DRAFT WORKING DOCUMENT FOR COMMENTS:

Good reliance practices in regulatory
decision-making:
high-level principles and
recommendations

Please send your comments to Mrs Marie Valentin, Technical Officer, Regulatory Convergence and Networks, Regulation and Safety (valentinm@who.int), with a copy to Mrs Carolyn Doucelin (doucelinc@who.int) before 24 July 2020. Please use our attached Comments Table for this purpose.

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**SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/20.851:**

**Good reliance practices in regulatory decision-making:**

*high-level principles and recommendations*

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<th>Description of activity</th>
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<tr>
<td>Presentation of the concept to the 53rd Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).</td>
<td>22-26 October 2018</td>
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<td>Consultation with National Regulatory Authorities and regulatory organizations regarding the nature, structure and overall contents of a document outlining Good Reliance Practice was conducted in a meeting in Geneva, Switzerland.</td>
<td>19 September 2019</td>
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<td>Presentation and update of the various new activities regarding the development of new good practices in the area of regulatory science to 54th ECSPP.</td>
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Annex 1: Examples
1. Acronyms

ACSS  Australia-Canada-Singapore-Switzerland Consortium

AMRH  African Medical Products Regulatory Harmonisation

APEC  Asia-Pacific Economic Cooperation

API   Active Pharmaceutical Ingredient

ASEAN Association of Southeast Asian Nations

AVAREF African Vaccine Regulatory Forum

CEP   Certificate of Suitability to the monographs of the European Pharmacopoeia

CPQ   Confirmation of active pharmaceutical ingredient Prequalification

COFEPRIS Comisión Federal para la Protección Contra Riesgos Sanitarios (Mexico)

CRP   Collaborative Registration Procedure

EAC   East African Community

ECOWAS Economic Community of West African States

ECSPP Expert Committee on Specifications for Pharmaceutical Preparations

EMA   European Medicines Agency

EU    European Union

EU-M4 all European Union Medicines for all

GBT   Global Benchmarking Tool

GCP   Good Clinical Practices

GMP   Good Manufacturing Practices

GRP   Good Regulatory Practices

GReIP Good Reliance Practices

ICH   International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IMDRF International Medical Device Regulators Forum

IPRP  International Pharmaceutical Regulators Programme

MAGHP Marketing Authorization for Global Health Products

MERCOSUR Southern Common Market

MDSAP Medical Device Single Audit Program

NRA   National Regulatory Authority; for the purpose of this document, this term also includes regional regulatory authorities such as the European Medicines Agency (EMA)
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<tr>
<td>OMCL</td>
<td>Official Medicines Control Laboratories</td>
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<td>PAHO</td>
<td>Pan American Health Organization</td>
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<td>PANDRH</td>
<td>Pan American Network for Drug Regulatory Harmonization</td>
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<tr>
<td>PIC/S</td>
<td>Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme</td>
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<td>ASEAN PPWG</td>
<td>ASEAN Pharmaceutical Products Working Group</td>
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<td>REC</td>
<td>Regional Economic Communities in Africa</td>
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<td>SEARN</td>
<td>South-East Asia Regulatory Network</td>
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<td>SADC</td>
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<td>SRA</td>
<td>Stringent Regulatory Authority (1)</td>
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<td>UHC</td>
<td>Universal Health Coverage</td>
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2. **Background**

The World Health Organization (WHO) supports the implementation of reliance on other regulators’ work as a general principle in order to make the best use of available resources and expertise. This principle enables leveraging the output of others whenever possible while placing a greater focus at the national level on value added regulatory activities that cannot be undertaken by other authorities, such as in-country vigilance activities and oversight of local manufacturing and distribution. Reliance approaches facilitate timely access to safe, effective and quality-assured medical products and can help in regulatory preparedness and response, particularly during public health emergencies.

Good Reliance Practices (GReIP) are anchored in the overarching Good Regulatory Practices (GRP) which provide a means for establishing sound, affordable and effective regulation of medical products as an important part of health system strengthening. If implemented effectively, GRP can lead to consistent regulatory processes, sound regulatory decision-making, increased efficiency of regulatory systems and better public health outcomes.

An ongoing initiative at WHO aims at establishing and implementing a framework for evaluating national regulatory authorities (NRAs) and designating those that meet a specific standard as WHO-Listed Authorities (WLAs). Based on benchmarking using the WHO Global Benchmarking Tool (GBT), WHO will assess the NRA’s regulatory performance and maturity level in order to qualify an NRA as a WLA and thereby provide a globally recognized, evidence-based and transparent system that can be used by NRAs as a reference to practise reliance.

