around the world. AstraZeneca learned several lessons from this process:

- Reliance and work sharing were not optimal, even in a state of an emergency. AstraZeneca received thousands of questions, only a minority of which resulted in substantial changes to approvals. If questions are submitted but do not result in any changes, there is minimal value-add.
- Additionally, different authorities made different decisions based upon standard of care, medical practice, infrastructure and populations the vaccine would be used in.
- Countries wanted investment in regional supply chains.
- Many authorities did not have frameworks for reliance models in place.

Authorities need a sustainable toolkit of regulatory pathways, including reliance, work sharing, collaboration, as well as independent review capabilities. The ideal system would be submissions made in parallel across the world through a cloud-based system, with real-time review and real-time information, so all authorities have access to the information they need at the right time.

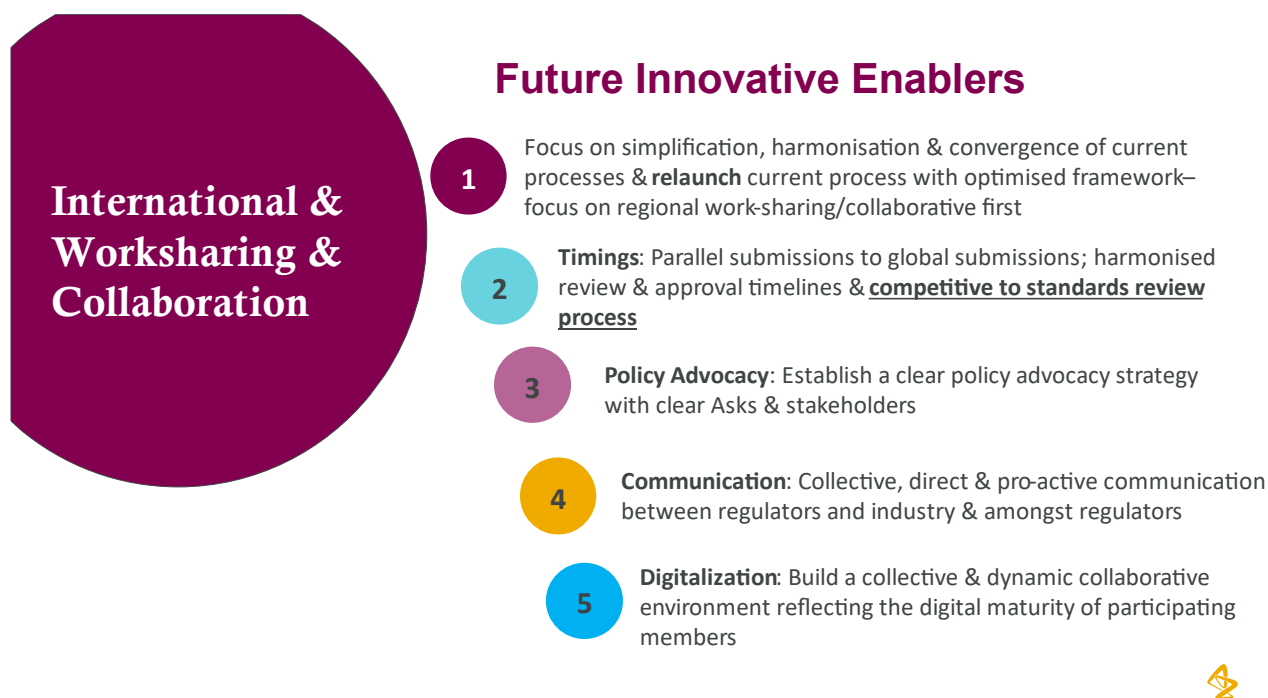
Key areas for consideration in terms of regional and collaborative frameworks

The fitness of regional and collaborative review frameworks must be evaluated end-to-end, looking at legal frameworks, harmonisation, ways of working, digitisation, labelling and packaging, transparency, and decision making. Key considerations include:

- There is limited transparency around predictability of approval and processes, how decisions are made, and timing. There are many different pathways available, e.g., WHO Collaborative Registration Procedure, EMA OPEN, ASEAN Joint Assessment etc; while it is positive that these opportunities exist, agencies need to be able to decide which pathway is right for a particular product.
- Even where reliance and work-sharing models exist, there are still country-specific requirements to be met.
- A convergent regulatory framework is needed.
- A system is needed that allows sharing of real-time data quickly.
- Harmonisation across labelling and packaging is needed – having country-specific packaging actually stops the supply chain.

