IFPMA

Best practices for unilateral reliance for initial marketing authorization and post-approval changes

Introduction

Regulatory reliance has emerged as a key strategy for strengthening regulatory systems by optimizing resources, reducing duplication, and accelerating access to high-quality medicines. By leveraging the expertise and prior decisions of trusted national regulatory authorities (NRAs), reliance allows NRAs to focus their efforts on critical public health priorities while maintaining sovereignty over final regulatory decisions. Reliance-based approaches have been widely recognized in international frameworks, including WHO Good Reliance Practices (GRelP)[1], as a means to enhance regulatory efficiency, promote collaboration among NRAs, reduce review timelines, and increase predictability for industry. More information on the benefits of regulatory reliance and practical industry recommendations can be found in the IFPMA Position Paper on reliance[2].

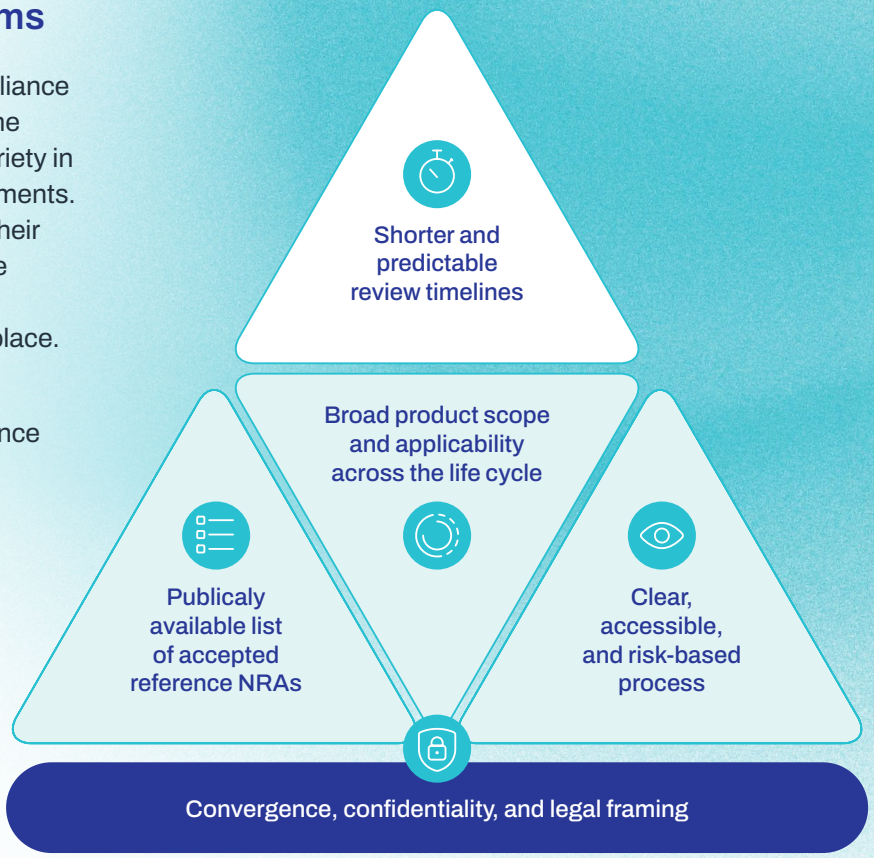
Far from undermining sovereignty, reliance in fact strengthens regulatory decision-making by allowing NRAs to make science-based judgments while maintaining full authority over their processes. The decision to apply reliance, and how best to do so, rests entirely with the NRA. As explained in the WHO GRelPs, regulatory reliance does not imply "outsourcing of regulatory mandates, nor does it compromise independence." NRAs remain fully accountable for their decisions and maintain full authority to act in the interest of public health.

This paper reflects upon industry experience with reliance-based processes and identifies critical success factors and best practices underpinning their effective implementation. By identifying practical solutions to common challenges and promoting effective reliance mechanisms, this paper aims to support the broader adoption of reliance as a sustainable approach to regulatory decision-making.

General principles for the successful implementation of unilateral reliance mechanisms

The growing adoption of fit-for-purpose reliance pathways by NRAs worldwide is a welcome development. Yet, there is a significant variety in the procedural guidance and data requirements. To ensure that reliance pathways deliver their intended benefits and function as effective alternatives to full assessments, IFPMA recommends having certain elements in place.