The WHO held a consultative meeting in September 2019 in order to solicit input on the nature, structure and overall content of a document outlining GReIP. The meeting concluded that the Pan American Health Organization (PAHO)/Pan American Network for Drug Regulatory Harmonization (PANDRH) concept note and recommendations on regulatory reliance principles should be used as a starting point for the development of a WHO GReIP document. The high-level document would be complemented in a second step by a repository of case studies, practice guides and examples of practical applications of GReIP.
3. Introduction

The United Nations Sustainable Development Goals and the drive for Universal Health Coverage (UHC) require that patients have access to quality-assured medical products, hence, strong regulatory systems for medical products remain a critical element of well-functioning health systems and an important contributor to improving access and ultimately achieving UHC.

It is widely recognized, however, that regulatory systems can be very resource-intensive. Establishing and sustaining mature regulatory systems is a high resourced enterprise that requires skilled human resources and significant public investments. Moreover, the globalization of markets, the sophistication of health technologies, the rapid evolution of regulatory science and the increasing complexity of supply chains have led regulators to recognize the importance of international cooperation in order to ensure the safety, quality and efficacy of locally used products. In view of the extent and complexity of regulatory oversight required to address these challenges, NRAs must consider enhanced, innovative and more effective forms of collaboration in order to make the best use of the available resources and expertise, avoid duplication and concentrate their regulatory efforts and resources where most needed.

Reliance represents a smarter way of regulating medical products in a modern regulatory world. Towards this end, countries are encouraged to formulate and implement strategies to strengthen their regulatory systems consistently with GRP, including pursuing regulatory cooperation and convergence, as well as reliance. Reliance brings benefit to the industry, patients and consumers, national governments, as well as the donor community, and international development partners by facilitating and accelerating access to quality medical products.

There is a long history of enhancing the efficiency of regulatory systems through reliance. The WHO Certification scheme on the quality of pharmaceutical products moving in international commerce (6), introduced by WHO in 1969, is a form of reliance providing assurance to countries participating in the Scheme about the quality of pharmaceutical products. The European Union (EU) introduced the mutual recognition procedure for marketing authorizations between Member States in 1995, and outcomes of Good Manufacturing Practice (GMP) inspections have been shared for years in the context of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S) and mutual recognition agreements.
The use of reliance was more recently investigated by WHO through a survey conducted on behalf of the International Pharmaceutical Regulators Programme (IPRP) (7). The results showed that regulatory reliance is a broadly accepted and widely practiced approach in the area of medical products, especially among the participating well-resourced regulatory authorities. At the same time, responses also reflected an evolving situation marked by varying degrees of experience and promise in the use of reliance-based approaches. While the use of reliance in some regions may be characterized as an emerging trend, the commonly stated goals are to bring efficiency, to help strengthen regulatory systems and to optimize the use of resources. The results and suggestions from this survey were taken into account for the preparation of this document.

Given the increased prevalence and importance of reliance in the regulation of medical products, countries have requested WHO to develop practical guidance on the topic while ensuring that approaches meet the intended objectives. This document, and the companion documents that will follow, are intended to assist countries in implementing a sound, evidence-based and effective approach to reliance.

4. Purpose

The objective of this document is to promote a more effective and efficient approach to regulation as part of a “smart regulation” approach, thereby promoting access to quality-assured medical products. It aims at presenting the overarching principles under which regulatory reliance in the field of oversight of medical products should operate and use reliance as a tool for effective regulation and regulatory system strengthening.

This document is intended to provide high-level guidance, definitions, key concepts and considerations in order to guide reliance activities, illustrative examples of reliance approaches and conclusions. It will be complemented by a “reliance toolbox” consisting of practice guides, case studies and a comprehensive repository of examples.
5. Scope

This document covers reliance activities in the field of regulatory oversight of medical products (i.e. medicines, vaccines, blood and blood products and medical devices including in-vitro diagnostics), addressing all regulatory functions spanning the full life cycle of a medical product.

In addition, this document is intended for all NRAs, irrespective of their level of maturity or resources, as well as policy makers, governments, the industry and other developers of medical products, and other relevant stakeholders.

6. Definitions and key concepts

6.1 Definitions

Definitions are essential to ensure a common understanding of concepts and clarity in interpreting guidance related to reliance. In addition to the definitions provided below, reference is made to the WHO Guideline on good regulatory practices: Guidelines for national regulatory authorities for medical products (2), which includes definitions for harmonization, convergence and other relevant terms.

Abridged regulatory pathways. Abridged regulatory pathways are regulatory procedures facilitated by the use of reliance, whereby the regulatory decision is solely or widely based on the application of reliance. Normally this would also involve some degree of work by the relying NRA (see “risk-based approach”, p. 13). The expectation is that the use of reliance in these pathways would save resources and shorten the timelines compared to the standard pathways, while ensuring that the standards for regulatory oversight are maintained.