The future

In future, the focus will be on what the healthcare ecosystem looks like, and how new products and data change the way we do things. Transparency around timings and ways of working, and earlier communication with real-time information release, will be critical. Simplification and harmonisation are important, and digitalisation (e.g., cloud-based submission and real-time reviews) will help to achieve this.



Summary

Every regulatory authority is looking at regional work sharing and collaborative pathways to facilitate faster access to life-saving medicines and innovation. Global collaboration is urgently needed. Working together allows patients earlier access to medicines, which is both an industry and regulatory objective, and is beneficial for the health ecosystem. However, there is a need to future-proof regulatory processes to prepare for changes on the horizon. Transparency around timings and ways of working, alongside earlier communication with real-time information release will be critical; digitalisation will help to achieve that.

Session 5: Roundtable discussions and feedback

Workshop participants were assigned to a roundtable group and provided with a handout of background information and questions for discussion (developed by CIRS). The Chairs and Rapporteurs of each roundtable were asked to facilitate and document the discussion, respectively. The Rapporteurs then fed back to all workshop participants in the main plenary session.

Roundtable Discussion A: Regional collaboration – what are the key considerations or framework that enable the construction and delivery of an efficient and effective regional/trans regional model?

Chair: Prof Steffen Thstrup, Chief Medical Officer, European Medicines Agency

Rapporteur: Marite Prieto, South Latam Cluster Lead, Pfizer, Brazil

The group were asked to discuss key considerations for the creation and utilisation of regional and collaboration models. The following considerations were identified:

- Regional models must be *attractive* to regulators and companies, and this is based on the models' predictability, efficiency, cost, and life cycle management.
- There must be *transparency* in processes and harmonised procedures. There should be clear, common guidance in place for how to apply reliance and timelines should be predictable. Agencies and companies should follow best regulatory practices.
- There must be *trust* between regulators and *benchmarking* of quality should take place (e.g. WHO-Listed Authorities, GBT). There is also a need to define what is needed to be a reference agency.
- *Equity* in the distribution of work between partnering regulators is important. Resources and the level of knowledge available in each of the authority must be considered (in terms of quality, efficacy and safety).

The group ranked possible solutions to the key needs identified above (see table below). The solutions were ranked in terms of importance (1= most important, 4 = least important) for both industry and regulators and considered in terms of priority (short term = to be addressed in <12 months, long term = to be addressed in >12 months).

Solutions (long/short term)	Rank – Industry view	Rank - Regulator view
<ul style="list-style-type: none"> • Transparent timelines defined by legislation (long term) • Measure timelines for work sharing, priority and ordinary reviews (short term) 	1	4
<ul style="list-style-type: none"> • Good Regulatory Practices and convergency (long term) • Landscaping exercise on regulators' collaboration (deep dive into memorandums of understanding) (short term) 	2	1
<ul style="list-style-type: none"> • Commitment to a shared decision model (long term) • Investigate a shared benefit-risk model (short term) • Landscaping on WHO GBT and WHO-Listed Authorities (short term) 	3	3
<ul style="list-style-type: none"> • Work-sharing agreements based on each agency's capacity (long term) 	4	2

The group identified how regulators and companies can ensure they obtain and evolve necessary subject matter expertise and build capacity, as follows:

- Create training centres for regulators regarding how to do a reliance review.
- Focus on multisector efforts to take advantage of the experience-sharing network within regulators, industry, academies, associations, etc.
- Implement staff rotation programmes amongst regulators, as well as visits between regulators and industry.
- Regulators and industry to work together for regulatory preparedness.
- Horizon scanning and sharing of pipelines so regulators are prepared to face upcoming challenges and opportunities.
- Provide templates for measuring timelines and monitoring (e.g., [OpERA Programme](#)).
- Develop collaborative tools.

The group's recommendations for future work to enable the construction and delivery of an efficient and effective regional model were to:

- Define criteria for determining 'like-mindedness' and measure this across agencies.
- Characterise the strengths needed for agencies to collaborate with each other.
- Conduct a landscaping exercise to better understand how agencies are using MoUs to facilitate collaboration.
- Investigate a shared risk-benefit model.
- Map out the capabilities of different agencies based on information from the WHO GBT and List of WHO-Listed Authorities.
- Conduct research studies comparing target versus actual timelines for work sharing and regional review pathways.
- Measure local timelines for work sharing, priority and standard pathways.

Roundtable Discussion B: Changing mindset – How can this best be achieved within companies and agencies to enable reliance and collaborative models?

There were two Roundtable groups tasked with discussing changing mindsets to enable reliance and collaborative models: one for English-speaking participants and one for Spanish-speaking participants. The key discussion points from each group are summarised as follows.

