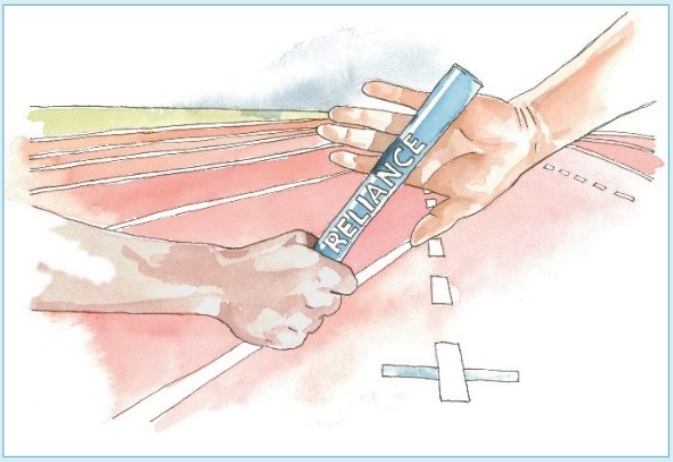
Regulatory reliance pathways: What are the opportunities and barriers?

Introduction

An increasing number of National Regulatory Authorities (NRAs) are turning to reliance as a way to conserve resources, build expertise and capacity, increase the quality of their regulatory decisions, reduce duplication and, ultimately, promote timely access to safe, effective and quality products. Reliance encompasses a wide range of regulatory approaches and practices involving two or more NRAs (including work sharing) and can be applied to many aspects of regulatory oversight across the medical product life cycle. This includes marketing authorisation, pharmacovigilance, inspections, quality testing, clinical trials oversight and post-approval changes.

Regulatory reliance is being actively promoted by organisations such as the International Coalition of Medicine Regulatory Authorities (ICMRA), industry trade associations and the World Health Organisation (WHO) through its Good Reliance Practices [1]. Over the last five years, CIRS has held a series of multi-stakeholder workshops focused on reliance and has monitored its use in agency processes through the Optimising Efficiencies in Regulatory Agencies (OpERA) programme [2,3].



As the concept of reliance is still relatively new, companies and NRAs may have limited experience in using it to register new medicines. To help improve understanding of the return on investment (ROI) for using reliance pathways, CIRS carried out a perception survey of its company members in September 2020. The results, which are presented here in this Briefing, are not only useful for companies but also for NRAs as they look to identify the barriers to using their reliance pathways and areas for improvement.

Recognition

Abridged

Reliance

Verification

Worksharing

Equivalence

**Definitions listed on p6.*

Study Objectives

- Identify and characterise strengths and weaknesses of reliance pathways and what companies perceive as enablers and barriers to their use.
- Share companies' experiences of using these pathways, and whether they are working for them.
- Identify opportunities for further use of reliance pathways and share success stories.
- Determine what companies perceive as the ROI of using reliance pathways and work-sharing procedures.

Reliance pathways and their utilisation

Methods

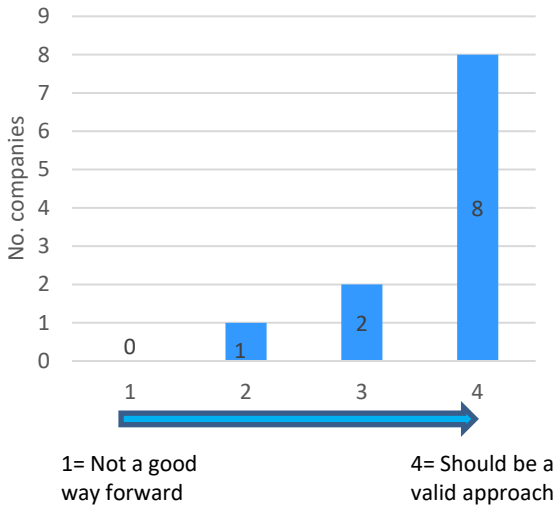
A three-part survey was sent out in September 2020 to 13 major international pharmaceutical companies who are members of the CIRS Emerging Markets Programme. This Briefing reports findings from survey parts 1 & 2 on reliance pathways and work-sharing procedures, respectively.