Assessment. For the purpose of this document, the term “assessment” covers the outcome of any evaluation conducted for a regulatory function (e.g. evaluation for a clinical trial application, evaluation of an initial authorization for a medical product or any subsequent post-authorization changes, evaluation of safety data, evaluation as part of an inspection, etc.).
equivalence of regulatory systems. Equivalence (or comparability) of regulatory systems implies a high degree of similarity between two regulatory systems as 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 guidelines and standards, experience gained through the use of assessments for regulatory decision-making, joint activities and exchange of staff, among others. The expectation is that equivalent regulatory systems should lead to similar standards and levels of regulatory oversight or “level of control”.

joint activity. A joint activity is a process whereby a regulatory function 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 being evaluated. For example, a joint assessment is a procedure in which the same application is simultaneously submitted to two or more NRAs in order for the (assigned) NRAs to conduct their evaluations in parallel and share their respective scientific assessments with each other. The NRAs participating in the joint assessment can combine their list of questions or deficiencies to send to the manufacturer and base their respective independent regulatory decision on the outcome of these assessments. Similarly, a joint inspection is an inspection involving two or more NRAs sharing the activities and assessment performed during an inspection.

recognition. The acceptance of the regulatory decision of another regulator or other trusted institution. Recognition should be based on evidence of conformity that the regulatory requirements of the reference regulatory authority is 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, the reference regulatory authority is a national or regional authority being relied upon by another regulatory authority.

reliance. The act whereby the NRA in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others.
**work-sharing.** Work-sharing is a process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task. The opportunities for work-sharing include but are not limited to: jointly assessing applications for authorization of clinical trials, marketing authorizations or product manufacturing site inspections, joint work in the post-marketing surveillance of medical product quality and safety, joint development of technical guidelines or regulatory standards, and collaboration on information platforms and technology. Work-sharing also entails the 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.

### 6.2 Key concepts

The diagram below illustrates some of the key concepts explained in the document, notably how NRAs can gain efficiencies in their regulatory operations and how they avoid duplication by increasing the use of reliance approaches.
reliance versus recognition. Reliance may take many forms and reflect varying degrees of application in recognizing or taking account of the assessments, decisions or any other authoritative information available from other authorities and institutions. Recognition may be seen as a special and more complete form of reliance whereby one regulatory authority relies on the decisions of another regulatory authority, system or institution, obviating the need for additional regulatory assessment in reaching its own decision. Recognition usually requires formal and enabling legal provisions.

unilateral vs. mutual reliance/recognition. Reliance can be unilateral, for example, when a country chooses to rely on the assessment from another country unilaterally and without reciprocity. In other cases, reliance may be based on binding mutual agreements or treaties negotiated at the level of governments. These agreements may take considerable time and resources to set up as the regulatory systems involved need to be mutually assessed and shown to be equivalent before implementation. The demonstration of equivalence (or comparability) of regulatory systems is normally a prerequisite to mutual reliance and recognition.

life cycle approach. The concept of reliance for regulatory oversight of medical products can be applied across the full life cycle of medical products, from clinical trial authorization to marketing authorization, including post-authorization procedures, vigilance, inspections, testing and lot release. While reliance approaches are widely used for the initial authorization of medical products, it is equally important to consider the use of reliance for pharmacovigilance and post-authorization activities given the substantial regulatory resources required for evaluating safety and variations over the product life cycle. Reviewing post-authorization changes to a product approved by a different authority may present some challenges. Therefore, if an NRA has relied upon another NRA’s decision for its initial approval, there is a strong benefit for similar reliance measures for post-authorization changes and pharmacovigilance activities. This also avoids the situation of different changes being accepted in the originating and receiving countries over time.

Reliance has also been shown to offer significant advantages in avoiding duplication in the field of inspections and lot release between countries.

risk-based approach. Each NRA should define its own strategy regarding the appropriate risk-based approach to reliance that considers 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,
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and opportunities for reliance. Using marketing authorization as an example, one could envisage four models and levels of reliance involving an increasing degree of additional assessment by the relying NRA:

- Confirmation of sameness of the product to ensure that the medical product is the same as the one that had been assessed by the reference regulatory authority.
- Verification of 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, unmet medical needs, risk management plans and any quality-related specificities such as climatic zones for product stability.
- Abridged assessment of the quality, safety and efficacy/performance data taking into account information in the assessment reports of the reference regulatory authority.
- Joint assessment or work-sharing between two or more regulatory authorities. This could take various forms, including a primary review by one authority followed by a joint assessment session to finalize the assessment report and comments, or a distribution of the different modules (quality, non-clinical and safety/efficacy) between authorities.

Similar models can also be developed or used for other regulatory functions (e.g. inspection).