English-speaking group

Chair: Dr Boitumelo (Tumi) Semete, Chief Executive Officer, SAHPRA

Rapporteur: Sheila Inada, Regulatory Affairs Manager, AstraZeneca, Brazil

Before starting the exercise, five steps for changing mindset were discussed by the group:

- **AWARENESS:** of the business reasons for change. Awareness is a goal or outcome of early communication related to organisational change.
- **DESIRE:** to engage and participate in the change. Desire is a goal or outcome of sponsorship and resistance to change.
- **KNOWLEDGE:** is about how to change. Knowledge is a goal or outcome of training and coaching.
- **ABILITY:** to realise or implement the change at the required performance level. Ability is a goal or outcome of additional coaching, practice and time.
- **REINFORCEMENT:** to ensure that change sticks. Reinforcement is a goal or outcome of adoption measurement, corrective actions, and recognition of a successful change.

The group were asked to discuss key needs for mindset change / cultural transformation for the creation and utilisation of reliance and collaborative models by companies and agencies in global submission and assessment of new medicines. These were identified as follows:

Agencies

- Identify reliance champions to address any uncertainty, anxieties or fears from wider staff.
- Run pilots using the design-thinking approach.
- Offer training to staff via webinars, exchange programmes, etc.
- Build strong relationships with reference agencies.
- Keep the assessment team engaged in the science and keep them challenged.
- Set up a regulatory science academy in either countries or regions.
- Get buy-in from senior leadership.

Companies

- Be open to taking part in pilots and taking risks.
- Ensure senior leadership buy-in.
- Offer full support to the NRA's pilot projects.

The group then discussed practical approaches that need to be addressed to achieve this cultural transformation and organised them according to company/agency involvement and whether they are short or long-term approaches (see below).

Approaches	Company and/or agency	Addressed in the short term (<12 months)	Addressed in the long term (>12 months)
Training offered by reference health authorities related to their risk-based analysis/internal structure for review/benefit-risk approaches	Company and agency	Yes	Yes
Staff exchanging comments with other NRAs (observers, joint reviews)	Agencies	Yes	Yes
Include reliance approaches in Key Performance Indicators	Company and agency	Yes	Yes
Implement a survey for identifying products to be submitted through specific procedures (Orbis, ACCESS, reliance, etc)	Company and agency	Yes	Yes
Incorporate reliance procedure within regulatory strategy decisions	Company and agency	Yes	-
Set up Regulatory Science Academy in countries or regions	Company and agency	No	Yes

The group discussed potential challenges and solutions to utilising the approaches identified in the table above, for both companies and agencies.

Approach	Company and/or agency	Challenge	Solution
Training offered by reference agencies related to their risk-based analysis/ structure for review/benefit-risk approaches	Company and agency	<ul style="list-style-type: none"> - Time investment - Different tools used by agencies - Limited engagement with reference agencies (training, documents) - Lack of skills/knowledge for implementing - Lack of buy-in from senior management 	<ul style="list-style-type: none"> - Seeing training as an investment for future capability - Collaborative work between reference and relying agencies which may include changes in the current way of working for all stakeholders - Identifying reliance champions - Implement a coach for assessors
Strengthen tripartite relationship between companies, reference agencies and relying agencies through mechanisms like surveys identifying products to be submitted through specific procedures (Orbis, ACCESS, reliance, etc)	Company and agency	<ul style="list-style-type: none"> - Lack of sharing documentation - Different local procedures, different ways of working and concepts 	<ul style="list-style-type: none"> - SOPs, templates, clarity on documents to be provided and type of information expected – request ICH support on this - Establish a model of monitoring reliance results - Utilise data-sharing platforms
Staff exchanging with other agencies (observers, joint reviews)	Agency	<ul style="list-style-type: none"> - Time investment - Limited formal relationships between the agencies 	<ul style="list-style-type: none"> - Standardised templates for making communication between agencies easier
Regulatory Science Academy	Agency	<ul style="list-style-type: none"> - Inability to find the right partners/experts - Limited financial support 	<ul style="list-style-type: none"> - Establish international partnerships at a local level to create the Regulatory Science Academy - Leverage ex-Regulatory Experts
Incorporate reliance procedures into regulatory strategy decisions	Company	<ul style="list-style-type: none"> - Resistance due to the lack of understanding of the requirements and benefits 	<ul style="list-style-type: none"> - Increase awareness of reliance benefits and metrics - Knowledge sharing - Identifying reliance champions

The group's recommendations for future work to enable mindset changes in companies and agencies to support the use of reliance and collaborative/workshare models are as follows:

- **CIRS** to develop an overarching roadmap for reliance based on previous workshops and research, including steps on how to change mindsets. This should involve interactions with other organisations including agencies and industry trade associations.
- In the short term, **WHO** to expand the current Good Reliance Practices document to include guidelines for implementing reliance for both relying and reference agencies, with support from **ICH**.
- **CIRS** to continue fostering awareness of reliance, and to develop a database for reliance and work-sharing resources.
- **Reference agencies** to be made aware of the extent of agencies that are relying on their decisions and offer training and access to the required documentation to enable good reliance practices.
- **Reference agencies** should evaluate the current content in their PARs to allow sameness verification by relying companies.
- **Regulators** and **sponsors** should establish a platform for sharing data between themselves.

