IPRP
International Pharmaceutical Regulators Programme

IPRP Questions and Answers document[1] on Reliance
Version dated 30 September 2022

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[1] The information contained in this document is based on the WHO Good Reliance Practices in the regulation of medical products: high level principles and considerations. Annex 10 of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 55th Report; World Health Organization. 2021 https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf

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1. What is reliance?

Reliance as defined in the WHO Good Reliance Practices[1] is "*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. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others*."

Leveraging the output of other regulators makes the global regulatory oversight more efficient and helps the work of regulators, allowing the allocation of resources to value-added regulatory functions, such as in-country vigilance or post authorization activities, that cannot be undertaken by other authorities. In addition, reliance can result in more evidence-based, better-quality decisions by making the best use of the global expertise and should increase the efficiency of a regulatory system in a country or region.

Use of reliance approaches means moving to a more innovative, effective way of working, based on trust and relying on the outputs of other national regulatory authorities (NRAs). Reliance is relevant for all resource settings.

As per the Pan American Health Organization Concept Note and Recommendations on Reliance [2], reliance implies "*that the work done is shared by the trusted authority (e.g. through assessment or inspection reports), while the receiving authority uses this work according to its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities*." Thus, NRAs that adopt regulatory reliance pathways leverage the work performed by other regulatory bodies to a variable degree: an NRA may rely fully or partially on a process and/or decision of another entity and implies the use of regulatory decisions/information produced by another party (for example other NRAs, third-party auditor, pre-qualifications) as the basis for their own regulatory decisions.

2. What is "not" reliance?

Reliance does not represent nor imply:

- A less stringent form of regulatory oversight, but rather a strategy for making the best use of available resources and expertise in any setting.
- Compromise independence. It is not an agency outsourcing its decision-making authority or responsibility. On the contrary, a decision to "regulate through reliance" is the hallmark of a modern and efficient regulatory authority.
- Obviate the need for a capable local regulatory authority. Conversely, it should be used to maintain and build local capacity for regulatory decision making. Implementation of reliance requires that NRAs have the necessary competence for critical decision-making.

[2] Pan American Health Organization, Pan American Network for Drug Regulatory Harmonization. Regulatory reliance principles: concept note and recommendations. Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH) (San Salvador, 24 to 26 October, 2018. Washington DC: Pan American Health Organization; 2019 https://iris.paho.org/handle/10665.2/51549

- A tool to be used only by low-resourced regulatory authorities. It is equally relevant for well-resourced NRAs. Reliance is an approach to be used by all NRAs and should therefore become an integral part of regulatory operations.
- Adoption of legal frameworks to minimize resources for regulatory functions. Instead, the reasons for such frameworks should be the efficiency and capacity to be gained through reliance. Application of reliance should be anchored in high-level national policy and the NRA strategy, including a sustainable funding model.

3. Why is reliance important for the regulatory oversight of medical products?

Regulators face many challenges globally in terms of the increasing complexity of supply chains, globalization of markets, rapidly evolving science and managing emergencies. In addition, the global regulatory oversight has to be coordinated in an environment of limited human and financial resources therefore the global regulatory community has the responsibility to ensure best use of the limited resources and avoid duplication where possible to concentrate efforts and resources where they are most needed. Sharing information and efficiency are two important good regulatory practices and reliance is a powerful tool for implementing these two principles.
Leveraging the output of others whenever possible allows to place a greater focus at national level on value-added regulatory activities that cannot be undertaken by other authorities, such as, but not limited to: vigilance, market surveillance, and oversight of local manufacturing and distribution.

Establishing and sustaining mature regulatory systems requires adequate resources, including skilled, capable human resources and a significant financial investment. Reliance represents a smarter form of regulatory oversight and more effective way of regulating medical products in the modern world. It benefits patients and consumers, industry, national governments, the donor community, and international development partners by facilitating and potentially accelerating access to quality-assured, effective and safe medical products. Additionally, reliance can support regulatory preparedness and response, particularly during public health emergencies.

4. Do National Regulatory Authorities maintain their independence and sovereignty when using reliance?

In applying reliance in daily practice, national regulatory authorities (NRAs) do not compromise their independence. On the contrary, a decision to “regulate through reliance” is the hallmark of a modern and efficient regulatory authority. The NRAs maintain independence, sovereignty and accountability in regulatory decision-making. The information shared is the basis for the relying NRA to decide themselves what to do, to make their own regulatory decisions. The relying authority remains responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information from others. The decision to practice reliance and the best way to do so also rest with each NRA.