11 companies responded to the survey and these responses were aggregated to give an overview of current company perceptions of reliance-based approval pathways. We use the term 'perception' irrespectively of whether the respondent had experience of using each pathway or not.

Results

Companies were initially asked to what extent do they believe that reliance pathways are a good way forward for approving new medicines in emerging markets. The majority of respondents felt that reliance should be a valid approach for use in emerging markets (Figure 1).

Figure 1: Support for reliance as an approach to approve new medicines in emerging markets

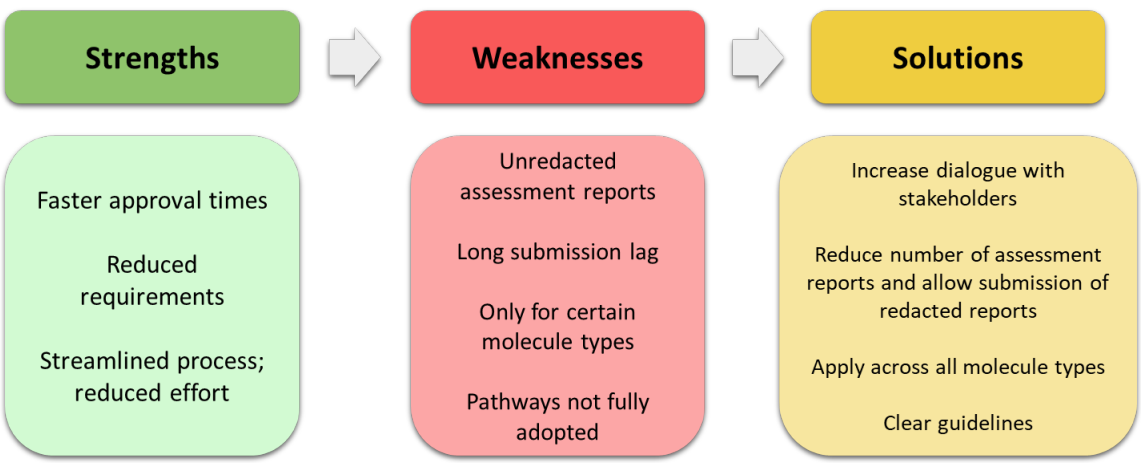


Companies were next asked to share their perceptions of the strengths and weaknesses of reliance pathways used by NRAs across Latin America, Asia, Africa and the Middle East (listed on p3), and where relevant, solutions and opportunities to improve these pathways (Figure 2). A commonly reported strength was faster approval times, and for some jurisdictions, reduced requirements were also indicated as a strength.

A commonly reported weakness was requirements for unredacted assessment reports, which applied to the majority of the jurisdictions assessed, as well as long submission lags. Reliance routes for some countries are only applicable to certain types of molecules and as these pathways are still fairly new for some jurisdictions, companies also reported that many agencies had not fully adopted the process.

Potential solutions were suggested to help formalise reliance pathways from a company perspective, including increasing stakeholder dialogue/interactions, reducing the number of assessment reports required from reference agencies and having the ability to submit redacted reports.