Spanish-speaking group (feedback was translated into English)

Chair: Patricio Enrique Reyes Sepúlveda, Head of New Product Registration Section, Institute of Public Health, Chile

Rapporteur: Ana Gabriela Trejos Vásquez, Regulatory Affairs Lead, Caribbean, Central America and Venezuela, Roche, Costa Rica

The group were asked to discuss key needs for mindset change / cultural transformation for the creation and utilisation of reliance and collaborative models by companies and agencies in global submission and assessment of new medicines. These were identified as follows:

Agencies

- Reliance must have a legal basis and formal backing.
- Support is needed for technical staff to be able to apply reliance.
- Assertive communication about the objectives and benefits of reliance is needed at all levels.
- Education is needed about the opportunities that reliance provides (e.g., to alleviate the workload of the institution and redirect resources to other areas, such as pharmacovigilance).
- Staff should be motivated to implement reliance as good practice.
- Metrics that show the benefit of using reliance should be defined (response times and efficiency in the evaluation process).
- Public policies and country-level strategies are needed, where agencies base their decisions on regulatory science and adopt risk-based decision making (definition, classification and tools for risk assessment).

Companies

- Ambassadors are needed to raise awareness of the benefits of reliance and its broader impact on accelerating medicine availability.
- Companies need training from regulatory agencies on their requirements. Clarity is needed on what is expected and what must be adhered to, enabling industry to fulfil these requirements. This could be facilitated by trade associations.
- Internal efforts are needed to provide information to local associations so they can support agencies.
- Domestic companies must understand the benefits of reliance implementation and have incentives to comply with international standards.

The group then discussed practical approaches that need to be addressed to achieve this cultural transformation and organised them according to company/agency involvement and whether they are short or long-term approaches (see below).

Approaches	Company and/or agency	Addressed in the short term (<12 months)	Addressed in the long term (>12 months)
Positioning reliance as a country framework priority	Agency	Yes (unilateral reliance)	Yes (collaborative review)
Review and update the regulatory framework	Agency	Yes	
Implement abridged review guidelines (pilots and internal peer review)	Agency	Yes	
Ongoing training	Agency & Company	Yes	Yes
Establish and monitor indicators/metrics	Agency & Company	Yes	Yes
Feedback loop between company and agency	Agency & Company	Yes	Yes

The group discussed potential challenges and solutions to utilising the approaches identified above, for companies and agencies.

Approach	Challenge	Solution
Agency		
Positioning reliance as a country framework priority	Acceptance and alignment by different stakeholders. Resistance to change.	Educating/training all stakeholders
Review and update of the regulatory framework	Time the process takes and possible opposition from domestic industry.	Risk/benefit justification of regulation and sharing of experience with other regulatory authorities
Demonstrate benefits of reliance - impact for stakeholders through indicators/metrics	Quantify impact through indicators/metrics.	Transparency of indicator/metrics data for all stakeholders
Company		
Positioning reliance as a priority	Resistance to change by all parties involved	Educating/training all stakeholders
Feedback loop between company and agency	Perception that company-agency interaction is a conflict of interest	Open spaces for interaction - facilitate communication and transparency

The group's recommendations for future research or work to enable mindset changes in companies and agencies to support the use of reliance and collaborative/workshare models were to:

- Examine the 'sameness concept' in more detail to facilitate alignment on the definition of sameness.
- Agencies should offer a pre-submission process/meeting to help clarify if companies have the right information to submit via a reliance route. This will help to conserve authority time and resources.
- Compare PARs and unredacted reports - is the additional information sufficient for agency decision making or not?
- Standardising PARs from reference agencies.

Roundtable Discussion C: Good Reliance/collaborative practices for companies and agencies – what needs to be in place moving from principle to implementation?