**Regional reliance mechanisms.** In some regions, an assessment for medical products can be conducted centrally based on a regional regulatory system for a group of countries. The decision is then implemented in all the countries that are part of the regional system, such as the authorization system in the EU, the Gulf Health Council (GHC) and the Caribbean Regulatory System (CRS).

### 7. Principles underpinning good reliance practices

In developing a strategy on the use of reliance in regulatory functions, an NRA should consider possible approaches in the context of the needs and characteristics of the national health and regulatory system. The decision to practise reliance should take into consideration the existing capacities, regulatory systems’ needs, the availability of an authority that the NRA can rely upon with confidence, and how reliance can complement these capacities to drive efficiencies and the optimal use of resources. Reliance is not a lesser form of regulatory oversight but rather a strategy seeking to make the best use of the available resources in any given setting. This would allow the allocation of resources to other areas of regulatory functions, such as vigilance and post-authorization activities, and increase the
effectiveness of the local regulatory oversight. In addition, reliance can lead to more evidence-based and better quality decisions.

The following principles are meant to complement and expand upon the basic principles of GRP and are based on the principles presented in the PAHO/ PANDRH concept note and recommendations on regulatory reliance principles (5).

a) 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. Indeed, reliance is relevant for all resource settings, representing an increasingly important mechanism for improving regulatory efficiency and effectiveness.

b) Sovereignty of decision-making

The decision to practise reliance, and how best to implement reliance, rests with the country. Reliance does not imply dependence. In applying reliance in their daily practice, NRAs maintain independence, sovereignty and accountability in regulatory decision-making.

c) Transparency

Transparency is a key enabler to adopting new, more efficient ways of conducting regulatory operations, both locally and internationally. NRAs should be transparent regarding the standards, processes and approaches adopted in implementing reliance measures. In addition, the basis and rationale for relying on a specific entity should be disclosed and fully understood by all parties.

Furthermore, it is incumbent upon NRAs to practise transparency in regulatory operations and decisions, not only as a fundamental principle of GRP and “open government”, but also towards building trust and maximizing opportunities for cooperation and reliance as part of a shared regulatory community responsibility. In other words, regulatory authorities are an increasingly important audience and beneficiaries of measures that promote transparency in regulation through the publishing and sharing of regulatory information.
d) Respect of national and regional legal basis

Reliance practices should be coherent with national and regional legal frameworks and medical products’ policy and supported by clear mandates and regulations that enable the efficient implementation of reliance as part of government policy on good regulation. The driving force behind the adoption of these legal frameworks should be the efficiencies and capacity to be gained by reliance, not the minimization of resources for regulatory functions. Where regulations giving explicit legal footing and visibility to reliance practice do not exist, reliance may still be adopted through the interpretation of existing regulations provided that the legal framework does not preclude the application of reliance approaches by the NRA. Implementing reliance can be done through policy changes as long as it is broadly consistent with the legislation. If prohibitions to apply reliance exist, they should be considered for revision.

e) Consistency

Reliance on a specific assessment or decision from another authority should be established for specific and well-defined categories of products and processes. The scope of regulatory activities where reliance may be practised should be clearly defined and the process for practising reliance should be transparent and predictable. Thus, it is expected that reliance shall be applied consistently for products/processes in the same predetermined categories.

f) Competency

The implementation of reliance approaches requires that NRAs have built the necessary competencies for critical decision-making. Setting up the reliance approach will normally require the involvement of senior regulatory staff and managers who are competent to make the best use of foreign information in the local context. NRAs should also maintain the appropriate scientific expertise of their staff needed for activities where they do not apply reliance, for example, such as in post-marketing surveillance activities.

Equally, authorities being relied upon should possess and maintain competencies and operate within a robust and transparent regulatory system, underpinned by international standards and practices as well
as a well-functioning quality system. Competencies may be benchmarked using transparent processes to develop trust and build confidence in the reference authorities.

### 8. Considerations

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

#### 8.1 General considerations

a) Reliance anchored in a national regulatory authority strategy

In addition to having a legal basis supporting, or at least not precluding reliance approaches (see above under “Principles underpinning good reliance practices”), the application of reliance should be anchored in the NRA’s strategy, endorsed by senior management and in the respective higher-level National Policy in order to provide a mandate, direction and expectations to NRA staff, guiding them in their day-to-day work. The strategy should be further detailed in procedures and integrated in processes to ensure that maximum benefits accrue. It should also include considerations on a sustainable funding model for the NRA when implementing reliance. The strategy should be published in order to make it accessible and understandable to external stakeholders. Additionally, the implementation of reliance should be supported by training and periodic reviews in order to ensure that standards are being maintained, to assess whether or not objectives are being met, and to make refinements where warranted.

