

Annex 10

Good reliance practices in the regulation of medical products: high level principles and considerations

Background

WHO supports reliance on the work of other regulators as a general principle in order to make the best use of available resources and expertise. This principle allows leveraging the output of others whenever possible while placing 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. Reliance facilitates timely access to safe, effective, quality-assured medical products (see section 3. Scope) and can support regulatory preparedness and response, particularly during public health emergencies.

Good reliance practices (GRelP) are anchored in overall good regulatory practices (GRP) (1), which provide a means for establishing sound, affordable, effective regulation of medical products as an important part of health system strengthening. If implemented effectively, GRP can result in consistent regulatory processes, sound regulatory decision-making, increased efficiency of regulatory systems and better public health outcomes. NRAs are encouraged to adopt GRP to ensure that they are using the most efficient regulatory processes possible.

WHO is establishing and implementing a framework for evaluating regulatory authorities and designating those that meet the requirements as “WHO-listed authorities” (WLA) (4). Using the WHO Global Benchmarking Tool (5) and performance evaluation, WHO will assess the maturity and performance of a regulatory authority to determine whether it meets the requirements of a WLA and thereby provide a globally recognized, evidence-based, transparent system that can be used by NRAs as a basis for selecting reference regulatory authorities to practise reliance. A list of reference regulatory authorities is available on the WHO website (6).

In September 2019, WHO held a consultation to solicit input on the nature, structure and overall content of a document outlining GRelP. The meeting concluded that the concept note and recommendations on regulatory reliance principles of the Pan American Health Organization (PAHO) and the Pan American Network for Drug Regulatory Harmonization (7) should be used as a basis for the WHO document on GRelP. The high-level document would be complemented by a repository of case studies, practice guides and examples of practical application of GRelP.

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Abbreviations to Annex 10

AMRH	African Medicines Regulatory Harmonisation
APEC	Asia-Pacific Economic Cooperation
API	active pharmaceutical ingredient
ASEAN	Association of Southeast Asian Nations
CRP	collaborative registration procedure
GRP	good regulatory practices
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMDRF	International Medical Device Regulators Forum
NRA	national regulatory authority; for the purpose of this document, the term also refers to regional regulatory authorities such as the European Medicines Agency
OECD	Organisation for Economic Co-operation and Development
PAHO	Pan American Health Organization
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co operation Scheme
ZAZIBONA	Zambia, Zimbabwe, Botswana and Namibia; initial participants in the Southern African Development Community collaborative procedure for joint assessment of medicines

1. Introduction

The United Nations Sustainable Development Goals and the drive for universal health coverage require that patients have access to quality-assured, effective and safe medical products. Strong regulatory systems for medical products remain a critical element of well-functioning health systems and important contributors to improving access and ultimately achieving universal health coverage.

Establishing and sustaining mature regulatory systems requires adequate resources, including skilled, capable human resources and a significant financial investment. The globalization of markets, the sophistication of health technologies, the rapid evolution of regulatory science and the increasing complexity of supply chains have shown regulators the importance of international cooperation in ensuring the safety, quality, efficacy or performance¹ of locally used products. In view of the extent and complexity of the regulatory oversight required to address these challenges, NRAs must consider enhanced, innovative, more effective forms of collaboration to make the best use of the available resources and expertise, avoid duplication and concentrate their regulatory efforts and resources where they are most needed.

Reliance represents a smarter, more efficient way of regulating medical products in the modern world. Countries are therefore encouraged to formulate and implement strategies to strengthen their regulatory systems consistent with GRP, including pursuing regulatory cooperation and convergence, as well as reliance. Reliance benefits patients and consumers, industry, national governments, the donor community and international development partners by facilitating and accelerating access to quality-assured, effective and safe medical products.

The use of reliance to enhance the efficiency of regulatory systems has a long history. The WHO Certification scheme on the quality of pharmaceutical products moving in international commerce (8), introduced in 1969, is a form of reliance, as it provides assurance to countries that participate in the Scheme of the quality of pharmaceutical products. The European Union introduced the “mutual recognition procedure” for marketing authorizations between its member states in 1995, and the outcomes of good manufacturing practices inspections have been shared for years in the context of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) (9) and mutual recognition agreements.

WHO investigated the use of reliance more recently in a survey conducted on behalf of the International Pharmaceutical Regulators Programme (10). The

¹ “Efficacy” applies to medicines and vaccines and “performance” to medical devices, including in-vitro diagnostics.

results showed that regulatory reliance is broadly accepted and widely practised with regard to medical products, especially among well resourced regulatory authorities. The responses also reflected an evolving situation, with varying experience and promise in the use of reliance-based approaches. While use of reliance may be an emerging trend in some regions, the commonly stated goals are to increase efficiency, help to strengthen regulatory systems and optimize the use of resources. The results and suggestions from the survey were taken into account in preparation of this document.

In view of the increasing prevalence and importance of reliance in the regulation of medical products, Member States have requested WHO to prepare practical guidance on the topic while ensuring that the approaches meet the intended objectives. This document and additional guidance that follow are intended to assist countries in implementing a sound, evidence-based, practical, effective approach to reliance.