Figure 2: Strengths, weaknesses and solutions for using reliance pathways



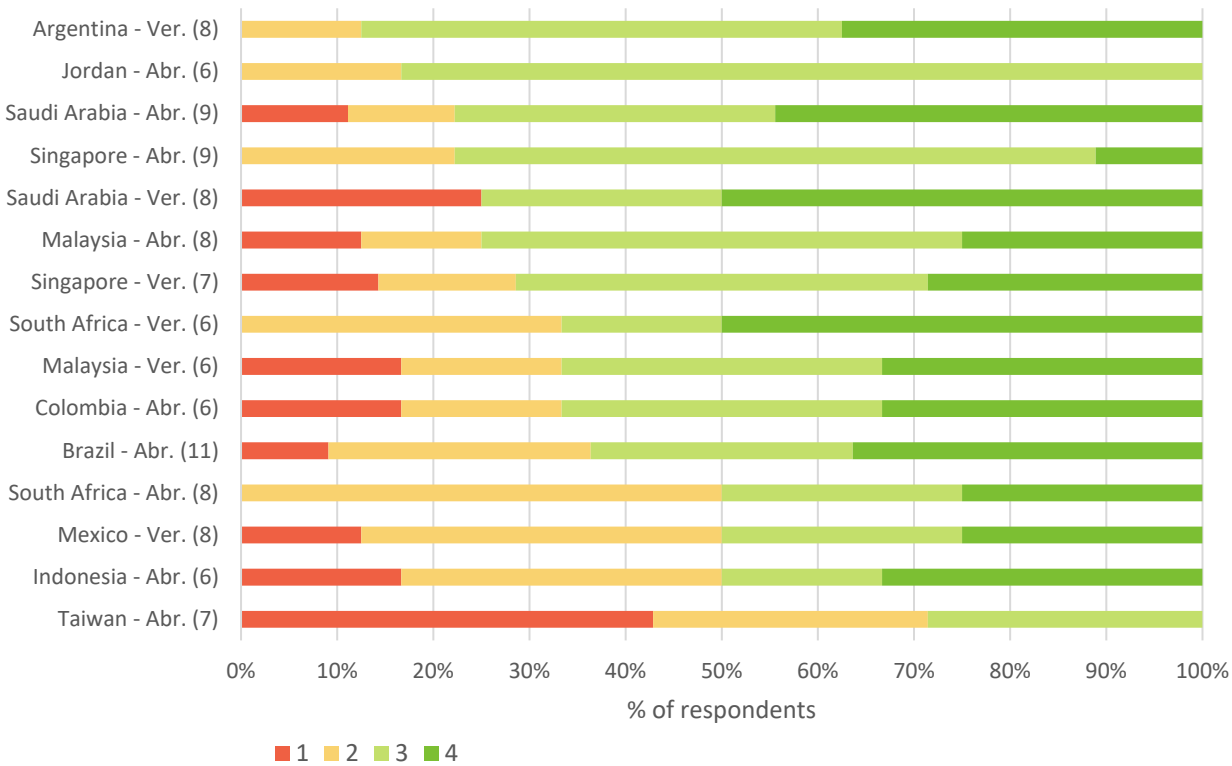
Reliance pathways and their utilisation

Companies were then asked to score specific reliance pathways in terms of ROI/attractiveness (Table 1). The top three pathways were seen to be Argentina's verification route, followed by Jordan's abridged pathway and Saudi Arabia's abridged pathway (Figure 3).

Table 1: Reliance pathways used by NRAs in Latin America, Asia, Africa and the Middle East

Argentina (Verification)	Mexico (Equivalence agreements aka Verification)
Brazil (Abridged)	Saudi Arabia (Abridged)
Colombia (Abridged)	Saudi Arabia (Verification)
Egypt (Verification)	Singapore (Abridged)
Indonesia (Abridged)	Singapore (Verification)
Jordan (Abridged)	South Africa (Abridged)
Jordan (Verification)	South Africa (Verification)
Malaysia (Abbreviated review aka Abridged)	Taiwan (Abridged)
Malaysia (Verification)	Other (Respondents could specify and rate other reliance pathways they have used)

Figure 3: ROI/attractiveness of reliance pathways, ranked by number of positive responses



(where 1= poor and 4 = excellent)

Ver. = Verification pathway
Abr. = Abridged pathway
(Definitions listed on p6)

(n) = number of company responses
Only countries with >50% response rate are shown

Reliance pathways and their utilisation

Regarding the use of reliance pathways in general, companies were asked to give their perceptions of the enablers and barriers for choosing these pathways for registrations of new medicines. A list of enablers and barriers was provided and the respondents could tick all that applied. The greatest enabler was standardising international requirements and the greatest barrier was accessing supportive information, such as unredacted assessment reports (Figure 4).