NRAs that are practising reliance should establish and publish a list of reference regulatory authorities together with the criteria used for identifying them. In order to qualify reference regulatory authorities, an NRA may refer to an assessment performed by an independent organization (e.g. WHO Benchmarking, International Organization for Standardization (ISO) accreditation, etc.).
WHO encourages NRAs to monitor and evaluate the impact of regulatory reliance in their country and region and to share their experiences with other regulatory authorities. Where possible, specific measurement of the impact of reliance is encouraged, for example, in terms of cost savings, efficiencies in the number of products reaching markets, a redirection of scarce resources to areas of higher regulatory risks, and so on.

b) Cultural change

The implementation of reliance approaches means moving to a more innovative, effective way of working, based on trust and relying on other NRA outputs. It is essential that the benefits of the strategy be understood and supported at the operational level and that staff expected to implement reliance approaches have input into their development.

This will require effective preparation, messaging and support from management and peers that articulates the importance of reliance in better addressing workload pressures without minimizing the rigor of regulatory work or causing the loss of scientific and regulatory competence and capacity. In fact, the use of assessments and information from other trusted regulatory authorities can help build capacity and competence (e.g. through networking, twinning, staff visits/staff exchanges, etc.). Furthermore, the effective use of such information within the local context requires skills, ability and experience. Thus, the skill set needed to practice reliance will need to be developed in the NRA’s workforce.

It also requires that upper management, reviewers, inspectors and other staff build confidence and trust in work that has been done by other NRAs or trusted authorities. Building trust in other NRAs’ work requires time and a change in the culture within the relying NRA. Some regulatory authorities and systems already practise reliance and that experience should be leveraged to promote acceptance and avoid pitfalls.

Trust should also be built with the public and healthcare professionals in order to inform and assure them that the use of reliance offers a more efficient and effective regulatory oversight.
c) Flexibility in approach: “one size doesn’t fit all”

Following the principles listed above, reliance strategies should be tailored to the needs of the national health and regulatory systems. NRAs may choose to rely on others as part of their routine regulatory oversight and/or during special circumstances such as public health emergencies. Reliance is a tool offering flexibility to NRAs. Whatever the approach, the NRA needs to consider its own capacities and to establish clear goals when adopting reliance.

d) Implementing reliance needs investment

As stated above, reliance should increase the efficiency and effectiveness of a regulatory system in a country and/or region. Nevertheless, it is important to recognize that the implementation of reliance approaches will first require time and investment. This may include but may not be limited to: legislative changes and the development of guidance documents, the development of approaches and elaboration of procedures and processes, confidence-building through parallel or joint reviews and supported by staff exchanges, the training of staff, dialogue with industry and other stakeholders, as well as the establishment of, or access to, information-sharing platforms. To the best extent possible, the use of publicly available information should also be pursued.

e) “Sameness” of the product in different jurisdictions

One of the most critical aspects when applying reliance is the verification of the “sameness” of the medical product in different jurisdictions. Reliance can only be applied if the NRAs have the assurance that the medical product assessed by the reference regulatory authority is the same as the one submitted to the NRA, intending to use a foreign assessment as the basis for its own assessment and regulatory decision-making. The role of the manufacturer is essential here in order to confirm the sameness of a product and to provide the same documentation to different NRAs. As part of the process, the manufacturer should confirm in the application that the product is the same and that the dossier contains the same information as much as possible, taking into consideration any potential national requirements.

When addressing the sameness of the medical product, all relevant aspects have to be considered in order to confirm that the product is the same (e.g. same qualitative and quantitative composition, same
strength, same pharmaceutical form, same manufacturing process and site of production, etc.).

Additionally, supporting safety, efficacy and quality studies, indications and conditions of use, and so on, should be the same. The impact of potential justified differences should be assessed by the manufacturer and the relying NRA in determining the merit of using foreign regulatory reports or decisions.

f) The role of industry

Industry plays a crucial role in the successful application of reliance mechanisms by NRAs. While industry is widely supportive of reliance as a concept and practice that can bring about efficiency gains, industry must also have clear guidance on its application and see meaningful benefits.

Industry’s support and stringent adherence to the factors that give validity to the reliance process is vital for filing applications in multiple countries or regions, ensuring the sameness of products submitted to reference regulatory authorities and relying NRAs, and sharing unredacted and complete information.

g) Reliance in case of a public health emergency

In case of a public health emergency, reliance approaches represent an even more essential tool and should be applied to accelerate access to medical products needed in the context of the emergency.

8.2 Barriers

a) Lack of political will

The lack of political will and support at government level can make it difficult for NRAs to implement reliance in their daily practice, even if a legal basis is established supporting (or not precluding) reliance and NRAs’ support reliance as a strategy and approach.
b) Lack of accessible information and confidentiality of information

The lack of access to assessments of reference regulatory authorities can pose a major barrier to implementing effective reliance strategies. Reference regulatory authorities should strive to make assessments and other regulatory information publicly available whenever possible.