2. Purpose

The purpose is to promote a more efficient approach to regulation, thereby improving access to quality-assured, effective and safe medical products. The document presents the overarching principles of regulatory reliance in the oversight of medical products and use of reliance to enhance the effectiveness and efficiency of regulatory oversight. It provides high-level guidance, definitions, key concepts and considerations to guide reliance mechanisms and activities, illustrative examples of reliance approaches and conclusions. It will be complemented by a “reliance toolbox”, consisting of practice guides, case studies and a more comprehensive repository of examples.

3. Scope

The document covers reliance activities in the field of regulation of medical products (i.e. medicines, vaccines, blood and blood products and medical devices including in-vitro diagnostics), addressing all the regulatory functions in the full life cycle of a medical product, as defined in the Global Benchmarking Tool (5): registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspection, laboratory testing, clinical trials oversight and NRA lot release. The document is intended for all NRAs, irrespective of their level of maturity or resources, and also for policy-makers, governments, industry, other developers of medical products and other relevant stakeholders.

The concept of reliance covers all types of medical products and regulatory activities. Reliance approaches should be given consideration in

particular for medical products for priority diseases for which there are unmet medical needs, medical products to be used in public health emergencies or during shortages and also for orphan and paediatric medical products.

4. Glossary

Definitions are essential to ensure a common understanding of concepts and clarity in interpreting guidance on reliance. In addition to the definitions provided below, reference is made to the WHO document on good regulatory practices (1), which includes definitions of harmonization, convergence and other relevant terms.

Abridged regulatory pathways. 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 practising reliance (see section 5.4 Risk-based approach). 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.

Assessment. For the purpose of this document, this term covers any evaluation conducted for a regulatory function (e.g. evaluation of a clinical trial application or of an initial marketing authorization for a medical product or any subsequent post-authorization changes, evaluation of safety data, evaluation as part of an inspection).

Equivalence of regulatory systems. 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”.

International standards and guidelines. For the purpose of this document, the term includes relevant WHO standards and guidelines and any other relevant internationally recognized standards (e.g. International Organization for Standardization or pharmacopoeial standards) and guidelines (e.g. International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] or guidelines of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co operation Scheme [PIC/S]).

Mutual recognition agreement. According to a definition issued by the Organisation for Economic Co-operation and Development (OECD), a mutual recognition agreement is:

a principle of international law whereby states party to mutual recognition agreements recognize and uphold legal decisions taken by competent authorities in another member state. Mutual recognition is a process which allows conformity assessments (of qualifications, product...) carried out in one country to be recognized in another country (2).

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. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement.

Reference regulatory authority. For the purpose of this document, a national or regional authority or a trusted institution such as WHO prequalification (WHO PQ) whose regulatory decisions and/or regulatory work products are relied upon by another regulatory authority to inform its own regulatory decisions.

Regional regulatory system. A system composed of individual regulatory authorities, or a regional body composed of individual regulatory authorities, operating under a common regulatory framework but not necessarily under a common legal framework. The common framework must at least ensure equivalence among the members in terms of regulatory requirements, practices and quality assurance policies. The system or regional body may have enforcement powers to ensure compliance with the common regulatory framework.

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. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others.

Sameness of product. For the purpose of this document, sameness of product means that two products have identical essential characteristics (i.e. the product being submitted to the relying authority and the product approved by the reference regulatory authority should be essentially the same). All relevant

aspects of drugs, medical devices and in vitro diagnostics, 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. The impact of potential, justified differences should be assessed by the manufacturer (for the purpose of this document, manufacturer also means marketing authorization holder) and the relying national regulatory authority (NRA) in determining the possibility of using foreign regulatory assessments or decisions.

Stringent regulatory authority. A regulatory authority which is: (a) a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); or (b) an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015) (3).

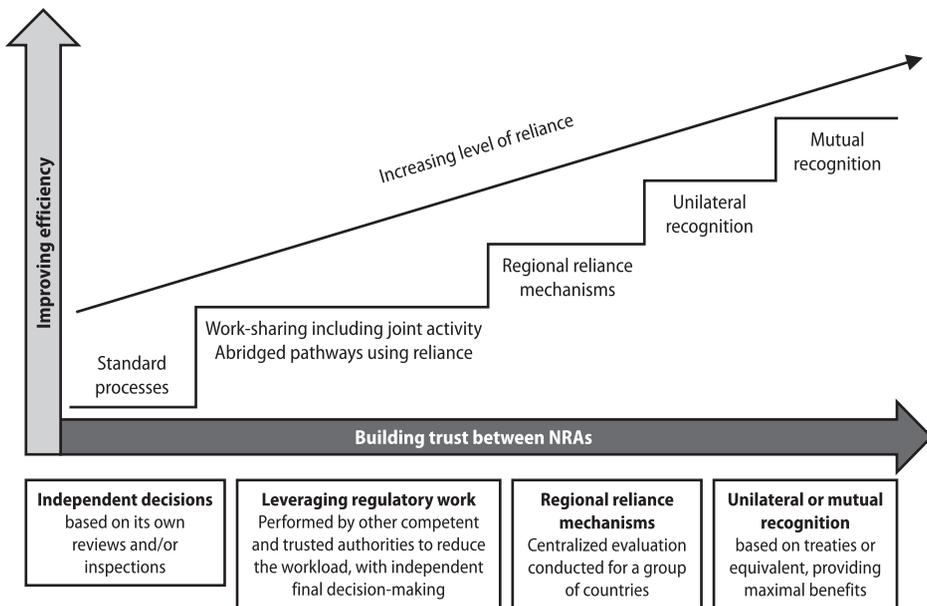
Work-sharing. A process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task. The opportunities for work-sharing include joint assessment of applications for authorization of clinical trials or marketing authorizations, joint inspections for good practices, joint post marketing surveillance of the quality and safety of medical products, joint development of technical guidelines or regulatory standards and collaboration on information platforms and technology. Work-sharing 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. 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. For example, a joint assessment is a procedure in which the same application is submitted simultaneously to two or more NRAs so that they conduct their evaluations in parallel and share their scientific assessments (e.g. the different modules for quality, nonclinical and clinical data can be assigned to different NRAs for review). The NRAs participating in a joint assessment can combine their lists of questions or