There were two Roundtable groups tasked with discussing good collaborative practices: one for English-speaking participants and one for Spanish-speaking participants. The WHO definition of Good Review Practices was provided to aid the discussion:

Good Review Practices: *Documented best practices for any aspect related to the process, format, content and management of a medical product review. The objective of Good Review Practices is to help achieve timeliness, predictability, consistency, transparency, clarity, efficiency and high quality in both the content and management of reviews. This is done through the development of review tools (for example, SOPs and templates) and reviewer learning activities (for example, training courses, mentoring, orientation packages and discussion sessions). To promote continuous improvement, all aspects of Good Review Practices should be continuously evaluated and updated.*

The key discussion points from each Roundtable group are summarised as follows.

English-speaking group

Chair: Cynthia Ban, Global Head, Regulatory CMC, Vaccines, Sanofi, Canada

Rapporteur: Luciana Carla Duran, Senior Regulatory Affairs Manager/ Regional Regulatory Affairs Lead, Novo Nordisk, Brazil

The group reviewed the definition of Good Review Practices for agencies for use in global submission and assessment and discussed whether the definition is fit for purpose for collaborative models. The group agreed that the definition works but is quite technical. It should include a reference to the collaborative trust-building relationship that is needed for reliance. The group also highlighted the importance of strong leadership teams within both agencies and companies to ensure that staff are engaged with reliance.

The group were then asked to discuss and propose key areas and practices that should be considered to allow agencies and companies to implement collaborative models, which were identified as follows:

- Conduct a global mapping exercise to identify expertise that can be leveraged, as a first step towards fostering Centres of Excellence and coping with expanding portfolios and therapeutic areas.
- Consider the concepts of 'sameness' and interpretation. There is a need for some flexibility in the interpretation of this concept.
- Requirements should be harmonised across countries, to support faster more efficient submissions.
- Predictable timelines should be built into this model. This could help secure buy-in from the leadership for reliance.
- There should be a secure, easy-to-use digital platform to exchange information and documentation.
- Harmonisation of assessment reports is needed, with additional clarification about Q&A rounds. The more harmonised these documents are, the easier is it for agencies and industry to work with them.

The group identified how Good Review Practices can be built into existing processes and how the benefits can be measured (see below).

Stakeholder	What is needed to ensure good practices are built in into processes?	Comment on how this can be measured
Agencies & Companies	Define a metric to measure the effort put into securing/conducting reliance and the return on investment Assess time to approval and number / complexity of Q&A rounds	Important to keep monitoring the impact of reliance over time, as the benefits may not be immediately obvious
Agency	Capacity building	
Company	Prevention of product shortages and supply by using reliance	
Company	Feasibility of using reliance for all possible submissions Understanding the key factors to consider when deciding to submit using reliance	e.g., looking at all possible submissions during a period of time and analysing which ones could potentially be submitted under a reliance pathway
Agency	Engagement and willingness to conduct reliance	Measure agencies' perspectives

The group's recommendations for future research or work to facilitate the implementation of good collaborative practices in companies and agencies were as follows:

- Examine how assessment reports are developed, who is using them and how they are being used.
- Harmonise assessment reports to facilitate review across agencies.
- Develop a framework that shows reviewers how they should undertake reliance.
- Improve agencies' transparency on the reasons for accepting or rejecting reliance requests.
- Conduct research comparing life cycle management products that have undergone reliance versus non-reliance pathways.
- Develop an IT tool/data-sharing platform that is secure and easy to use.
- Agencies with established reliance processes should facilitate training for agencies with less experience.
- Companies should provide unredacted assessment reports and Q&A documents to facilitate review.

Spanish-speaking group (feedback translated into English)

Chair: Maria Antonieta Román, Regional Regulatory Policy Lead, Emerging Markets - Latam, Novartis

Rapporteur: Heloísa Fávaro, Regulatory Affairs Director, AbbVie, Brazil

The group reviewed the definition of Good Review Practices for agencies for use in global submission and assessment and discussed whether the definition is fit for purpose for collaborative models. The group agreed that it is important to add 'flexibility' to the given definition to enhance collaboration.

The group then identified and proposed key areas that should be considered to allow agencies and companies to implement collaborative models: communications, agency autonomy, resources, convergence and the development of legal documentation. It was felt that there is a lot to work to do in order to move towards collaborative models, as some authorities lack even basic regulatory practices. There are varied levels of implementation and specific good review practices for collaborative models are not outlined.

The group were asked to discuss how to integrate and evaluate Good Review Practices in stakeholder processes (see below).