Figure 4: Enablers and barriers to using reliance pathways

Enablers	% response rate
Standardisation of international requirements	95%
Clear guidelines on requirements	89%
Transparent, and predictable reliance procedures	89%
Mechanism used for life-cycle management (including post-approval)	89%
Reliance pathway adhering to the shorter timelines stipulated	89%
Agencies willingness to accept redacted Public Assessment Reports	84%
Stipulated target times	84%
Secure electronic platform for sharing of reports/comments	79%
Request for one reference agency approval (rather than 2 or more)	79%
Introduction of pilot reliance programmes	58%

Barriers	% response rate
Accessing difficult to obtain supportive information (i.e. unredacted assessment reports)	95%
Requesting full documentation submitted to reference agency	68%
Differences in regulatory requirements for reliance pathways across NRAs	63%
Lack of willingness from agencies to adopt reliance pathways	53%
No clear guidance on the minimal evidence package to be reviewed by the agency	53%
Lack of legal framework within agency to use reliance	53%
Stakeholders within companies are not confident in the process	47%
No clear definition of "sameness" of product by the agencies	42%
Industry do not see ROI for using these pathways	32%
Distrust in reference agency decision	21%
No confidential guidelines for agency staff, or patent laws in country, therefore potential breach of confidential information	21%

Companies were then asked for forward-looking views of what may be opportunities for reliance pathways as well as suggestions for improvement. Key themes were drawn out of the aggregated responses (Figure 5).

Figure 5: Opportunities and suggestions to improve the use of reliance pathways

Theme	Opportunities	Suggestions to improve
Timelines	**Reduced timelines** for approval **Early access** to markets and patients	Set up **realistic timelines** – call for agencies / Ministry of Health to define more clearly what conditions or therapy areas they will consider
Dossier requirements	Agency resources will be better allocated and in the longer term this will help their endogenous industries develop and grow	Focus on key local requirements and **harmonisation across NRAs**; pursue convergence
Strategy	**Predictability** of regulatory decision and timelines	**Raising more awareness of the benefits for the NRA** of using these pathways vs the standard pathways for approval
Processes	Increased regulatory **efficiencies** **Work sharing**, as well as collaborative projects can be great opportunities **to improve trust between NRAs and accelerate access**	**Clear procedures, timelines and objectives** for evaluators – should be formally presented in country legislations to ensure adequate implementation and benefits. **Training for evaluators** on requirements

Work-sharing procedures

There is a growing awareness of the need for regulators to work together to maximise their use of resources and avoid duplication of work, especially by those agencies that are resource limited. The European medicines system is probably the best-established example of regulatory cooperation between medicines authorities, with a legal basis dating from 1965. Several countries and regions have also developed or are developing formal and informal frameworks for cooperation and worksharing, helping to avoid duplication of regulatory assessment and encouraging the efficient use of resources.

For these collaborative procedures to be fully implemented, companies need to participate and encourage their use. However, as some of these procedures are not fully implemented or are in a pilot stage, companies may be reluctant to include them as part of their regulatory strategy.

The results from this survey demonstrate that many companies see the benefit of using work-sharing procedures, particularly the overall benefit to patients and to the efficiency of the regulatory process (Figure 6). When considering specific work-sharing procedures, companies thought ACSS (now known as Access) had the highest ROI/impact, followed by the EMA centralised procedure (Figure 7).

Figure 6: Benefits of work-sharing procedures, ranked by number of positive responses