deficiencies to the manufacturer and base their respective independent regulatory decisions on the outcome of these assessments. Similarly, a joint inspection is one in which two or more NRAs share the activities and assessments performed during an inspection.

5. Key concepts

Fig. 1 illustrates some of the key concepts explained in the document, notably how NRAs can gain efficiency in regulatory operations and how to avoid duplication by using reliance approaches.

Fig. 1
Key concepts of reliance



5.1 Reliance versus recognition

Reliance may take many forms and be applied to varying degrees in recognizing or taking account of the assessments, decisions or other authoritative information of other authorities and institutions. Recognition may be seen as a special and more formalized approach to reliance, whereby one regulatory authority recognizes the decisions of another regulatory authority, system or institution, obviating additional regulatory assessment to reach its own decision. Recognition usually requires formal and binding legal provisions.

5.2 Unilateral versus mutual reliance or recognition

Reliance and recognition may be unilateral, for example, when a country chooses to rely on or formally recognize an assessment from another country unilaterally and without reciprocity. In other cases, mutual recognition may be based on binding mutual agreements or treaties negotiated at the level of governments. Such agreements take considerable time and resources to set up, as the regulatory systems involved must be mutually assessed and shown to be equivalent before agreement can be reached. A demonstration of the equivalence of regulatory systems is usually a prerequisite for mutual reliance or recognition. Work-sharing and joint activities are examples of mutual reliance.

5.3 Life cycle approach

The concept of reliance for regulation of medical products should be applied throughout the life cycle of medical products and in all regulatory functions (see 3. Scope). 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. Review of post approval changes to a product that was approved by a different authority may present challenges. Assuring "sameness of product" (see 4. Glossary) 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 originating and in receiving countries over time.

5.4 Risk-based approach

Each 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. 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 to ensure that it is the same as that assessed by the reference regulatory authority (see section 7.1.4 Sameness of a product in different jurisdictions). 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, taking into account information in the assessment reports of the reference regulatory authority; and
- joint assessment or work-sharing between two or more regulatory authorities. This may take various forms, including a primary review by one authority followed by a joint assessment session to finalize the report and comments or distribution of the modules (quality, non-clinical and safety or efficacy) between the authorities.

Regardless of the approach, it is expected that the timelines will be shorter than the standard timelines and resources will be used more effectively when reliance is used. The reduction in timelines will depend on the level of reliance and any additional assessment required locally. It is important that the timeline established for reliance procedures should be sufficient for the relying authority to properly review the assessment of the reference authority and perform the necessary local assessments, including of local labelling, product sameness and the applicability of the data to the country.

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

5.5 Regional reliance mechanisms

In some regions, medical products can be assessed centrally in a regional regulatory system. 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 Southern African Development Community collaborative procedure ZAZIBONA [Zambia, Zimbabwe, Botswana and Namibia; initial participants in the Southern African Development Community collaborative procedure for joint assessment of medicines], the Gulf Health Council and the Caribbean Regulatory System).

6. Principles of good reliance practices

In developing a strategy on the use of reliance in regulatory functions and activities, an NRA should consider the needs and characteristics of the national health and regulatory systems. A decision to practise reliance should consider existing capacity, regulatory systems' needs, the availability of an authority on which the NRA can rely with confidence and how reliance could complement the capacity to increase efficiency and make optimal use of resources. Reliance is not a lesser form of regulatory oversight but rather a strategy for making the best use of the available resources in any setting. This would allow the allocation of resources to other regulatory functions, such as in-country vigilance and post authorization activities, thereby increasing the effectiveness of local regulatory oversight. In addition, reliance can result in more evidence-based, better-quality decisions.

The following principles are meant to complement and extend the basic principles of GRP. They are based on the principles presented in the concept note and recommendations on regulatory reliance principles of PAHO and the Pan American Network for Drug Regulatory Harmonization (7).

6.1 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. Some use it to increase or build in-house capacity when there is the requisite expertise but not enough to perform their regulatory work as efficiently as they would like. Others use reliance to gain expertise that they do not have locally. Reliance is relevant for all resource settings.

6.2 Sovereignty of decision-making

The decision to practise reliance and how best to do so rests with the national health regulatory authority. Reliance does not imply dependence; it is not an agency out-sourcing its decision-making authority or responsibility. In applying reliance in daily practice, NRAs maintain independence, sovereignty and accountability in regulatory decision-making.

6.3 Transparency

Transparency is a key enabler to adopting new, more efficient ways of conducting regulatory operations, both locally and internationally. 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. NRAs should

engage with all stakeholders, including industry, to ensure the appropriateness and awareness of reliance processes.