5. What are the main principles of reliance?

The WHO Good Reliance Practices[1] details six main high-level principles for reliance:

1. **Universality**—Reliance applies to all NRAs, irrespective of their levels of maturity or resources. Lack of resources or capacity are not the exclusive drivers for reliance. Different NRAs use reliance for different reasons. The exchange or gain of expertise may be one of them.
2. **Sovereignty of decision-making**—The decision to practice reliance and how best to do so rests with the NRA. In applying reliance in daily practice, NRAs maintain independence, sovereignty, and accountability in regulatory decision-making.
3. **Transparency**—NRAs should be transparent about the standards, processes and approaches they adopt in implementing reliance measures. The basis and rationale for relying on a specific entity should be disclosed and fully understood by all parties. Conducting transparent regulatory operations and decision-making is critical to enable reliance. Publishing of regulatory information to facilitate information exchange among NRAs is encouraged.
4. **Respect of national and regional legal bases**—Reliance practices should be coherent with national and regional legal frameworks and policies on medical products. It can be implemented through policy change, as long as it is broadly consistent with national legislation.
5. **Consistency**—Reliance on an assessment or decision from another authority should be established for specific, well-defined categories of products and processes. Reliance should be expected to be applied in a consistent manner for products and processes in the same categories in order for the users to have clarity on expected processes.
6. **Competence**—The implementation of reliance approaches requires that NRAs have the necessary competence for critical decision-making and maintain the appropriate expertise of their staff. Competence may be benchmarked through transparent processes for developing trust and building confidence in the reference authorities.

6. What competences are required in applying reliance?

Implementation of reliance approaches requires that NRAs have the necessary competence for critical decision-making with the involvement of senior regulatory staff, managers and experts who are competent to make the best use of foreign information in the local context.

The authorities being relied upon, should have and maintain competence and operate within a robust, transparent regulatory system based on international standards and guidelines, as well as good regulatory practices, and a well-functioning quality management system.
The effective use of information in the local context requires skill, ability and experience, the skill set and competence necessary to practise reliance have to be developed in the NRA workforce.
Senior management, reviewers, inspectors and other staff should build confidence and trust in the work done by other NRAs or trusted authorities. This requires an adequate culture/mindset of the relying NRA. The staff who are expected to implement reliance approaches must contribute to their development. Engagement, willingness, effective preparation, messaging and support from management and peers on the importance of reliance are key in better addressing workload pressures without minimizing the rigor of regulatory work or losing scientific or regulatory competence or capacity.

7. What is the sameness of product and how can it be assessed?

No reliance model can be successful without the critical aspect of ensuring that documentation received for an application assessed by the national regulatory authority (NRA) using reliance refers to the same medical product as the one that was assessed by the reference NRA.
Sameness of product means that two products have identical essential characteristics. All relevant aspects of drugs, including those related to the quality of the product and its components, should be considered to confirm that the product is the same or sufficiently similar (e.g. same qualitative and quantitative composition, same strength, same pharmaceutical form, same intended use, same manufacturing process, same suppliers of active pharmaceutical ingredients, same quality of all excipients). Additionally, the results of supporting studies of safety, efficacy and quality, indications and conditions of use should be the same.

Sameness of product should always be verified in any reliance approaches. Industry plays a crucial role in successful use of reliance mechanisms by NRAs, including by providing the relevant information to ensure the sameness of product. Assessment reports provide key information regarding the sameness of products. In case of doubts about the sameness of the product, the relying NRA can request additional information such as a confirmation from the manufacturer/ marketing authorization holder or contact the NRA of reference.

The impact of potential justified differences should be assessed by the manufacturer/marketing authorization holder and the relying NRA in determining the possibility of using reference NRA's assessments or decisions.

Assuring "sameness of product" is essential for the use of reliance. If an NRA has relied on another NRA's assessment for its initial approval, use of similar reliance measures for post approval changes and vigilance activities is beneficial, as long as the sameness of the product from the initial authorization is maintained. This also avoids the situation in which different changes are accepted in reference and in relying countries over time.

8. What type of reliance models exist?

Reliance can take many different forms and shapes depending on the needs of the national regulatory authorities (NRAs). It can be limited in scope in terms or products or can be built in for any regulatory activity or medical product. Illustrative examples of reliance model includes:

- **Work-sharing**—A process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task (e.g., joint assessment of applications for authorization of clinical trials, marketing authorizations or new indications, joint inspections for good practices, joint development of technical guidelines or regulatory standards, etc.). Work-sharing also entails exchange of information consistent with the provisions of existing agreements and compliant with each agency or institution's legislative framework for sharing such information with other NRAs.
- **Abridged regulatory pathways using reliance**—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 national regulatory authority (NRA) that is practicing reliance, for

example in terms of confirmation of the sameness of the medical product, while saving resources and ensuring that the standards of regulatory oversight are maintained.