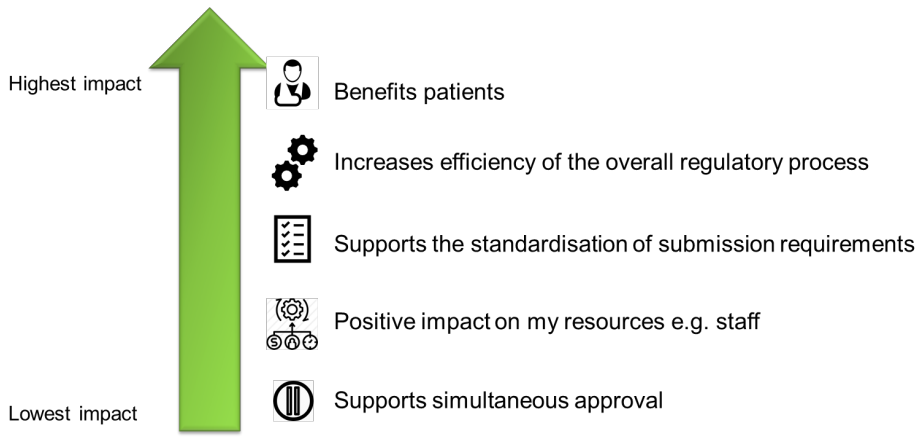
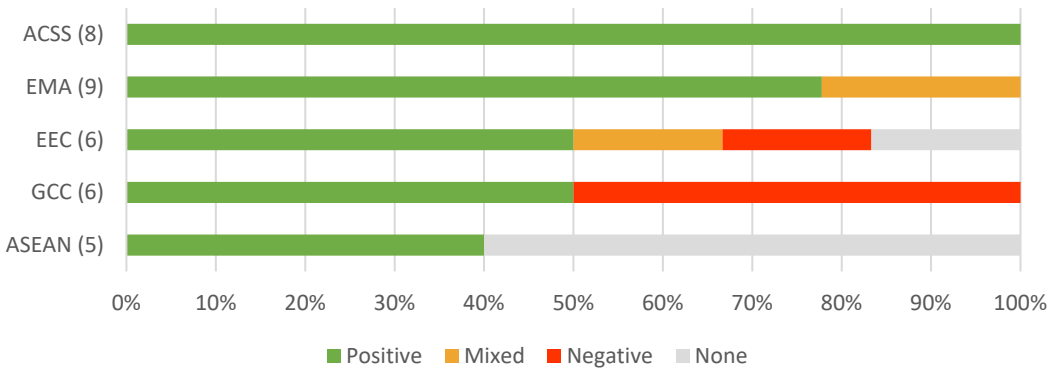


Figure 7: ROI/impact of work-sharing procedures, ranked by number of positive responses



ACSS: Australia-Canada-Singapore-Switzerland Consortium (now known as Access)
EMA: European Medicines Agency centralised procedure
EEC: Eurasian Economic Commission
GCC: Gulf Central Committee for Drug Registrations
ASEAN: Association of Southeast Asian Nations Common Technical Dossier

(n) = number of responses

14 work-sharing procedures were listed in the survey but only those with >40% response rate are shown.

Appendix

Definitions:

Abridged regulatory pathways
Regulatory procedures facilitated by reliance, whereby a regulatory decision is solely or widely based on the application of reliance. This usually involves some degree of work by the relying agency. The expectation is that the use of reliance in these pathways will save resources and shorten assessment timelines compared with standard pathways, while ensuring that the standards for regulatory oversight are maintained [1].

Equivalence
Implies strong similarity between two regulatory systems, as mutually established and documented through objective evidence. Equivalence can be established using criteria and approaches such as similarity of the regulatory framework and practices, adherence to the same international standards and guidelines, experience gained in use of assessments for regulatory decision making, joint activities and exchanges of staff. It is expected that equivalent regulatory systems will result in similar standards and levels of regulatory oversight or "control" [1].

Recognition
Acceptance of the regulatory decision by another regulator or trusted institution. Recognition should be based on evidence that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement [1].

Reliance
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 decision [1].

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

Worksharing
A process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task. Opportunities for worksharing include joint assessment of applications for authorisation of clinical trials or marketing authorisations, joint inspections for good practices, joint post-marketing surveillance, joint development of technical guidelines or regulatory standards and collaboration on information platforms and technology. Worksharing also entails exchange of information consistent with the provisions of existing agreements and compliant with each agency's or institution's legislative framework for sharing such information with other NRAs [1].

References:

[1] WHO (2021) WHO Expert Committee on Specifications for Pharmaceutical Preparations: Fifty-fifth report (WHO Technical Report Series, No. 1033). Annex 10 - Good reliance practices in the regulation of medical products: high level principles and considerations. Accessed on 25th May 2021 at: https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf

[2] CIRS 2017-2019 Workshop reports. Available at: https://cirsci.org/tag/reliance/

[3] CIRS (2020) CIRS R&D Briefing 74 - Measuring process and performance in regulatory agencies: The OpERA Programme. Available at: https://cirsci.org/download/rdb74-opera-programme/

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