Furthermore, NRAs should conduct transparent regulatory operations and decision-making, not only as a fundamental principle of GRP but also to build trust and maximize opportunities for cooperation and reliance as part of a shared regulatory community responsibility. Transparency measures should be encouraged through the publishing and sharing of regulatory information to facilitate information exchange among NRAs. NRAs that seek to act as reference agencies are encouraged to issue public assessment reports in a common language to document their regulatory decisions. Relying NRAs should use such reports as the primary source of information for assessments. If no public assessment reports are available or when additional information of a confidential nature is required, the manufacturer should provide an assessment report when available to them. If the relying NRA requests non public assessment reports from a reference agency, they may be provided with the consent of the manufacturer, if necessary.

6.4 **Respect of national and regional legal bases**

Reliance practices should be coherent with national and regional legal frameworks and policies on medical products, supported by clear mandates and regulations that ensure efficient implementation of reliance as part of government policy on good regulation. The reasons for adopting such legal frameworks should be the efficiency and capacity to be gained and not minimization of resources for regulatory functions. Use of reliance does not obviate the need for a capable local regulatory authority; on the contrary, it should be used to maintain and build local capacity for regulatory decision-making. When regulations do not make explicit provision for the application of reliance, it may be adopted through interpretation of existing regulations, if the legal framework does not explicitly preclude application of reliance approaches by the NRA. Reliance can be implemented through policy change, as long as it is broadly consistent with national legislation. If application of reliance is prohibited, revision of the legislation should be considered within a reasonable timeframe.

6.5 **Consistency**

Reliance on an assessment or decision from another authority should be established for specific, well-defined categories of products and processes. The scope of regulatory activities in which reliance may be practised should be clearly defined, and the practise of reliance should be transparent and predictable. Thus, reliance should be expected to be applied consistently for products and processes in the same categories.

6.6 Competence

Implementation of reliance approaches requires that NRAs have the necessary competence for critical decision-making. Introduction of the reliance approach usually requires the involvement of senior regulatory staff, managers and experts who are competent to make the best use of foreign information in the local context. NRAs should maintain the appropriate scientific expertise of their staff for activities in which they do not apply reliance, such as monitoring local adverse events, market surveillance and control, national labelling and product information activities and for oversight of locally manufactured products.

Equally, 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 GRP, and a well-functioning quality management system (11). Competence may be benchmarked through transparent processes for developing trust and building confidence in the reference authorities.

7. Considerations

A number of considerations can guide reliance approaches and facilitate their implementation. These include general aspects, barriers that NRAs may have to overcome and enablers for implementing reliance approaches. The non-exhaustive list of considerations below will be further elaborated in case studies, practice guides and the reliance repository.

Reliance is encouraged in any setting when supported by a common legal or regulatory framework in a regional regulatory system, by bilateral agreements, by mutual recognition agreements or on a purely voluntary, networking or ad-hoc basis. It is recommended that reliance be based on the original assessment. In some cases, however, it may be based on a decision made by reliance on another assessment.

7.1 General considerations

7.1.1 Reliance anchored in a national regulatory authority strategy

Application of reliance should have not only a legal basis that supports or at least does not preclude it (see section 6. Principles of good reliance practices) but should also be anchored in high-level national policy and the NRA strategy endorsed by senior management. This is necessary to provide a mandate for, direction to and expectations of NRA staff, to guide them in their daily work. The strategy should be detailed in procedures and integrated into processes to ensure the maximum benefits. It should include a sustainable funding model when implementing reliance, so that it does not negatively impact the financial sustainability and competence of the NRA. The strategy should be published

in order to make it accessible and understandable to external stakeholders. Implementation of reliance should be supported by training and periodic reviews to ensure that the standards are being maintained, to assess whether the objectives are being met and to revise it when warranted.

NRAs that practise reliance should establish and publish a list of reference regulatory authorities, with the criteria used in identifying them. They should decide and establish the criteria they will use for selecting reference authorities, such as application of international standards, long standing recognition in the international community, proximity and commonality of medical products. To qualify reference regulatory authorities or specific oversight of a regulatory function, an NRA may refer to an assessment by an independent organization (e.g. WHO benchmarking, WHO-listed authority, International Organization for Standardization accreditation, the Medical Device Single Audit Program, PIC/S).

WHO encourages NRAs to monitor and evaluate the impact of regulatory reliance, including its benefits, in their country and region and to share their experiences with other regulatory authorities. When possible, the impact should be measured specifically, and the NRA should establish the metrics they will use to measure the impact of using reliance in regulatory decision-making and the time for conducting the assessment. The metrics may include costs saved, efficiency in the number of products reaching the market or time to market, and redirection of scarce resources to areas of higher regulatory risk. NRAs should consider methods for sharing best practices and experience in establishing reliance arrangements in international forums for regulation of medical products to increase understanding of the opportunities and challenges of reliance, subject to agreement with the other party(s) involved and information disclosure requirements.