Based on industry experience, five key factors can enhance the efficiency of reliance mechanisms for NRAs and industry.



1

Reliance-compatible frameworks: Convergence, confidentiality, and legal framing

Regulatory convergence facilitates reliance by allowing NRAs to draw on one another's decisions when the same standards and requirements apply. However, full harmonization of standards and requirements is not a prerequisite for implementing reliance.

To be effective, national legal frameworks should explicitly enable reliance mechanisms and be supported by strong systems for managing confidential information and protecting intellectual property, as highlighted in WHO's Global Benchmarking Tool (GBT)[3].

Reliance-compatible frameworks can be created in the following ways:

- **Legal and regulatory frameworks:** Reliance mechanisms function more effectively when they are embedded within clear national or regional legal frameworks that explicitly support their use as part of good regulatory practice. Well-defined mandates and procedures with clear timelines help ensure efficient implementation while providing clarity to both NRAs and applicants. These legal foundations are critical enablers of reliance-based pathways—whether through unilateral mechanisms, collaborative reviews, or capacity-building pilots. Procedures for applying reliance may be set out in adaptable guidelines to allow adjustments when needed. Converging country-specific requirements globally toward aligned international standards is an enabler for reliance, yet full harmonization is not a prerequisite.

Certain local administrative requirements, such as the legalization or translation of certificates for pharmaceutical products (CPP), that do not add scientific value to the review process, may reduce the efficiency gains offered by reliance pathways.

- **Confidentiality and information-sharing mechanisms:** Effective reliance depends on strong internal systems for managing confidential information. These frameworks ensure that sensitive materials, such as the same dossier as the reference NRA and non-public assessment reports, are handled in a secure and compliant manner. This expectation is reflected in international best practices, including WHO's GRelP and the WHO GBT. For instance, GBT sub-indicator RS09.06 emphasizes the importance of having procedures for managing confidential information within the NRA's regulatory system.

  NRAs may also put in place mechanisms to securely exchange regulatory information with trusted NRAs. These mechanisms facilitate the sharing of non-public documents, when legally required. Tools such as Confidentiality Agreements and Memoranda of Understanding (MoUs) serve as key enablers of secure information flow. These agreements clarify how sensitive information can be shared, managed, and protected in company and NRA-owned documents containing personal data or commercially confidential data from a reference NRA. When such frameworks are in place and communicated, they foster trust and legal clarity, enabling greater participation in reliance pathways for both NRAs and industry.

2

Publicly available list of accepted reference NRAs

As recommended by WHO in its GRelP, maintaining a publicly accessible list of NRAs that may serve as reference can increase predictability. Ideally, such a list would be available on the relying NRA's website, allowing applicants to identify the most appropriate reference NRA for each case and helping to prevent procedural bottlenecks. Reference NRAs generally hold WHO-Listed Authority (WLA) status[4], reflecting their high maturity level and advanced regulatory performance.

Regulatory frameworks that provide flexibility to engage different reference NRAs throughout a product's life cycle can make reliance pathways more practical. For example, one NRA may be designated as the reference for initial approval, while another may be considered as a reference for post-approval changes, provided that the rational for each selection is defined and transparent. Furthermore, to streamline reliance pathways, instead of selecting multiple reference NRAs for a specific unilateral reliance procedure, only one reference NRA could be used per procedure. This approach simplifies documentation requirements and reduces submission lag time.

3

Broad product scope and applicability across the life cycle

Clear eligibility criteria for products to go through a reliance-based pathway, coupled with clarity on which regulatory aspects can be expedited through reliance, help ensure transparency and consistency. The scope and applicability of reliance may be aligned with each NRA's priorities. A broad product scope (e.g., small molecules, vaccines, biotherapeutics, advanced therapy medicinal products) and the ability to use reliance across the entire product life cycle (e.g., regulatory assessment for clinical trial applications, initial marketing authorization (MA) and post-approval changes (PACs), inspections, quality testing / batch release) can increase the usability and benefit of the procedure.

Based on experience to date, there is also value in allowing applicants to use reliance during the lifecycle of products that have been initially authorized via a standard procedure. Conversely, where a product has been authorized via a reliance-based procedure, flexibility can be given to allow the submission of post-approval changes / line extension via a standard procedure.