Sensitive, non-public information included in unredacted assessment or inspection reports can also be shared between regulatory authorities upon request. This may include confidential, commercial, trade secret or personal information. In some circumstances, the sharing of such information may require the prior consent of the manufacturer. Given the sensitivity of such information, NRAs may require that confidentiality agreements be signed which govern the exchange, management and disclosure of such information. Such information should always be exchanged using secure channels or information-sharing platforms.

Non-public regulatory reports might also be obtained directly from the manufacturer when the company is able to access these reports from the reference regulatory authority. In that case, manufacturers are encouraged to submit complete and unredacted reports to NRAs.

c) Other considerations

Additional barriers can include language, differences in country-specific regulatory requirements and evidentiary standards, the level of detail in regulatory reports 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 the appropriate reliance strategies, as will be further elucidated in the companion documents to follow.

8.3 Enablers

a) Trust

Trust is a critical element since the reliance requires confidence that the regulatory outcome is based on strong regulatory processes and standards and is, thus, trustworthy. Consequently, initiatives that
foster trust among regulatory authorities are essential to promoting reliance. Trust comes from increasing familiarity and understanding in what stands behind regulatory outputs. By sharing information, including the standards applied to regulatory decisions, working together and learning each other’s ways of working, confidence can be built which thereafter leads to the effective use of reliance in regulatory work. Trust can be built in phases, starting with reliance using the exchange of reports and moving to work-sharing or joint assessments. Regulatory authorities may also consider using applications of lower risk to initiate reliance processes.

b) Convergence and harmonization

Convergence and the harmonization of requirements and standards are important enablers of regulatory cooperation and reliance. The more requirements and standards are alike, the more opportunity for collaboration and reliance exists.

The 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 upon 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 preferably rely on assessments or decisions from reference regulatory authorities that apply international standards and guidelines (e.g. guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), WHO guidelines).

c) Information-sharing and dialogue between regulators

Information-sharing is an essential part of reliance and NRAs are encouraged to share information and good practices with other NRAs as much as possible. The increasing dialogue between regulators is seen in the growing number of international initiatives such as the IPRP or the International Conference of Drug Regulatory Authorities (ICDRA), as well as regulatory information- and work-sharing networks such as PANDRH, the South-East Asia Regulatory Network (SEARN), regulatory networks in the Regional Economic Communities (RECs) under the African Medicines Regulatory Harmonisation (AMRH) Initiative or the Association of Southeast Asian Nations (ASEAN) Pharmaceutical Products Working Group (PPWG), and so on, which are great facilitators for reliance.
d) Economic or legal integration

In situations where there is economic or legal integration in a region or for a group of countries, reliance is facilitated and strengthened by the existing mutual provisions, such as the EU, the Eurasian Economic Union, RECs in Africa, ASEAN, the Asia-Pacific Economic Cooperation (APEC) or the Southern Common Market (MERCOSUR).

e) Engagement of stakeholders

All relevant stakeholders, including industry, healthcare professionals, policy makers and the public, should be engaged and/or informed in order to increase the understanding and acceptance of reliance approaches as they present some clear benefits for all parties involved. Communications and engagement with stakeholders should be tailored to the target audience.

9. Conclusions

Reliance is seen by a growing number of regulatory authorities as an important means of improving the efficiency and effectiveness of regulatory operations in the oversight of medical products. It allows NRAs to make the best use of resources, build capacity, increase the quality of regulatory decisions, reduce duplication of effort and, ultimately, promote access to safe, efficacious and quality-assured medical products. By adopting reliance measures whenever possible within a well-structured framework, underpinned by national or regional policies and strategies, regulators may focus their resources on key activities that cannot be undertaken by others and that contribute to public health.

Reliance represents a “smarter” form of regulation based on constructive regional and international collaboration, one that will also facilitate and promote convergence and the use of common international standards.

Reliance does not represent a less stringent form of regulation nor an outsourcing of regulatory mandates or a compromise to independence. On the contrary, the decision to “regulate through reliance” is the hallmark of a modern and efficient regulatory authority.
The inclusion of reliance-related provisions as part of their flexible regulatory pathways is encouraged and should be considered for all regulatory functions over the medical product life cycle, as appropriate.

The principles and considerations presented in this document should be taken into consideration when implementing regulatory reliance frameworks or strategies. While reliance may be viewed as a particularly useful strategy for regulatory authorities with very limited resources and capacity, it is equally relevant for well-resourced NRAs. It is an approach to be used by all NRAs and, as such, should become an integral part of regulatory operations and regulatory lexicon.
Annex 1: Examples

Regulatory reliance can take many forms and encompasses a broad array of regulatory approaches and practices that can involve two or more regulatory authorities. In addition, it can be limited to a discrete regulatory process or function or include the full scope of regulatory functions over the entire life cycle of a medical product.