7.1.2 Cultural change

Use of reliance approaches means moving to a more innovative, effective way of working, based on trust and relying on the outputs of other NRAs. The benefits must be understood and supported at operational level, and the staff who are expected to implement reliance approaches must contribute to their development. This will require engagement, willingness, effective preparation, messaging and support from management and peers on the importance of reliance in better addressing workload pressures without minimizing the rigor of regulatory work or losing scientific or regulatory competence or capacity. Use of assessments and information from other trusted regulatory authorities can help build capacity and competence (e.g. through exposure to the reviews and decisions of the reference authority, networking, twinning, staff visits and exchanges). Furthermore, as effective use of such information in the local context requires skill, ability and experience, the skill set and competence necessary to practise reliance will 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 will take time and require a change in the culture of the relying NRA. The experience of regulatory authorities and systems that already practise reliance should be leveraged to promote acceptance and avoid pitfalls. Trust should also be built with the public, health care professionals and the industry by assuring them that reliance offers more efficient regulatory oversight.

7.1.3 Flexibility in approach: “one size doesn’t fit all”

In accordance with the principles outlined above, reliance strategies should be tailored to the needs of the national health and regulatory systems. NRAs may choose to rely on others in routine regulatory oversight and/or in special circumstances, such as a public health emergency. Reliance offers flexibility to NRAs. When adopting reliance, whatever the approach, the NRA should consider its capacity, establish clear goals and efficient processes and ensure that the standards and criteria are transparent and well established.

7.1.4 Investment of resources and time in implementing reliance

As stated above, reliance should increase the efficiency of a regulatory system in a country or region. Nevertheless, implementation of reliance approaches will first require investment of resources and time for activities such as legislative changes, preparation of guidance documents and approaches, pathways and processes, building confidence by preparing parallel or joint reviews supported by staff exchanges, training staff, dialogue with industry and other stakeholders and establishment of or access to information-sharing platforms, communication links and networks with other NRAs.

7.1.5 “Sameness” of a product in different jurisdictions

A critical aspect of the application of reliance is verification of the “sameness” of a medical product (see 4. Glossary and section 5.4 Risk-based approach) in different jurisdictions. Reliance can be practised only if the NRA that intends to use a foreign assessment as the basis for its own assessment and regulatory decision making has the assurance that the medical product being assessed is essentially the same as the one submitted to the reference NRA. The role of the manufacturer is essential to confirm the sameness of a product and to provide the same documentation to different NRAs, except for additional country-specific information submitted for review, such as product stability data according to the stability zone and the local product label. The manufacturer should confirm in the application that the product is the same and that the application contains essentially the same information, taking into consideration any potential national requirements. If the application is not submitted simultaneously to the

agencies, the manufacturer should highlight any new information about the product acquired since the application was submitted to the reference agency, with the corresponding assessment.

7.1.6 **The role of industry**

Industry plays a crucial role in successful use of reliance mechanisms by NRAs. While industry widely supports reliance as a concept and practice that can increase efficiency, it must have clear guidance on its application and see meaningful benefits. Industry support and stringent adherence to the factors that validate the reliance process are essential for filing applications in several countries or regions to ensure the sameness of products submitted to reference regulatory authorities and relying NRAs. They should share complete, unredacted information.

Review and discussion of pilot programs to quickly adapt and improve guidance will be key to benefit from key learnings and improve implementation. Collaboration and dialogue among all stakeholders participating in regulatory reliance activities will help to create and build trust, which is the foundation of regulatory reliance. Transparent publication of an NRA's reliance framework and strategies, including the metrics used and benefits achieved, will encourage industry to support and promote the reliance approach.

7.1.7 **Reliance in a public health emergency**

In case of a public health emergency, reliance approaches are even more essential and should be given more importance in order to accelerate access to the medical products required.

7.2 **Potential barriers**

7.2.1 **Lack of political will**

Lack of political will and government support can make it difficult for NRAs to implement or facilitate reliance in their daily practice, even if a legal basis is established that supports (or does not preclude) reliance and if NRAs support reliance as a strategy and approach.

7.2.2 **Lack of accessible information and confidentiality of information**

Lack of access to complete assessments of reference regulatory authorities can be a major barrier to effective reliance. Reference regulatory authorities should make their assessments and other regulatory information publicly available. Non-public regulatory reports might be available directly from the manufacturer when the company is able to access these reports from the reference regulatory authority. If this is not possible, the relying NRA should approach the reference

regulatory authority. In these cases, arrangements among NRAs on the exchange of confidential information would facilitate the reliance process.

Sensitive, non-public information in unredacted assessment or inspection reports can also be shared between regulatory authorities upon request. This may include confidential commercial information, trade secrets or personal information. In some circumstances, the sharing of such information may require the consent of the manufacturer. Sharing of personal information may also require consent from individuals in order to comply with data protection regulations. Given the sensitivity of such non-public information, NRAs may require that confidentiality agreements be signed that govern the exchange, management and disclosure of such information to ensure that the confidentiality of the information is protected by the relying NRA. Such information should always be exchanged through secure channels or on information-sharing platforms.

7.2.3 Other barriers

Additional potential barriers include issues such as lack of a common language, difficulties in or the cost of translation, differences in national regulatory requirements and evidentiary standards, lack of regulatory alignment of product risk classifications, inconsistent practices regarding modifications to medical devices (including in-vitro diagnostics), the lack of acceptance of foreign clinical data and real world evidence, the level of detail in regulatory reports, different levels of competence and, as previously noted, internal resistance and insufficient knowledge of the reference regulatory authority and how it operates. All such factors should be considered in developing appropriate reliance strategies, as will be further elucidated in the additional guidance documents to follow.

