Regulatory Reliance Mechanisms: Current State, Potential, and the Role of Europe

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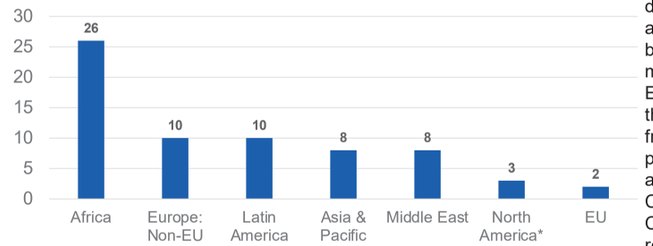
Global Adoption and Expansion of Regulatory Reliance

Regulatory reliance mechanisms are not new and have evolved considerably. Today, the degree of reliance and the maturity of these mechanisms vary globally. Regulatory reliance pathways reduce the burden of review, while maintaining high regulatory standards, offering improved availability of medicines globally. The COVID-19 pandemic highlighted the lack of regulatory capacity of National Regulatory Authorities (NRAs) globally and created an unparalleled opportunity to rapidly strengthen regulatory systems, particularly in regions where enhancements in regulatory capacity are needed (e.g., Africa, Latin America). As this landscape rapidly evolves, it is important to understand the state of regulatory reliance globally, and the critical roles of key regulators such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).

*Regulatory Reliance is defined by one regulatory authority relying on the decision(s) of a regulatory authority in a different jurisdiction

Number of Countries with Non-Centralized Reliance Pathways by Region[1]

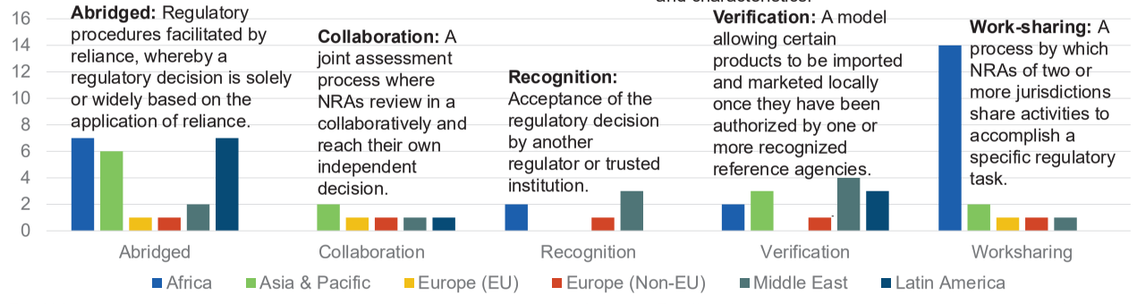


*For the purposes of this poster, "North America" includes the U.S. and Canada, with Mexico included as "Latin America"

Non-centralized reliance pathways, where registration is not dependent upon a decision made by an NRA in another region, are prevalent globally. The highest number of these pathways by country are in Africa where Zazibona, a collaborative medicines registration initiative, is in place. In non-EU European countries, there is reliance upon EMA decisions, and the UK participates in the FDA's Project Orbis program, a framework for concurrent submission and review of oncology products among international partners. In North America there are only two pathways, Project Orbis and Access Consortium. Canada participates in Project Orbis and the Access Consortium, a work-sharing coalition of medium-sized regulatory authorities. In the EU, Swissmedic participates in Project Orbis and Access Consortium.

Non-centralized pathways are in place in Latin America, Asia & Pacific, and the Middle East, and are heterogeneous in scope and characteristics.

Regional Breakdown of Pathways by Type[1]



Abridged: Regulatory procedures facilitated by reliance, whereby a regulatory decision is solely or widely based on the application of reliance.

Collaboration: A joint assessment process where NRAs review in a collaboratively and reach their own independent decision.

Recognition: Acceptance of the regulatory decision by another regulator or trusted institution.

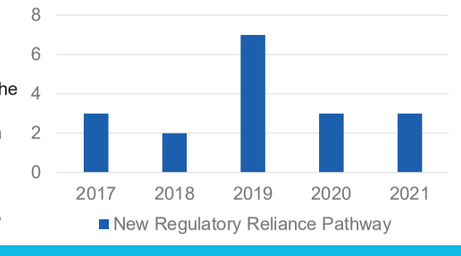
Verification: A model allowing certain products to be imported and marketed locally once they have been authorized by one or more recognized reference agencies.

Work-sharing: A process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task.

For Africa, work-sharing and abridged pathways are most prominent. In Asia and Pacific, abridged pathways are the most prevalent form of reliance. In Latin America, abridged and verification pathways are the most prevalent. All regions that use collaboration participate in Project ORBIS, which shows the global reach of this program.

New Regulatory Reliance Pathways Continue to Emerge*

New regulatory reliance pathways continue to emerge enabling acceleration of the availability of medicines globally. Data provided through Amgen's collaboration with the FRPath Project** indicate 68 reliance pathways globally all of which are designed to accelerate the review process. Also, 63 of 68 pathways include specific reliance on a prior regulatory decision (but not all specify what the reference agencies were).