- **Regional reliance mechanisms**— Medical products can be assessed centrally in a regional regulatory system. While in some regional reliance mechanisms the regional decision is binding on the member states (e.g., European Union), in others, regional decisions are recommendations that member states take into consideration when making national regulatory decisions (e.g., the Caribbean Regulatory System).
- **Unilateral or mutual recognition**—Acceptance of the regulatory decision of 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. It may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement.

9. Where can I find actual examples of reliance models?

Many examples around the world illustrate current use of reliance and the diverse ways in which national regulatory authorities (NRAs) leverage the work of others. Appendix 1 of the WHO Good Reliance Practices[1] presents a non-exhaustive list of current global practices in reliance in different regulatory functions (clinical trials, marketing authorization, post-approval changes, testing and lot release, pharmacovigilance, inspections, medical devices and public health emergencies). It will be completed in the future by a comprehensive repository of reliance approaches.

10. How can an NRA start using reliance models?

Initiatives to foster trust among regulatory authorities are essential to build up reliance models. Trust develops with increasing familiarity and understanding of what is behind regulatory outputs. Confidence can be built throughout the organization by sharing information, including the standards applied to regulatory decisions, working together and learning each other's ways of working, which then leads to effective use of reliance in regulatory work. Trust can be built in phases, starting for example with exchange of assessment reports and moving to work-sharing or joint assessments. Regulatory authorities may consider initiating reliance processes with applications for medical products of lower risk. Reliance may take many different shapes and forms and the NRA should define the more appropriate model depending on their needs and based on a risk-based approach, please see question below.

It is worth noting that reliance practices should be coherent with national and regional legal frameworks and policies on medical products, supported by clear mandates and regulations. Reliance can also be implemented through policy change.

11. What is the risk-based approach in reliance?

Each national regulatory authorities (NRA) should define its own strategy for an appropriate risk-based approach to reliance, which includes factors such as the type and source of products evaluated, the level of resources and expertise available in the NRA, the public health needs and priorities of the country and

opportunities for reliance. Regulatory systems with fewer resources can be as effective as those with more resources if they use a risk-based approach, take advantage of the work and decisions of other regulatory authorities and focus their resources on essential, value-added activities that can be provided only by their regulatory authority.

Depending on the activity or information in which the reliance is applied, there are different aspects to be consider in the risk-based approach. Using marketing authorization as an example, four different reliance based regulatory pathways and levels of reliance could be envisaged, with increasing degrees of assessment by the relying NRA:

- Verification of sameness of the medical product. Sameness should always be verified in any of the reliance approaches listed here.

- Confirmation of the applicability of the assessment outcomes of another authority for regulatory decision making in the national context, for example, in terms of legal and regulatory settings, benefit-risk assessment, co-morbidities, unmet medical needs, risk management plans and any quality-related specificities such as climatic zones for product stability. In case of differences, such as in target population, epidemiology and other features of the disease, medicines used concomitantly and other factors that can substantially affect the benefit–risk profile of a medicine, as well as quality parameters, especially in relation to the stability under different climatic conditions, appropriate evidence should be provided by the manufacturer.

- Abridged assessment of data on quality, safety and efficacy or performance, considering information in the assessment reports of the reference regulatory authority.

- Joint assessment or work-sharing between two or more regulatory authorities. For example, a primary review by one authority followed by a joint assessment session or distribution of the CTD modules between the authorities.

Similar reliance-based regulatory pathways can be used for other regulatory functions, such as inspection, lot release or import testing.

Regardless of the approach, when reliance is used, the authorization/review timelines may be shorter than the standard timelines and resources will be used more effectively. The reduction will depend on the level of reliance and any additional assessment required locally.

12. At which stages of the product life cycle can reliance be used?

The concept of reliance for regulation of medical products should be applied throughout the life cycle of medical products and in all regulatory functions (registration and marketing authorization, vigilance, market surveillance and control, regulatory inspection, laboratory testing, clinical trials oversight and national regulatory authorities lot release). While reliance approaches are widely used for the initial authorization of medical products, they should also be used for vigilance and other post-authorization activities (e.g. post approval changes, inspections and lot release), in view of the substantial regulatory resources required for evaluating safety and post-approval changes during a product's life cycle.

Assuring 'sameness of product' is essential for the use of reliance, avoiding the situation in which different changes are accepted in reference and in relying countries over time.