4

Clear, accessible, and risk-based process

For reliance mechanisms to be effective and widely used, the steps of the process should be clearly documented, easy to follow, and readily accessible. Providing step-by-step guidance in a transparent and public format enables applicants to understand and navigate the reliance pathway. A pragmatic, risk-based approach to documentation requirements allows for "informed reliance," focusing on the applicability of prior assessments to the national context and in compliance with local regulations (Ex: EU regulations[5]). This aligns with WHO GRelP, and helps ensure that reliance pathways deliver on their promise of shorter review timelines and optimized resource use.

5

Shorter and predictable review timelines

For reliance mechanisms to be a compelling alternative to full assessments, they are generally expected to offer shorter timelines and more efficient use of resources, as described in WHO's GRelPs. Predictable review timelines give applicants the confidence to use these pathways, knowing that decisions will be made within a predefined timeframe. Based on industry experience to date, we recommend a 90- day maximum for the review of a reliance-based MA and a 30-day maximum for the review of a reliance-based PAC (major change).

Additionally, applying and publishing Key Performance Indicators (KPIs) for the use of reliance pathways can help both NRAs and industry track their effectiveness and encourage broader adoption. In this context, it is also important to distinguish between capacity-building exercises and routine reliance pathways. Reliance should be set up to ultimately improve efficiency of regulatory processes in routine practice. With the introduction of new complex product modalities, it should be acknowledged that not every NRA will have full expertise in all areas of regulatory science, further emphasizing the value of reliance as a collaborative approach.

Supporting documentation for initial MA and for PACs

A reliance-based procedure leverages the Common Technical Document (CTD) components (ICH M4) as in a standard procedure, together with reliance tools[6] or regulatory outputs from the reference NRA assessment. Documentation requirements can be tailored to the context of use (e.g., WHO collaborative pathway, unilateral reliance pathway, capacity building exercise), the purpose, and opportunities to reduce redundancies. For PACs, requirements should also be proportionate to the type and risk level of the change, in line with ICH Q12 principles, which support a structured, science-based framework for product lifecycle management. Differences in risk classification between the reference and relying NRAs should not hinder the implementation of reliance. The basis for decision-making in regulatory reliance lies in the supportive documentation and respective reference assessments, which can then be reviewed in accordance with local regulations. Convergence of categorization, requirements, and timelines is an important enabler of reliance.

Supporting reliance documentation includes:

- **Full CTD dossier (MA) or updated sections affected by the change (PACs):**
  CTD format is recommended.
- **Reference NRA assessment report(s):**
  1. **Public assessment report:**
     Documents available in the public domain should be used as the primary source of information. Public assessment reports reflect the scientific conclusions of an assessment process. The assessment report is redacted in such a way that commercially confidential information or personal data is not disclosed.
  2. **Non-public assessment information:**
     When a public assessment report is not available or deemed insufficient by the relying NRA, a non-public assessment report could be used following appropriate sharing mechanisms. The final assessment report from only one reference NRA can effectively serve to support reliance. This document represents the final scientific discussion and conclusion on the benefit risk assessment of the reference NRA, as explained in the EMA pre-authorization procedural advice for users of the centralized procedure[8].

     For PACs, when available, the final assessment report[7] for the specific change can serve as the basis for reliance. Depending upon the categorization, an assessment report may be issued, for example, by EMA (e.g., type IB, type II) and made publicly available in some specific instances (especially for changes affecting the safety / efficacy of the product as outlined in the product information). If not made available by the reference NRA, other documents (i.e. Q&As) might be considered.

     More details on the use of assessment reports to support regulatory reliance can be found in the IFPMA Position Paper on assessment reports[9].
- **Evidence of GMP compliance (when applicable):** A document confirming compliance for relevant manufacturing sites, such as a GMP certificate, whether for the MA or PACs involving manufacturing.
- **Evidence of approval:** Document that attests the product's approval by the reference NRA.

or

- **Proof of regulatory outcome from the reference NRA (only for PACs)[10]:**
  - ***Minor (e.g.: EMA Type IA changes[11]):***
    Evidence of submission to the reference NRA (when available this could be an acknowledgment of receipt).
  - ***Moderate (e.g.: EMA Type IB changes):***
    A notification or similar regulatory communication indicating acceptance of the change.
  - ***Major (e.g.: EMA Type II changes):***
    The approval (when available) and / or scientific opinion from the reference NRA confirming the change has been reviewed and approved.