There are many examples around the world that illustrate the current use of reliance and the diverse models in which national regulatory authorities (NRAs) leverage the work done by others.

Examples are given below to illustrate the different points addressed in this document and to show the use of reliance in the different regulatory functions. The list below is not exhaustive but just an illustration of the current practices of reliance taking place globally. It may be replaced in future by a comprehensive repository of reliance approaches to be established as a part of the Good Reliance Practices (GRelP) toolbox.

a) Clinical trials

Work-sharing for clinical trial assessment is happening in some regions, such as the Voluntary Harmonisation Procedure in the European Union (8) and via the African Vaccine Regulatory Forum (AVAREF) (9). By assessing clinical trial applications together, NRAs, and in some cases ethic committees from different countries, can benefit from the assessments performed by the different participating countries with a view to facilitating and ensuring the robustness of the approval process across countries. The AVAREF platform has been instrumental in building the 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 normal circumstances. Towards this end, a guideline and platform for joint assessment of clinical trials applications, as well as Good Clinical Practices (GCP) site inspections, have been developed and implemented in order to facilitate product development, regulatory decision-making and access to promising new medical products.
b) Marketing authorization

Abridged regulatory pathways using reliance for initial marketing authorization

Several pathways are available through stringent regulatory authorities (SRAs) or the World Health Organization (WHO) in order to enable the use of an abridged reliance pathway. The EU Article 58, also referred to as European Union Medicines for all (EU-M4 all) (10), the Swissmedic Marketing Authorisation for Global Health Products (MAGHP) (11) procedures and the WHO Collaborative Registration Procedure (CRP) (12) are three examples of abridged regulatory pathways using reliance to facilitate the registration of medicinal products in target countries.

In addition to facilitating in-country registration, the EU Article 58 and the Swissmedic MAGHP procedures provide experts from target NRAs the opportunity to both observe and participate actively in the assessment procedures, with the aim of building their own capacities and to establish confidence in the processes.

The CRP facilitates the assessment and accelerates the national registration of WHO prequalified medical products and medicines approved by an SRA. The CRP operates by providing unredacted assessment, inspection and performance evaluation (in the case of in vitro diagnostics) reports 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 receiving NRAs can make the most efficient use of the reports in reaching their own decisions. Participating NRAs are expected to reach a decision on authorization within 90 calendar days (regulatory time). The CRP tool has shown to be successful in both accelerating decisions in countries and building the capacity of regulatory authorities.

Quality information

Many NRAs, as well as the WHO Prequalification Programme (WHO PQ), recognize Certificates of Suitability to the monographs of the European Pharmacopoeia (CEP) (13) for active pharmaceutical ingredients (API) as a validation of the quality of a certain API. Some countries also recognize the Confirmation of API Prequalification (CPQ) issued by the WHO PQ for APIs (14). These two examples not only provide assured mechanisms of reliance, but also reduce the documentation requirements for
countries that recognize these certificates. Where a CEP or CPQ is issued, the receiving NRA does not have to duplicate the API assessment but can focus on specific sections not covered under CEP or CPQ.

Work-sharing

The Australia-Canada-Singapore-Switzerland Consortium (ACSS Consortium) (15) is a coalition which was formed in 2007 by “like-minded” medium-sized regulatory authorities in order to promote work-sharing based on greater regulatory collaboration and the alignment of regulatory requirements. The ACSS Consortium explores opportunities for information- and work-sharing initiatives in areas including biosimilar products, complementary medicines, generic medicines, new prescription medicines, medical devices and information technology. The Consortium capitalizes on each country’s area of strength, addresses gaps in science, knowledge and expertise and leverages resources to help expedite risk assessment processes, all the while maintaining or raising quality and safety standards. The Consortium builds on existing international networks, initiatives and mechanisms in order to advance work- and information-sharing along health product life cycles.

Joint assessments

Joint assessments can provide significant benefits to NRAs by sharing the workload, building capacity by bringing broader experience and expertise to bear, and helping to build trust in one another’s assessments and decision-making processes. Similarly, industry can benefit from a common review process and set of questions in terms of both resource and time-savings as compared to interacting separately with multiple countries. In recognition of these benefits, a growing number of joint assessment initiatives have been established within the framework of regional regulatory networks, sometimes driven by the higher-level priorities of economic blocks seeking to create common markets. Examples of joint assessments initiatives include, for example, those in the Regional Economic Communities in Africa (East African Community (EAC) (16), ZAZIBONA (17) in the Southern African Development Community (SADC), the Economic Community of West African States (ECOWAS)/West African Health Organization (WAHO) (18), as well as the Association of Southeast Asian Nations (ASEAN) Joint Assessment Coordinating Group (19), and so on.
Unilateral recognition

The Mexican Federal Commission for the Protection against Sanitary Risk (COFEPRIS) has implemented a unilateral recognition of marketing authorizations from reference regulatory authorities (20). This Agreement recognizes the requirements and procedures authorized by the reference health authorities as being equivalent for the purposes of evaluation of the marketing authorization applications for allopathic medicinal products, biological medicinal products, vaccines and blood products in Mexico.