7.3 Enablers

7.3.1 Trust

Trust is a critical element, as reliance requires confidence that the regulatory outcome is based on strong regulatory processes and standards and is, thus, trustworthy. Consequently, initiatives to foster trust among regulatory authorities are essential. 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 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.

In addition, industry and other stakeholders must trust regulatory authorities, for example, to respect the confidentiality of information.

7.3.2 Convergence and harmonization

Convergence and harmonization of requirements, standards and guidelines are important enablers of regulatory cooperation and reliance. The more similar requirements, standards and guidelines are, the greater the opportunity for collaboration and reliance. Use of the ICH Common Technical Document (CTD) and the electronic CTD (eCTD) as a common format for regulatory submissions around the globe is one example of how harmonization can facilitate and enable 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.

7.3.3 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 such as the International Pharmaceutical Regulators Programme and in networks for sharing regulatory information and work such as the Pan American Network for Drug Regulatory Harmonization, the Southeast Asia Regulatory Network, regulatory networks in the Regional Economic Communities under the African Medicines Regulatory Harmonisation (AMRH) Initiative and the Association of Southeast Asian Nations (ASEAN) Pharmaceutical Products Working Group, the International Coalition of Medicines Regulatory Authorities, the Caribbean Community and Common Market's (CARICOM) Caribbean Regulatory System, the Western Pacific Region Alliance of NRAs for Medical Products and others, which greatly facilitate reliance.

Scientific and technical events, such as the International Conference of Drug Regulatory Authorities, ICH and PIC/S, are platforms for disseminating regulatory information and for building knowledge and trust among NRAs.

7.3.4 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. Examples are the Asia–Pacific Economic Cooperation (APEC), ASEAN, CARICOM, the European Union, the Eurasian Economic Union, the Gulf Cooperation Council,

the Pacific Alliance, the Regional Economic Communities in Africa and the Southern Common Market (MERCOSUR).

7.3.5 Engagement of stakeholders

All relevant stakeholders, including industry, health care professionals, policy-makers 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. Communication and engagement with stakeholders should be tailored to each target audience.

8. Conclusions

Reliance is being practised by a growing number of regulatory authorities as a means of improving the effectiveness and efficiency of regulation of medical products. It allows NRAs to make the best use of resources, build expertise and capacity, increase the quality of their regulatory decisions, reduce duplication of effort and, ultimately, promote timely access to safe, effective and quality assured medical products. Adoption of reliance measures whenever possible, in a well structured framework underpinned by national or regional policies and strategies, will allow regulators to focus their resources on activities that contribute to public health that cannot be undertaken by others.

Reliance represents a “smarter” form of regulatory oversight, based on constructive regional and international collaboration, that will facilitate and promote convergence and the use of common international standards and guidelines, resulting in more predictable, faster approval to improve access to quality-assured medical products for patients worldwide.

Reliance does not represent a less stringent form of regulatory oversight or outsourcing of regulatory mandates, nor does it compromise independence. On the contrary, a decision to “regulate through reliance” is the hallmark of a modern and efficient regulatory authority.

NRAs are encouraged to include reliance-related provisions as part of their flexible regulatory pathways, and reliance should be considered in all regulatory functions of the life cycle of a medical product, as appropriate.

The principles and considerations presented in this document should be considered in implementing regulatory reliance frameworks or strategies. Effective implementation of reliance will benefit not only NRAs but also patients, health care providers and industry.

While reliance may be viewed as particularly useful for 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.

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Appendix 1

Examples of use of reliance

Regulatory reliance can take many forms and encompasses a wide range of regulatory approaches and practices that involve two or more regulatory authorities. It may be limited to a discrete regulatory process or function or comprise the full scope of regulatory functions throughout the life cycle of a medical product. Many examples around the world illustrate current use of reliance and the diverse ways in which NRAs leverage the work of others. The examples below illustrate the points raised in the GRelP, to show use of reliance in different regulatory functions. The list is not exhaustive but an illustration of current global practices in reliance. It may be replaced in the future by a comprehensive repository of reliance approaches to be established as a part of a toolbox of GRelP.

A1. Clinical trials

Work-sharing in the assessment of clinical trials is being used in some regions, such as the Voluntary Harmonisation Procedure in the European Union (1) and the African Vaccine Regulatory Forum (AVAREF) (2). By assessing clinical trial applications together, NRAs and, in some cases, ethics committees in different countries can benefit from the assessments performed by the different participating countries with a view to facilitating and ensuring the robustness of the clinical trials application assessment process across countries. The AVAREF platform has been instrumental in building the expertise and capacity of regulators and ethics committees, promoting the use of international standards and expediting clinical trial assessments and decisions for medical products of high public health interest in both emergency and other circumstances. A guideline and a platform for joint assessment of applications for clinical trials as well as guidelines for site inspections for good clinical practices have been set up to facilitate product development, regulatory decision-making and access to promising new medical products (3).

A2. Marketing authorization

A2.1 Abridged regulatory pathways with reliance for initial marketing authorization

Several procedures are available through regulatory authorities or the WHO prequalification programme for use of an abridged regulatory pathway by a relying NRA. The European Union Article 58 (also referred to as European

Union Medicines for all) (4), the Swissmedic Marketing Authorisation for Global Health Products (5) procedures and the WHO collaborative procedure (CRP) for accelerated registration (CRP) (6) are three examples of abridged regulatory pathways in which reliance is used to facilitate the registration of medical products.