13. Which potential barriers may be faced for the use of reliance?

For the application of reliance, the NRAs may face some difficulties that should be considered in developing appropriate reliance strategies. An example of these factors are:

- Lack of political will and government support, even if a legal basis is established and if NRAs support reliance as a strategy and approach.
- Lack of accessible information and confidentiality of information, including the level of detail in regulatory reports. When assessments and other regulatory information are not publicly available, the relying NRA has to develop agreements to establish secure mechanisms or channels that allow the confidential access to the information with the reference regulatory authority or the manufacturer.
- Lack of a common language, with difficulties and cost of translation.
- Differences in national regulatory requirements and evidentiary standards.
- Lack of regulatory alignment of product risk classifications.
- Lack of use of reliance pathways (e.g. lack of knowledge of the pathways, manufacturer wishes to have independent reviews or due to confidentiality of information).
- Lack of acceptance of foreign clinical data and real world evidence.
- Different levels of competence.
- Internal resistance and insufficient knowledge of the reference regulatory authority and how it operates.

14. Which elements can be used to enable reliance?

There are some important elements that allow the application of reliance by the NRAs, such as:

- Trust. This is a critical element, as reliance requires confidence that the regulatory outcome is based on strong regulatory processes and standards and is, thus, trustworthy. Trust develops with increasing familiarity and understanding of what is behind regulatory outputs, this can be built in phases, for example, starting with exchange of assessment reports for medical products of lower risk and moving to work-sharing or joint assessments.
- Convergence and harmonization. The more similar requirements, standards and guidelines are, the greater the opportunity for collaboration and reliance. Differences in standards and practices, however, do not prevent one authority from relying on another, particularly when the relying authority has limited capacity and expertise. The system on which an NRA relies should be at least equivalent to or superior to the standards it applies. As a matter of good practice, NRAs should rely on assessments or decisions from reference regulatory authorities that apply international standards and guidelines.
- Economic or legal integration. When there is economic or legal integration in a region or a group of countries, reliance is facilitated and strengthened by the existing mutual provisions.
- Engagement of stakeholders. All relevant stakeholders, including industry, health care professionals, policymakers and the public, should be engaged and informed in order to increase their understanding and acceptance of reliance approaches and the clear benefits they present for all parties.
- Information-sharing and dialogue among regulators. Information-sharing is an essential part of reliance, and NRAs are encouraged to share information and good practices with other NRAs.

Increasing dialogue among regulators is seen in the growing number of international initiatives, which greatly facilitate reliance. Scientific and technical events, are platforms for disseminating regulatory information and for building knowledge and trust among NRAs.

15. What is the position of the International Pharmaceuticals Regulators Programme regarding reliance?

Reliance is one of the focus topic of the International Pharmaceuticals Regulators Programme (IPRP) and is strongly supported considering that the purpose, goals, objectives, scope of activities, as well as the mission and vision of the programme are closely related with the principles and considerations of good reliance practices in the regulation of medical products, related to aspects as:

- Promotion of regulatory convergence understanding the range of challenges for stakeholders facing each regulatory authority and addressing the increasingly complex global regulatory environment.
- Creating a trusting environment for regulators to exchange information on issues of mutual concern.
- Working closely with other international organisations to further extend the benefits of international regulatory collaboration.
- Regularly communicating on respective activities and sharing lessons learned.
- Encouraging engagement and consultation with regulatory stakeholders when appropriate.
- Exchanging information on issues of mutual interest and enabling regulatory cooperation.
- Facilitating the implementation of internationally harmonised technical guidelines for pharmaceuticals for human use.
- Promoting information sharing and collaboration to advance public health, facilitating access to medicines and addressing emerging regulatory challenges of mutual interest.

16. Where can I find additional information?

Please refer to the WHO Good Reliance Practices document[1] for more detailed information on the six principles, some key concepts, general considerations, potential barriers and enablers and examples of reliance.

In addition, the World Health Organization (WHO) conducted in 2019 a survey, on behalf of IPRP, among IPRP parties on their experiences, challenges, perceived benefits and opportunities of reliance. The outcome of this survey is available for download[3] and an article was published on the results of this survey[4]. A new article was recently published on the use of reliance in case of public health emergency[5].

[3] IPRP - Reliance - WHO Survey Outcomes, dated 18 June 2019. https://admin.iprp.global/sites/default/files/2019-06/IPRP_Reliance_WHOSurveyOutcomes_2019_0618.pdf

[4] Petra Doerr , Marie Valentin , Nobumasa Nakashima et al. Reliance: a smarter way of regulating medical products - The IPRP survey. Expert Rev Clin Pharmacol. 2021 Feb;14(2):173-177. doi: 10.1080/17512433.2021.1865798. Epub 2020 Dec 23 https://pubmed.ncbi.nlm.nih.gov/33355025/

[5] Agnes Saint Raymond , Marie Valentin , Nobumasa Nakashima et al. Reliance is key to effective access and oversight of medical products in case of public health emergencies. Expert Rev of Clin Pharmacol. 2022Aug; 15(7):1-6 doi:10.1080/17512433.2022.2088503 https://www.tandfonline.com/doi/full/10.1080/17512433.2022.2088503