* Based on the 26 reliance pathways that had dates associated with them in the FRPath Project Database

** "The FRPath Project is an educational research project of the Erudee Foundation, designed to serve as the trusted repository of expertly evaluated and organized information about Facilitated Regulatory Pathways (FRPs), including reliance pathways." www.frpath.org

References and Acronyms

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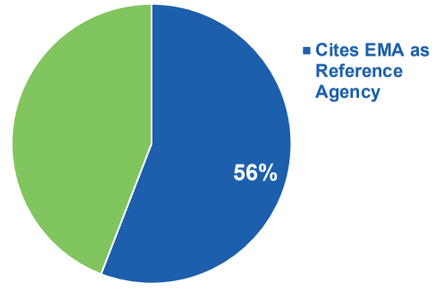
Acronyms: ANMAT: The National Administration of Drugs, Foods and Medical Devices; ANVISA: Brazilian Health Regulatory Agency; AU: African Union; COFEPRIS: Federal Committee for Protection from Sanitary Risks; CP: Centralized Procedure; CTD: Common Technical Document; DCP: Decentralized Procedure; EABF: EU AU Business Forum; ECDRP: European Commission (EC) Decision Reliance Procedure; ICH: International Counsel on Harmonization; LATAM: Latin America; MA: Marketing Authorization; MAA: Marketing authorisation application; MHRA: Medicines and Healthcare products Regulatory Agency; MRDCRP: Mutual Recognition and Decentralized Procedure; MRP: Mutual Recognition Procedure; SRA: Stringent Regulatory Agency

Reliance in Europe and Latin America

EMA Is the Most Frequently Cited Reference Regulator Across Reliance Pathways

Information associated with the 68 reliance pathways identified in the FRPath Project database indicate that 56% of these reliance pathways cite EMA as a reference agency. Further, EMA along with FDA are the most frequently cited reference regulators across all reliance pathways assessed by the FRPath database. These data indicate the importance of EMA regulatory decisions globally to support expedited authorizations in other countries and subsequently enhance availability of medicines globally.



* Reference pathway may also reference EMA as an SRA, ICH member or "Europe"

EMA Actively Supports Regulatory Reliance Globally

EMA is establishing a dedicated group to discuss the industry challenges in using different reliance pathways and to identify possible actions where EMA could provide support.[2] EMA is also expected to engage in an EMA-Industry focus group on regulatory reliance to understand from industry the barriers to adoption of reliance in some countries, work on a common position on sameness, and to inform the optimization of tools and pathways.

Reliance Approaches By Non-EU Member Countries in Europe

While some non-EU member countries are awaiting admission into the EU, these countries rely on regulatory decisions made by EMA to expedite their own review and make these products available in their countries. The UK maintains a framework to rely on EMA decisions, reducing workload for applicants and MHRA staff and accelerating approval after its departure from the EU in 2020.

Country	Reliance Mechanism	Criteria
Albania[3]	Verification	Products registered via EMA or US FDA only
Macedonia[3]	Verification	Products registered via EMA
Montenegro[3]	Verification	Products registered via CP/MRP/DCP in EU
Serbia/Bosnia-Herzegovina[3]	Verification	EMA approval
Turkey[4]	Recognition	Variations in registered medicine, letter of approval from EU country or EMA, non-redacted evaluation report, confirmation that the scope of the application made is the same as the relying country.
UK[5]	Worksharing (Access Consortium)	Application received through Access consortium requesting UK approval
UK[6]	Collaboration (Project Orbis)	Member of project ORBIS and selected by applicant
UK[7]	Abridged Review (ECDRP)	Available to MAs approved via the EMA CP
UK[8]	Verification (MRDCRP)	Relies on decision by EU member states (or Iceland, Liechtenstein, Norway)
Ukraine[3]	Abridged Review	Effective for products registered in the following countries: USA, Japan, Switzerland, Canada, EU (in case of CP only)

Latin America Regulatory Reliance Landscape [1]

Country	Current Status	Use by Global Companies?	Likely to Change or Develop New Soon?	Likelihood Current Pathway Will Expedite Approvals
Argentina	Established	Yes	Yes	Low
Brazil	Evolving	Yes	Yes	NA
Colombia	Not Available	No	Yes	NA
Mexico	Established	Yes	Yes	Medium

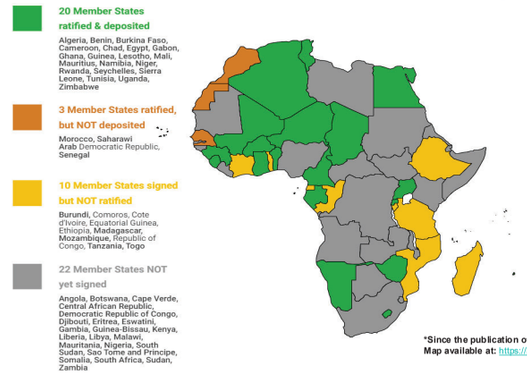
Established: Reliance pathways are implemented and available for use; **Evolving**: The government is in the process of developing, modifying existing, and/or implementing pathways; **Not Available:** No reliance pathways are available for use and there is no current effort to do so.