The European Union Article 58 and the Swissmedic Marketing Authorisation for Global Health Products not only facilitate national registration but also provide an opportunity for experts from NRAs to both observe and participate in assessment and scientific advice procedures, thus building their capacity and establishing confidence in the processes.

The CRP facilitates the assessment and accelerates national registration of WHO-prequalified medical products and medicines approved by a stringent regulatory authority. The CRP provides unredacted reports on the assessment, inspection and performance evaluation (in the case of in-vitro diagnostics) upon request (and with the consent of the manufacturer) to participating NRAs, primarily in low- and middle-income countries. The procedures are detailed in WHO guidelines, which also include guidance on how NRAs can make the most efficient use of the reports in reaching their own decisions, as participating NRAs are expected to reach a decision on marketing authorization within 90 calendar days (regulatory time). The CRP has been successful in both accelerating decisions in countries and building the capacity of regulatory authorities.

The WHO certificate of a pharmaceutical product (CPP) is also used as a reliance tool, in lieu of full or partial assessment for marketing authorization (7). NRAs are encouraged to consider use of electronic CPP. These certificates are being used in lieu of a full or partial review, accelerating assessment in many countries such as Benin, Bolivia, Cameroon, Congo, Cuba, Curaçao (Netherlands), Guinea, Haiti, Honduras and Hong Kong (China).

A2.2 Quality information

Many NRAs, and the WHO Prequalification programme, recognize certificates of suitability for monographs in *The European Pharmacopoeia* (8) for active pharmaceutical ingredients (APIs) as validation of the quality of a certain API. Some countries also recognize confirmation of API prequalification by the WHO Prequalification programme for APIs (9). These two examples provide assured mechanisms of reliance and also reduce the documentation requirements for countries that rely upon or recognize those certificates. When a certificate of suitability for the monographs of *The European Pharmacopoeia* or confirmation of prequalification of an API is issued, the receiving NRA need not duplicate the API assessment but can focus on sections not covered by either document.

A2.3 Work-sharing

The Australia–Canada–Singapore–Switzerland United Kingdom ACCESS Consortium (10) was formed in 2007 by “like-minded” medium-sized regulatory authorities to promote work sharing for greater regulatory collaboration and alignment of regulatory requirements. The ACCESS Consortium explores opportunities to share information and work in areas such as biosimilar products, complementary medicines, generic medicines, new prescription medicines, medical devices and information technology. The Consortium capitalizes on each country’s strengths, addresses gaps in science, knowledge and expertise and leverages resources to expedite risk assessment, while maintaining or raising quality and safety standards. The Consortium builds on international networks, initiatives and mechanisms to advance work- and information-sharing throughout the life cycles of health products.

A2.4 Joint assessments

Joint assessments can be beneficial to NRAs by spreading the workload, building capacity through broader experience and expertise and helping to build trust in each other’s assessments and decision making processes. Similarly, industry can benefit from a common review and a single set of questions, saving both resource and time as compared with separate interactions. In view of these benefits, several joint assessment initiatives have been introduced into regional regulatory networks, sometimes driven by the higher-level priorities of economic blocs seeking to create common markets. Examples of joint assessment initiatives include those in the Regional Economic Communities in Africa (East African Community (11)), ZAZIBONA (12) in the Southern African Development Community, the Economic Community of West African States/West African Health Organization (13) and the ASEAN Joint Assessment Coordinating Group (14).

A2.5 Unilateral recognition

The Mexican Federal Commission for Protection against Sanitary Risk unilaterally recognizes marketing authorizations from certain reference regulatory authorities (15).

A2.6 Mutual recognition

The European Union is an example of highly integrated regulatory cooperation, and its many regulatory pathways depend heavily on work-sharing, recognition and other forms of reliance. The approval of medicines is based on a single assessment system, so that an assessment report from any agency in the European Union network can be used as a basis for reliance by other regulators.

In this case, a strong, common legal framework and harmonized regulatory standards shared by all European Union countries has enabled and facilitated reliance and recognition (16).

A3. Post-approval changes

In accordance with the same principles as for initial marketing authorization, reliance can also be applied broadly in assessing post-approval changes already approved by NRAs considered to be reference authorities. In the case of CRP, for example, WHO informs the participating NRAs about any variations in prequalified products approved by the WHO Prequalification team (6).

The Health Sciences Authority in Singapore applies a verification route with shortened times for approving post-approval changes to quality and product labels, to increase leverage of reference agencies' assessments, minimize duplication of effort and increase efficiency as part of work that includes effective life cycle management of registered therapeutic medicinal products. To qualify, the proposed changes must be identical to those approved by one of the Authority's five reference agencies, with proof of the approval and the approved product label of that reference agency (17).

A4. Testing and lot release

A4.1 Network of Official Medicines Control Laboratories

The network of official medicines control laboratories supports regulatory authorities in controlling the quality of medicinal products on the market. Collaboration within the General European Official Medicines Control Laboratories Network (GEON) (18) makes the best use of resources by pooling resources and avoids duplication of work and testing. Some of the main goals of the GEON are to ensure mutual recognition among its members of tests conducted by national official medicines control laboratories, coordinate activities among official medicines control laboratories and facilitate sharing of knowledge and work.