What is needed to ensure good practices are built into processes?	Comment on how it can be measured
Commitment by agencies to build flexibility into evaluations, open dialogue, pre-submission meetings	Establish a normative instrument to aid agencies in their operations and review its applicability
Industry's commitment to full reporting and transparency on differences and impact	Establish controls within agencies to monitor data and track dossiers
Communication and validation of understanding by companies and agencies Debriefing after international forums to disseminate knowledge at all levels of agencies and industry Joint training/forums within companies and agencies to align regulatory understanding	Make a follow-up plan to evaluate understanding
Support for strengthening and autonomy of agencies (resources)	Structure, process and outcome indicators
Prioritisation of collaborative models at the agency level	To be reflected in agency targets

The group's recommendations for future research or work to facilitate the implementation of good collaborative practices in companies and agencies were as follows:

- Conduct a study on barriers and issues limiting access. For example, substantial funds are allocated to labour / human resource, yet products fail to reach the market. What is going wrong?
- Conduct a survey into how agencies are implementing good review practices, looking at which requirements are being addressed and which are not. The results should be compiled into a best practices document to support agencies that are lacking in these areas.

Session 6: Next steps for risk-based evaluations

Moving from regional to continental reliance – What is the approach for Africa and why is it important?

Alex Juma Ismail, Program Officer, Regulatory Systems Strengthening, African Union Development Agency's New Partnership for Africa's Development (AUDA NEPAD)

Any mature regulatory system requires a lot of resources, ranging from human to financial, to keep up with the ever-changing regulatory environment. The globalisation of markets, sophistication of health technologies, rapid evolution of regulatory science and increasing complexity of supply chains demands international cooperation in ensuring regulatory oversight of medical products.

Reliance – a concept that has been around for many years – is the 'smart' way to regulate medical products. Many agencies have implemented reliance for years:

- The WHO certification scheme was introduced in 1969
- The EU introduced mutual recognition in 1995
- WHO introduced SRAs, now WHO-Listed Authorities, and many countries keep relying on those agencies.
- Most African NRAs are relying either on WHO SRAs, other agencies within Africa, and within regional programmes.
 - In Africa, authorities have been grouped into a number of regional economic blocs, within which there have been harmonisation programmes active for several years.

Why is reliance important for Africa?

Around 17% of the world's population is in Africa, equivalent to 1.3 billion people. Africa accounts for a quarter of disease burden of the entire globe; for example, 90% of the world's annual malaria cases are in Africa. However, only 6% of global health spending and less than 1% of pharmaceutical market can be found in Africa, and Africa produces less than 3% of the medicines consumed by its people.

Pharmaceutical supply chains have multiple intermediaries, meaning medicines sold in Sub-Saharan Africa are some of the most expensive in the world. Africa also has a high prevalence of substandard and falsified medicines (20%). Moreover, there are issues related to capacity, since most countries are not able to assess or inspect products that are considered complex.

Without a mechanism where countries can come together and rely on each other, the African Medicines Agency (AMA) might not be able to address these issues. Africa does not have the luxury of not collaborating.

Situational analysis – *study not yet finalised*

A situational analysis was conducted to see what reliance models are being used by countries and regional blocs in Africa. In total, 29 countries were surveyed, equivalent to 58% of the African continent. The responding countries were based within the SADC (14 countries), the Arab Maghreb Union (1), the Economic Community of Central African States (1), the Economic Community of West African States (5), the EAC (5), and the Intergovernmental Authority on Development (IGAD) in the Horn of Africa (3).

Most of the surveyed countries rely on the WHO prequalification process, which is limited to certain types of products. Most countries indicated that they have formal agreements with WHO. Some countries also have formal agreements in place with other African countries, usually within the same regional economic community.

Out of the 29 responding countries, nine rely on other countries in Africa. Two countries do not have any forms of reliance (or do not have such processes documented in legislation or guidelines). Most countries also rely on the ICH founding members.

Most of the surveyed countries employ reliance only in terms of marketing authorisation and registration. There is no evidence that reliance is employed for other regulatory functions. There are a number of bilateral arrangements in Africa, especially for countries bordering one another; for example, Tanzania and Rwanda, within the East African region. For these bordering countries, reliance may include issues of post-market surveillance or pharmacovigilance.

Recommendations

A number of recommendations have emerged from this study:

- Develop a Continental Reliance Guidance for implementation of reliance across Africa.
- Develop a Continental Reliance Agreement to allow African NRAs to rely on each other and on other agencies or organisations outside Africa.
- Propose reliance between two NRAs – mutual or unilateral.

Africa's approach

When it comes to implementation of reliance, guidelines often do not speak to the people doing the implementing; they speak to the system, the agency, or the country. The aim in Africa is to come up with a guidance document for implementing reliance in a step-wise approach from the bottom-up.