Other documents may be used as alternative or complementary reliance tools:

1. **Declaration of sameness (if applicable):** Declaration of sameness, highlighting differences between the dossier submitted to the relying NRA and the one reviewed by the reference NRA may be included as a review aid. Differences may arise due to diverging local requirements (e.g., climatic zone stability data, pharmacopoeia), presentations, indications, or supply arrangements. For PACs, differences may be due to product history. This review of differences in dossier may be supported by structured tools such as IFPMA's template[12].
2. **Electronic Certificate of Pharmaceutical Product (eCPP):** The eCPP covers several aspects (registration, GMP compliance, and marketing status) and can be an alternative to the approval letter (EC decision) and GMP certificates for each manufacturing site.

Such a harmonized set of supporting documents enables reliance for both MAs and PACs, promotes consistency, reduces workload, and facilitates timely implementation of regulatory decisions—helping to maintain continuity of supply and accelerate patient access. Waiving country-specific requirements, where applicable, can further strengthen reliance pathways.

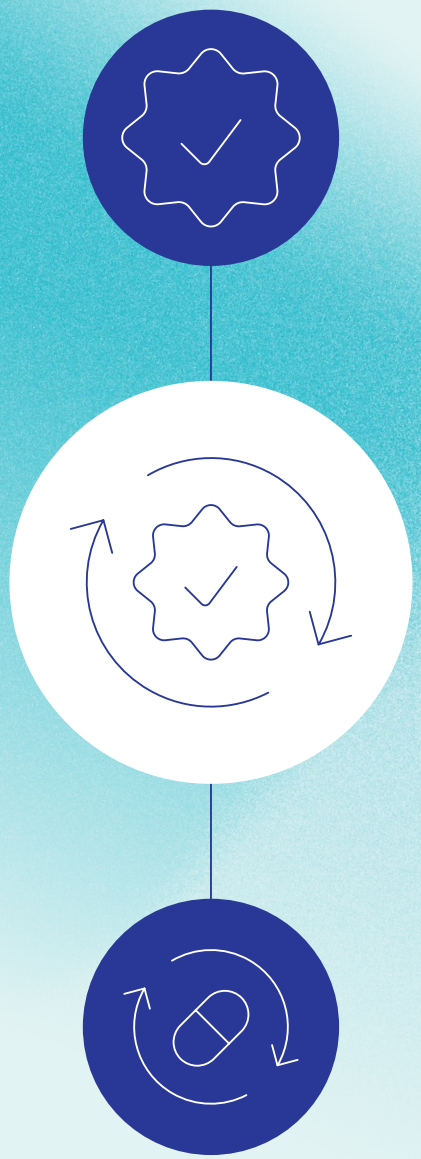
Document Type	Initial marketing authorization	Post-approval changes
Dossier (CTD format)	Full CTD dossier	Updated dossier sections affected by the change
Reference NRA assessment report	Public or non-public assessment report	Non-public assessment report (when applicable)
GMP status	Evidence of GMP compliance (when applicable)	Evidence of GMP compliance (when applicable)
Reference NRA regulatory outcome	Evidence of approval	Proof of regulatory outcome from reference NRA (PACs): — *Minor (e.g.: EMA Type IA changes):* Evidence of submission — *Moderate (e.g.: EMA Type IB changes):* Notification indicating acceptance of the change — *Major (e.g.: EMA Type II changes):* Approval (when available) and / or confirmation the change has been reviewed and approved
Alternative or complementary reliance tools	Declaration of sameness (if applicable) Electronic Certificate of Pharmaceutical Product (eCPP)	Declaration of sameness (if applicable) Electronic Certificate of Pharmaceutical Product (eCPP)

Assessing product sameness in the context of reliance

In the context of reliance, it is important to distinguish between dossier sameness and product sameness. Minor differences between the dossiers submitted to the reference NRA are to be expected and should not be seen as a barrier to reliance. These may include administrative details or updates to Module 1 and 3 of the CTD to meet national requirements. For PACs, differences in indications due to target population and local epidemiology may not impact the product's technical documentation, allowing reliance to be used for Chemistry, Manufacturing, and Controls (CMC) changes.