A4.2 Lot release and quality monitoring of vaccines and other biological products

Launched in 2017, the WHO National Control Laboratory Network for Biologicals (WHO-NNB) (19) brings together national control laboratories and NRAs of vaccine-producing and vaccine recipient countries, WHO contract laboratories, manufacturers' associations, WHO regional offices and other stakeholders, including donors. WHO-NNB ensures effective use of global resources by providing a platform and infrastructure for collaboration and exchange of information on quality and technical aspects. Its main objective

is to facilitate access to and the availability of prequalified vaccines (and other biotherapeutic products) through reliance on batch releases by NRAs and national control laboratories that are members of WHO-NNB, thereby reducing redundant testing and encouraging more cost-effective testing and more effective regulatory oversight.

A5. Pharmacovigilance

Exchanges and sharing of data are critical in pharmacovigilance. More than 100 Member States share data on the safety of medical products in the WHO database of individual case reports of safety, VigiBase, developed and maintained by the Uppsala Monitoring Centre (20). Member States use this database (and thereby each other's data) as a single source of pharmacovigilance information to confirm and validate any signals of adverse events associated with medicines and vaccines that they have observed. In Regulation EU No 1235/2010 (21), the European Union introduced the concept of a supervisory authority for pharmacovigilance, to be responsible for verifying on behalf of the Union that the marketing authorization holder for a medicinal product satisfies the pharmacovigilance requirements as per European Union legislation.

Countries in the Region of the Americas have been preparing joint assessments of periodic safety updates and risk management plans. Coordinated by Health Canada, pairs of countries have completed evaluation reports for several products. The reports are made available on a regional platform with access restricted to the pharmacovigilance focal points of the NRAs.

A6. Inspections

Governments and NRAs in various regions have made mutual recognition agreements so that they can rely on each other's inspections, avoiding duplication of work and making the best use of resources. These include agreements between the European Union (22) and Australia, Canada, Japan, Switzerland and the USA and ASEAN mutual recognition agreements (23).

PIC/S is a non-binding, informal cooperative arrangement among regulatory authorities in the field of good manufacturing and good distribution practices of medicinal products for human or veterinary use and, more recently, also in good clinical and good vigilance practices (24). Its aim is to facilitate cooperation and networking among competent authorities and regional and international organizations, thus increasing mutual confidence in inspections. PIC/S has issued guidance on inspection reliance, outlining a process for desktop assessment of compliance with good manufacturing practices (25). Reliance is an important aspect of desktop assessments of compliance with relevant good practice guidelines and requirements, as described in WHO guidance (26).

The OECD operates a system for mutual acceptance of data in the assessment of chemicals (including pharmaceuticals), in which data generated in any member country in accordance with OECD test guidelines and the principles of good laboratory practice are accepted by any other member country for assessing products for the protection of human health and the environment (27).

A7. Examples of medical devices

Reliance is prevalent in the regulation of medical devices, including in-vitro diagnostics. For example, the Medical Device Single Audit Program (28) was developed under the auspices of the International Medical Device Regulators Forum (IMDRF). Under this Program, the regulatory authorities of Australia, Brazil, Canada, Japan and the USA have pooled their resources into a robust system of oversight by third party auditing organizations, which, in turn, audit the quality management systems of medical device manufacturers. The Program permits an auditing organization to conduct a single regulatory audit that satisfies the requirements of the regulatory authorities that participate in the Program. The pooled resources are used to establish and maintain oversight of auditing organizations, resulting in more effective use of limited regulatory resources. A single audit programme allows regulatory authorities to leverage resources efficiently and to streamline the regulatory process without compromising public health and to promote better aligned, more consistent regulatory requirements.

The IMDRF has also issued guidance for exchanges of information on the safety of medical devices among participating NRAs (29). The system reports incidents that represent a serious threat public health beyond national borders. The IMDRF provides consistent terminology for reporting and coding adverse events for categorized reporting (30).

These activities are just two examples of the work of IMDRF in harmonization, convergence and reliance in the area of medical devices. Other examples are optimizing standards for regulatory use (31), essential principles of the safety and performance of medical devices (32) and requirements for the competence, training and conduct of regulatory reviewers (33).

In Singapore, medical devices and in vitro diagnostics that have been authorized through specific pathways in Australia, Canada, Europe, Japan or the USA are eligible for abridged evaluation. To qualify, the proposed intended use must be identical to that approved in the reference country. Typically the documentation includes proof of approval from the reference regulatory authority and summary technical documents to satisfy requirements for supporting documentation (34). Additionally, Australia recognizes registrations and certifications from notified bodies designated by the medical device

regulators of Health Canada, European member states, the Pharmaceuticals and Medical Devices Agency of Japan, the US Food and Drug Administration and organizations participating in the Medical Device Single Audit Program (35).

A8. Examples of public health emergencies

WHO developed the “emergency use assessment and listing” mechanism as a risk-based procedure for assessing and listing unlicensed vaccines, therapeutics and in-vitro diagnostics for use primarily during public health emergencies of international concern but also in other public health emergencies when appropriate.

PAHO has developed guidance for NRAs and regulatory systems on practical ways of implementing reliance for emergency use of medicines and other health technologies in a pandemic (36).

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