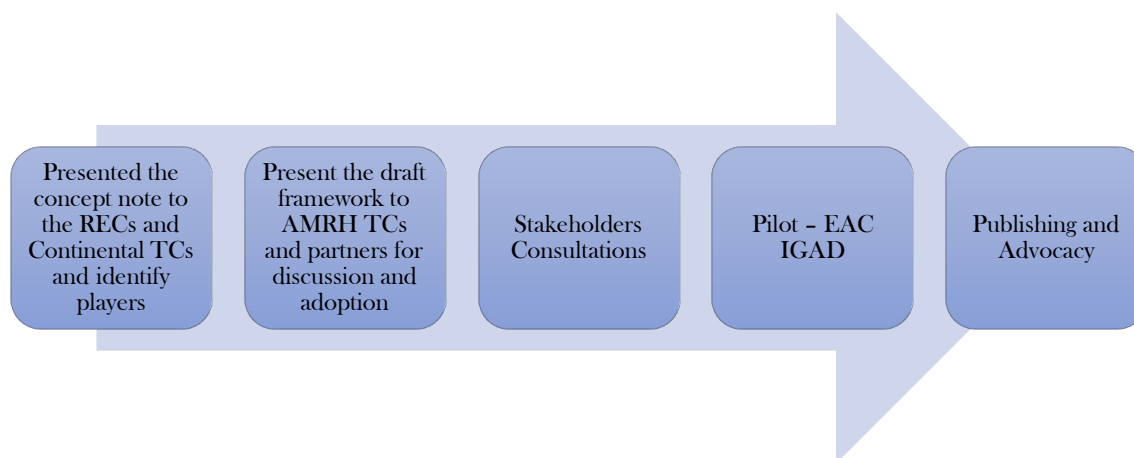
There will be documents for different experts: assessors, inspectors, lab analysts, and pharmacovigilance experts. They will be complemented with 'a reliance implementation tool', which will specifically guide countries. For example, documenting lessons learned within one country that might be useful in another.

There will be a framework in two parts: guidance and agreements. The agreement will be entered into by countries that have ratified the AMA Treaty, so they agree to implement those recommendations. The guidance will show countries how to go about implementing them.

Methodology (see slide below)

- The concept note was developed and presented to the five active regional economic communities. This was developed further and the approach agreed.
- It was presented to the continental technical committees, of which there are 10 supporting different functions for products.
- Once adopted, it was presented at a number of meetings convened in Africa, including the Scientific Conference on Medical Products Regulation.
- The next step is stakeholders' consultation, followed by a pilot within the EAC and IGAD. The aim is to see whether these two economic blocs can come together and implement these principles. Lessons will be learned and applied to support other regions – ultimately, the whole continent – to collaborate.

Methodology



REC: Regional Economic Community; TC: Technical Committee; AMRH: African Medicines Regional Harmonisation initiative; EAC: East African Community; IGAD: Intergovernmental Authority on Development

Summary

Without reliance mechanisms, the AMA might not be able to address the health and supply chain issues facing the African continent. A situational analysis was conducted to determine what reliance models are currently being implemented in different countries and regional blocs within Africa. Based on this, recommendations were developed to produce a guidance for implementing reliance from the bottom-up, along with an agreement to be ratified by countries who have signed the AMA Treaty.

Panel Discussion

What are the next steps in the implementation of risk-based evaluations?

Each panellist was asked to provide their thoughts on:

- What's next for jurisdictional/regional reliance models and collaborative efforts?
- Is continental convergence part of the plan moving forward?
- What are the opportunities and challenges?

Key points from the panel discussion are summarised below.

Alex Juma Ismail, Program Officer, Regulatory Systems Strengthening, AUDA NEPAD

- Implementation of reliance should be considered across all regulatory functions: not just marketing authorisation or product registration, but pharmacovigilance, post-market surveillance, laboratory testing etc.
- While it is important for countries to collaborate in product approvals, when products go into the market, there should be a continued effort to follow up and maintain standards post-approval.
- Regional Centres of Excellence help to ensure expertise across Africa. Individual country involvement in ICH is also important for bringing back learnings to share with other countries.

Dr Claus Bolte, Chief Medical Officer, Swissmedic

- There are three dimensions to consider when implementing risk-based evaluations:
 - *Operational*: Standard operating principles, including processes, procedures and templates, must be in place to guide reliance.
 - *Regional*: There is a need to consider which strategic partners are available regionally to undertake multi-collaborative reliance procedures. In addition to geographical proximity, agency 'like-mindedness' must also be considered.
 - *Strategic*: Reliance must be firmly embedded in the strategies of both regulators and industry.
 - There must be a balance across all three dimensions for risk-based evaluations to be implemented optimally.
- Political will is also imperative, which means there is a need to engage with politicians and policymakers to help them understand what reliance is aiming to achieve.
- Industry and regulators need to identify platforms to drive reliance forward on an international level. Organisations like the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Pharmaceutical Research and Manufacturers of America (PhRMA), and the Biotechnology Innovation Organization (BIO) may be well-positioned to do this on the industry side; however, for regulators, there are many workstreams and working parties, but there is currently no group solely focusing on promoting reliance.