Our landscape summary focuses on four countries in Latin America: Argentina, Brazil, Colombia, and Mexico. Of those countries, the availability and applicability of reliance pathways varies widely.

- **Argentina:** ANMAT gives significant weight to work performed by another regulator or trusted institution, making its own final decision. This process does not expedite approvals but does decrease workload. Industry is advocating for ANMAT to adhere to shorter, more predictable timelines for applications that rely on a prior decision since the workload is reduced.
- **Brazil:** ANVISA is currently modifying their reliance regulations. The draft text would address only initial product applications, although the majority of the current backlog is with post-approval variations. Under the new regulation ANVISA is expected to rely on decisions from major regulatory agencies (e.g., FDA, EMA, MHRA, Health Canada, SwissMedic, TGA), maintaining the final decision on initial marketing applications and post-approval variations.
- **Colombia:** Reliance pathways are essentially non-existent with only draft legislation from the prior government. There is potential that these pathways will be further developed and implemented at some point in the future.
- **Mexico:** Reliance pathways are established within COFEPRIS and used by global companies. However, applicants are transitioning towards other routes for approval because COFEPRIS is not meeting the legal time for approvals with regulatory reliance pathways. COFEPRIS is currently working with stakeholders to redefine the process, which may result in legislative changes.

Reliance in Africa and the Middle East

Africa – Formation of the African Medicines Agency (AMA)[9]



*Since the publication of this map, South Africa signed (ratification pending)
Map available at: https://healthpolicy-watch.news/ama-resources/

- AMA is a proposed agency of the African Union (AU) intended to facilitate the harmonization of medical regulation throughout the AU. AMA is intended to cover medicines, traditional medicine, and medical devices.
- AMA is expected to provide oversight and absorb roles currently carried out by other bodies in Africa (e.g., African Medicines Regulatory Harmonization Initiative, African Vaccines Regulatory Forum) and is likely to promote cooperation, regulation through work sharing and reliance.[10]
- AMA Treaty entered into force in November 2021.
- Final date of implementation remains to be determined.

Role of the EU in Supporting AMA

Europe has played an important role in supporting the establishment of AMA through discussion and recommendations, and through funding support. Based on recent discussions, AMA will likely adopt a worksharing model.[11]

- **DISCUSSION AND RECOMMENDATIONS:** Initial discussions between industry and the EU commission to help foster local production in Africa were held in November 2021. Regulatory reliance was a key topic and was also discussed during the EU AU Business Forum (EABF) in February 2022. To continue to progress and coordinate on these important topics, the establishment of an EABF Pharma group was agreed which serves as the interlocutor between the EC and AU for the promotion of pharmaceutical industry in general on the Africa continent.
- **FUNDING SUPPORT:** In February 15, 2022, the EU announced that Team Europe—the EC, the EMA, and EU Member States Belgium, France, and Germany—and the Bill & Melinda Gates Foundation will mobilize more than €100 million over the next five years to support the recently established AMA and other African medicines regulatory initiatives at regional and national levels.[12]

Amgen's Experience Using Regulatory Reliance Pathways - Considerations

Amgen has used reliance pathways for both originator and biosimilar products across 6 different countries in the Middle East and Africa. The timelines to marketing authorization were reduced from the standard review period. Reliance pathways are selected based on different considerations including a pathway's features and known regulatory or market access barriers.

Pathway Features

- Dossier requirements (e.g., whether full CTD & assessment reports must be un-redacted, including reference regulators Q&As)
- Overall review timelines
- Predictability and reliability

Barriers

- Transparency throughout the review stages
- Ensuring no clock stop for the review
- Recognize reliance beyond new MAAs
- Confirming sites registrations are completed

Conclusions

Enhancing existing regulatory reliance pathways is needed to improve availability of medicines. Looking at the different regions and regulators we observed that:

- For non-EU member European countries, EMA serves as the primary reference agency.
- EMA plays a critical role in regulatory reliance mechanisms with the EMA and the FDA being the most cited reference agencies globally.
- In Latin America implementation of reliance pathways, and optimization of existing reliance pathways would improve availability of medicines.
- Once implemented, the AMA is expected to benefit the African region through harmonization and worksharing. Certain details that are not yet finalized will dictate the extent to which AMA can enhance availability of medicines in Africa. The EU and EMA have played a role in helping to shape the AMA, and will continue to do so through EABF.

Many considerations are evaluated by applicants when deciding to use a regulatory reliance pathway, such as specific pathway considerations (i.e., pathway benefits) and potential barriers.