CIRS Centre for Innovation in Regulatory Science

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 SYNOPSIS

Background

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, worksharing 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. 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 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 (see programme), 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?

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 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, 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 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 such as 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 that 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 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 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. This is an important step 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 EMA Centralised Procedure is based on the political framework of the 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 (REC). 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 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 can 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, ANVISA in Brazil 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 financial support 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 to facilitate collaboration.
- Investigate a shared risk-benefit model.
- Map out the capabilities of different agencies based on information from the WHO Global Benchmarking Tool and List of WHO-Listed Authorities.
- Conduct research studies comparing target vs actual timelines for worksharing 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 public assessment reports can allow verification of product sameness?
- Compare public assessment reports and unredacted reports - is the additional information sufficient for agency decision making or not?
- Standardise public assessment reports 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

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	Session 2: Going beyond good reliance principles to good practice – What needs to be considered when implementing or using reliance models?
Co-Chair: Dr Lawrence Liberti, Director of the D.K. Kim International Center for Regulatory Science and Associate Professor, University of Southern California, USA	**Chair: Balbiana Sampaio,** Chief Advisor, ANVISA, Brazil
Co-Chair: Balbiana Sampaio, Chief Advisor, ANVISA, Brazil	**Dr Samvel Azatyan,** Team Lead, Regulatory Convergence and Networks, World Health Organisation
Dr Neil McAuslane, Director, CIRS, UK	**Dr Noraisyah Mohd Sani,** Senior Principal Assistant Director, Centre of Product & Cosmetics Evaluation, NPRA, Malaysia
Dr Fabrício Carneiro de Oliveira, Head of Biological Products, ANVISA, Brazil	**Prof John Skerritt,** Enterprise Professor in Health Research Impact at the University of Melbourne, Australia
Dr Boitumelo (Tumi) Semete, Chief Executive Officer, SAHPRA, South Africa	**Daniela Ulbricht,** Pharma Portfolio Strategy Director, Emerging Markets, GlaxoSmithKline, Brazil
Dr Daniela Bravo, Executive Manager Regulatory Policy and Intelligence Latam, AbbVie, Brazil	**Daniel Antonio Sanchez Procel**, Executive Director, ARCSA, Ecuador
Session 3: Leveraging information from reference agencies on their assessment – What is needed and how best can this be facilitated?	**Session 4: What frameworks have agencies implemented to practically use regional/trans-regional models and what are the learnings?**
Chair: Prof John Skerritt, Enterprise Professor in Health Research Impact at the University of Melbourne, Australia	**Chair: Prof John Skerritt,** Enterprise Professor in Health Research Impact at the University of Melbourne, Australia
Dr Magda Bujar, Senior Manager, Regulatory Programme and Strategic Partnerships, CIRS, UK	**Prof Steffen Thirstrup,** Chief Medical Officer, EMA
Luis Alejandro Rivera, Gerente de Administración y Desarrollo Institucional, El Salvador	**Jackson Kiberenge,** Drug Registration Officer, Tanzania Medicines and Medical Devices Authority, Tanzania
Dalia Abouhussein, QA General Manager, Egypt Drug Authority, Egypt	**Sophie Sommerer,** Director General, Biologics and Radiopharmaceuticals Drugs Directorate, Health Canada, Canada
Leonardo Semprún, Senior Director, Global Regulatory Policy Lead, LATAM, MSD, USA	**Dr Claus Bolte,** Chief Medical Officer, Swissmedic, Switzerland
	Priti Shah, Executive Director, International Regulatory Affairs, AstraZeneca, UK
Session 5: Syndicate discussions	**Session 6: Roundtable feedback and panel discussion**
Syndicate A) Regional collaboration	**Chair: Prof Steffen Thirstrup,** Chief Medical Officer, EMA
Chair: Prof Steffen Thirstrup, Chief Medical Officer, EMA	**Alex Juma Ismail,** Program Officer, Regulatory Systems Strengthening, AUDA NEPAD
Rapporteur: Marite Prieto, South Latam Cluster Lead, Pfizer, Brazil	**Dr Claus Bolte,** Chief Medical Officer, Swissmedic, Switzerland
Syndicate B) Changing mindset	**Balbiana Sampaio,** Chief Advisor, ANVISA, Brazil
Chair (English group): Dr Boitumelo (Tumi) Semete, Chief Executive Officer, SAHPRA, South Africa	**María Antonieta Román,** Head of Regulatory Policy in Latin America, Novartis
Rapporteur (English group): Sheila Inada, Regulatory Affairs Manager, AstraZeneca, Brazil	**Dr Lawrence Liberti,** Director of the D.K. Kim International Center for Regulatory Science and Associate Professor, University of Southern California, USA
Chair (Spanish group): Patricio Enrique Reyes Sepúlveda, Head of New Product Registration Section, Institute of Public Health, Chile	
Rapporteur (Spanish group): Ana Gabriela Trejos Vásquez, Regulatory Affairs Lead, Caribbean, Central America and Venezuela, Roche, Costa Rica	
Syndicate C) Good collaborative practices	
Chair (English group): Cynthia Ban, Global Head, Regulatory CMC, Vaccines, Sanofi, Canada	
Rapporteur (English group): Luciana Carla Duran, Senior Regulatory Affairs Manager, Novo Nordisk, Brazil	
Chair (Spanish group): Maria Antonieta Román, Regional Regulatory Policy Lead, Emerging Markets - Latam, Novartis	
Rapporteur (Spanish group): Heloísa Fávaro, Regulatory Affairs Director, AbbVie, Brazil	

About CIRS

The Centre for Innovation in Regulatory Science is a neutral, independent UK-based subsidiary of Clarivate plc. Its mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and Health Technology Assessment policies and processes. CIRS provides an international forum for industry, regulators, HTA bodies 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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