IFPMA aligns with the WHO's definition of product sameness, which focuses on ensuring the same quality, safety, and efficacy. IFPMA's approach to sameness advocates for additional flexibility—particularly where this enables a broader pool of manufacturing sites to be used[13]. Any differences in manufacturing sites between the reference and relying NRA should be justified by the applicant and properly documented (e.g., with comparability data, GMP documentation) and should form part of an abridged review by the relying NRA. This flexibility is essential to strengthen supply chain resilience and avoid supply disruptions that would ultimately impact product availability and patient use.

Industry is committed to supporting NRAs in assessing product sameness through transparent communication. Differences can be explained succinctly in a cover letter or, where needed, using structured tools such as IFPMA's template, to support communication with NRAs on product sameness evaluation for reliance application. Over time, convergence in timelines, requirements, and risk-based categorization of PACs, together with reduced local-specific requirements, will foster progress toward the submission of one global dossier and the effective implementation of regulatory reliance.



Annex: Importance of terminology – Glossary

A shared understanding of regulatory terminology is critical to ensure effective communication and alignment between industry and NRAs. Consistent use of terms also facilitates the implementation of reliance practices and supports their wider adoption across jurisdictions. The following definitions reflect internationally accepted terminology and have been proposed to promote clarity in the context of reliance-based regulatory procedures. WHO Definitions have been adapted from the **WHO Good Reliance Practices**.

Reliance (WHO Definition): The act whereby the NRA in one jurisdiction takes into account and gives significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information, in reaching its own decision. The relying NRA remains independent, responsible, and accountable for the decisions taken, even when it relies on the decisions, assessments, and information of others.

Unilateral reliance (WHO Definition): Reliance is said to be unilateral when a country chooses to rely on or formally recognize an assessment from another country unilaterally and without reciprocity.

Recognition (WHO Definition): Acceptance of the regulatory decision of another NRA or trusted institution. Recognition should be based on evidence that the regulatory requirements of the reference NRA 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.

Work-sharing (WHO Definition): A process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task (…). Work-sharing also entails exchange of information consistent with the provisions of existing agreements and compliant with each NRA's or institution's legislative framework for sharing such information with other NRAs. A joint activity is a form of work-sharing whereby a regulatory task is conducted by two or more NRAs in collaboration in order to share their assessments, benefit from each other's expertise, and discuss any shortcomings of the data evaluated (…).

Abridged regulatory pathways (WHO Definition): Regulatory procedures facilitated by reliance, whereby a regulatory decision is solely or partially based on application of reliance. This usually involves some work by the NRA that is practicing reliance. It is expected that use of reliance in these pathways will save resources and time as compared with standard pathways, while ensuring that the standards of regulatory oversight are maintained.

Expedited review: A regulatory pathway that shortens review timelines based on public health priorities or unmet medical needs. While expedited approval may leverage reliance, it is not necessarily dependent on it and can include independent assessments with accelerated timelines.

Endnotes

1. Technical Report Series, No.1033, Annex 10: Good reliance practices in the regulation of medical products: high level principles and considerations, WHO, 2021
2. Considerations for Effective Regulatory Reliance, IFPMA, 2019
3. WHO Webpage - Global Benchmarking Tools https://www.who.int/tools/global-benchmarking-tools
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5. Regulation (EC) 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency Regulation - 726/2004 - EN - EUR-Lex for commercially confidential information
6. Poulard, I.C., Ausborn, S., Allchurch, M.H. et al. Reliance into Action. Ther Innov Regul Sci (2025). https://doi.org/10.1007/s43441-025-00824-9
7. Final assessment report reference is made to reports that may not anymore be subject to re-examination
8. European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure, European Medicines Agency, 2025
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10. WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products, Annex 3, TRS No 1011, WHO, 2018
11. Based on the EMA change classification, Guidelines on (...) variations,to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures, EMA, 2025
12. Suggested template for Description of differences in CTD M3 (CMC) for MAAs and / or CMC post-approval changes, IFPMA, 2024
13. Points to consider: The importance of sameness of product in the context of regulatory reliance, IFPMA, 2022

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