Mutual recognition

The EU system is an example of highly integrated regulatory cooperation and its multiple regulatory pathways depend heavily on work-sharing, recognition and other forms of reliance. The various routes to the approval of medicines in the EU system are based on a single assessment system so that any assessment report from any of the agencies in the EU network can be used as a basis for reliance by other regulators. In this specific case, a strong and common legal framework and harmonized regulatory standards shared among all EU countries enabled and facilitated reliance.

c) Post-authorization procedures

When an NRA has relied upon another NRA for their initial approval, similar reliance measures should be considered for post-authorization changes such as variations. In the case of CRP, for example, the participating NRAs for prequalified products are informed by WHO of any variations approved by WHO Prequalification Team.

d) Testing and lot release

Network of Official Medicines Control Laboratories

The Network of Official Medicines Control Laboratories (OMCLs) support regulatory authorities in controlling the quality of medicinal products available on the market. Collaboration within the Council of Europe’s General European OMCL Network (GEON) (21) makes the best use of resources via resource pooling and avoids duplication of work or testing. Some of the main goals of the Network are to set
mutual recognition, within the members of the networks, of tests carried out by OMCLs at the national level, coordinate activities among the OMCLs, and facilitate knowledge and work-sharing.

Lot release and quality monitoring of vaccines and other biotherapeutic products

Launched in 2017, the WHO-National Control Laboratory Network for Biologicals (WHO-NNB) (22) brings together National Control Laboratories (NCLs) and NRAs of vaccine-producing and vaccine-recipient countries, WHO contract laboratories, manufacturer associations, WHO Regional Offices and other stakeholders, including donors. The Network works towards the effective use of globally available resources in providing a platform and infrastructure for the exchange of quality and technical information. The main objective of the Network is to facilitate the access to and availability of prequalified vaccines (or other biotherapeutic products) through reliance on the batch release of the respective Network member NRAs/NCLs by recipient countries, thereby reducing redundant testing and contributing to more cost-effective testing and more effective regulatory oversight.

e) Pharmacovigilance

In the field of pharmacovigilance, the exchange and sharing of data is critical. More than 100 Member States contribute by sharing their safety data to the WHO Global database of individual case safety reports (ICSR) - VigiBase - developed and maintained by the Uppsala Monitoring Center (UMC) (23). Member States rely upon this resource (and thereby, on each-others’ data) as a single point of pharmacovigilance information, to confirm and validate signals of adverse events with medicines and vaccines that they may have observed within their own jurisdictions.

f) Inspections

In the field of inspections, governments and NRAs in different regions and parts of the world have worked on mutual recognition agreements in order to rely on each other’s inspection outcomes, avoiding the duplication of inspections and making the best use of resources (e.g. EU Mutual Recognition Agreements (24) with Australia, Canada, Japan, Switzerland and the United States of America (USA); ASEAN Mutual Recognition Agreement (25), etc.).
The Pharmaceutical Inspection Co-operation Scheme (PIC/S) (26) is a non-binding, informal co-operative arrangement between regulatory authorities in the field of Good Manufacturing Practice (GMP) of medicinal products for human or veterinary use. It aims at facilitating cooperation and networking between competent authorities, regional and international organisations, thus increasing mutual confidence regarding GMP inspections.

Reliance is also an important aspect for conducting desktop assessment of compliance with relevant good practice guidelines and requirements, as described in the respective WHO guidance (27).

Examples in the field of medical devices

The use of reliance is equally prevalent in the regulation of medical devices. An example of this is the Medical Device Single Audit Program (MDSAP) (28) originally developed through 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 in order to develop and implement a robust system of oversight of third party auditing organizations that, in turn, conduct audits of the quality management systems of medical device manufacturers. The MDSAP allows an auditing organization recognized by the Program to conduct a single regulatory audit that satisfies the relevant requirements of the regulatory authorities participating in the program. Collective regulatory resources are directed at establishing and maintaining the oversight of auditing organizations, providing a more effective use of limited regulatory resources. Employing a single audit program allows regulatory authorities to efficiently leverage resources and streamline the regulatory process without compromising public health and to promote more aligned and consistent regulatory requirements.

Vigilance

The IMDRF has also set guidance for the exchange of information between national competent authorities with respect to medical device safety (29). The system focuses on incidents that represent a serious public health threat that goes beyond borders in order to inform other NRAs of such.
References


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