Balbiana Verazes Sampaio Oliveira, Chief Advisor, ANVISA, Brazil

- It is important that agencies remain interested in regulatory harmonisation and convergence. For example, ANVISA in Brazil has put a lot of effort into adopting ICH guidance and is now preparing for WHO GBT assessment.
- ANVISA is focusing on reducing its backlog and putting more effort into work-sharing initiatives, which will help to build trust with other regulators and advance the implementation of reliance.
- There is a lot of knowledge, experience and best practice that countries in Latin America can share amongst one another. ANVISA has bilateral agreements with regional agencies for the purpose of information exchange and to consider projects for potential collaboration.

María Antonieta Román, Head of Regulatory Policy in Latin America, Novartis

- There should be a focus on developing existing sub-regional collaborative efforts in Latin America, with a view towards larger Latin American integration, but more needs to happen before this is feasible.
- It is important to start by considering the maturity levels of different agencies. Smaller agencies with lower maturity levels should be supported with resources, which could include sponsorship from more mature agencies.
- Technical and financial independence from governments is also key; this can be a challenge for some Latin American countries.
- Industry should commit to supporting agencies, and agencies to improving communication with industry, with a focus on transparency, good submission practices, and provision of complete information. Sometimes agency backlogs occur as a result of poor communication (lack of clarity, not knowing what information to ask for, etc).

Dr Lawrence Liberti, Director of the D.K. Kim International Center for Regulatory Science and Associate Professor of the Department of Regulatory and Quality Sciences, University of Southern California

- Providing advanced education in regulatory science is important for advancing risk-based evaluations.
 - There are some programmes available globally in advanced regulatory science, but there is room for expansion of education in Latin America, and further afield.
 - Countries or agencies considering the implementation of education programmes should not “reinvent the wheel”. For example, there are opportunities to learn from programmes in place in North America.
- How to select countries to rely upon, and the factors that allow an agency to interact with another agency, are other important areas for consideration.
 - A contingency analysis has been developed in the [FRPath database](#) that can help to identify which agency is relying on whom etc.
 - The ‘Assessing Reliance for Collaborative Harmonisation’ (ARCH) archetype has also been developed to group countries according to how they conduct reliance and allow comparisons to be made.

Appendix: Workshop attendees

Affiliations are stated as they were at the time of the meeting 28th and 29th February 2024.

**Presented via recording*

Ass Prof Dalia Abouhusein	QA General Manager	Egyptian Drug Authority
Ligia Schaefer Almeida	Regulatory Affairs Manager	Takeda, Brazil
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Dr Claus Bolte	Chief Medical Officer	Swissmedic
Dr Daniela Bravo	Executive Manager Regulatory Policy and Intelligence Latam	AbbVie, Brazil
Dr Magda Bujar	Senior Manager, Regulatory Programme and Strategic Partnerships	Centre for Innovation in Regulatory Science
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Heloísa Fávaro	Regulatory Affairs Director	AbbVie, Brazil
Julian Figueredo	Senior Manager Regulatory Affairs	Biogen, Colombia
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Marcio Costa Oliveira e Silva	Regulatory Affairs Manager	Bayer, Brazil
Prof John Skerritt	Enterprise Professor in Health Research and Chair, Scientific Advisory Council, CIRS	University of Melbourne, Australia
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Anna Somuyiwa	Head	Centre for Innovation in Regulatory Science
Millena Tascone	Associate Director Regulatory Affairs	Eli Lilly and Company, Brazil
Prof Steffen Thirstrup	Chief Medical Officer	European Medicines Agency
Daniela Ulbricht	Pharma Portfolio Strategy Director, Emerging Markets	GlaxoSmithKline, Brazil
Dr Joice Valentim	Global HTA Strategy Lead	Roche, Switzerland
Ana Gabriela Trejos Vásquez	Regulatory Affairs Lead, Caribbean, Central America and Venezuela	Roche, Costa Rica
Prof Stuart Walker	Founder	Centre for Innovation in Regulatory Science
Ding Xu	Regulatory Strategy and Policy Lead	Roche, Brazil
Ana Carolina Yoshii	Coordinator of Regulatory Affairs	Amgen, Brazil