



DRAFT WORKING DOCUMENT FOR COMMENTS:

Good reliance practices in regulatory decision-making for medical products: high-level principles and considerations

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Good reliance practices in regulatory decision-making for medical
products: high-level principles and considerations

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84 1. Acronyms

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ACSS	Australia-Canada-Singapore-Switzerland Consortium
AMRH	African Medicines Regulatory Harmonisation
APEC	Asia-Pacific Economic Cooperation
API	Active Pharmaceutical Ingredient
ASEAN	Association of Southeast Asian Nations
ASEAN PPWG	ASEAN Pharmaceutical Products Working Group
AVAREF	African Vaccine Regulatory Forum
CARICOM	Caribbean Community and Common Market
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CPP	Certificate of Pharmaceutical Product
CPQ	Confirmation of active pharmaceutical ingredient Prequalification
CRP	Collaborative Registration Procedure
CRS	Caribbean Regulatory System
CTD	Common Technical Document
EAC	East African Community
ECOWAS	Economic Community of West African States
ECSP	Expert Committee on Specifications for Pharmaceutical Preparations
eCTD	Electronic Common Technical Document
EMA	European Medicines Agency
EU	European Union
EU-M4 all	European Union Medicines for all
GBT	Global Benchmarking Tool
GCC	Gulf Cooperation Council
GCP	Good Clinical Practices
GDP	Good Distribution Practices
GEON	General European OMCL Network
GHC	Gulf Health Council
GMP	Good Manufacturing Practices
GRP	Good Regulatory Practices
GRIP	Good Reliance Practices

GVP	Good Vigilance Practices
HC	Health Canada
HSA	Health Sciences Authority
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICDRA	International Conference of Drug Regulatory Authorities
ICMRA	International Coalition of Medicines Regulatory Authorities
ICSR	Individual Case Safety Report
IMDRF	International Medical Device Regulators Forum
IPRP	International Pharmaceutical Regulators Programme
ISO	International Organization for Standardization
IVD	In vitro diagnostic
MAGHP	Marketing Authorization for Global Health Products
MERCOSUR	Southern Common Market
MDSAP	Medical Device Single Audit Program
MRA	Mutual Recognition Agreement
NCL	National Control Laboratory
NRA	National Regulatory Authority; for the purpose of this document, this term also includes regional regulatory authorities such as the European Medicines Agency (EMA)
OECD	The Organisation for Economic Co-operation and Development
OMCL	Official Medicines Control Laboratories
PA	Pacific Alliance
PAHO	Pan American Health Organization
PANDRH	Pan American Network for Drug Regulatory Harmonization
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PMDA	Pharmaceuticals and Medical Devices Agency, Japan
REC	Regional Economic Communities in Africa
SEARN	South-East Asia Regulatory Network
SADC	Southern African Development Community
SRA	Stringent Regulatory Authority
TGA	Therapeutic Goods Administration, Australia

UHC	Universal Health Coverage
UMC	Uppsala Monitoring Centre
U.S. FDA	US Food and Drug Administration
WAHO	West African Health Organization
WHO	World Health Organization
WHO PQ	WHO Prequalification
WLA	WHO Listed Authorities
WHO-NNB	WHO-National Control Laboratory Network for Biologicals
ZAZIBONA	Zambia, Zimbabwe, Botswana and Namibia; initial participants of the SADC collaborative procedure for the joint assessment of medicines

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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, but not limited to, in-country vigilance and market surveillance and control activities and oversight of local manufacturing and distribution. Reliance approaches facilitate timely access to safe, effective and quality-assured medical products (*see 5. Scope*) and can help in regulatory preparedness and response, particularly during public health emergencies.

Good Reliance Practices (GRoIP) are anchored in the overarching Good Regulatory Practices (GRP) (1) which provide a means for establishing sound, affordable and effective regulatory oversight 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. National regulatory authorities (NRAs) are encouraged to adopt these best practices in order to ensure that they are using the most efficient regulatory processes possible.

An ongoing initiative at WHO aims at establishing and implementing a framework for evaluating regulatory authorities and designating them as WHO-Listed Authorities (WLAs) (2). Based on benchmarking using the WHO Global Benchmarking Tool (GBT) (3), along with a performance evaluation process, WHO will assess the regulatory authority's performance and maturity level in order to qualify a regulatory authority as a WLA and thereby provide a globally recognized, evidence-based and transparent system that can be used by NRAs as a reference for the selection of reference regulatory authority(ies) to practice reliance. A list of reference regulatory authorities is available on the WHO Website for NRAs to refer to (4).

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 GRoIP. The meeting concluded that the Pan American Health Organization (PAHO)/Pan American Network for Drug Regulatory Harmonization (PANDRH)'s concept note and recommendations on regulatory reliance principles (5) should be used as a starting point for the development of a WHO GRoIP 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 and safe 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.

Establishing and sustaining mature regulatory systems is an enterprise that requires adequate resources including skilled and capable 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 and more efficient 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 patients and consumers, the industry, national governments, as well as the donor community, and international development partners by facilitating and accelerating access to quality-assured, effective and safe 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) (7) 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) (8). The results showed that regulatory reliance is a broadly accepted and widely practised 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 regulatory oversight 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, practical and effective approach to reliance.

4. Purpose

The objective of this document is to promote a more efficient approach to regulatory oversight, thereby promoting access to quality-assured, effective and safe medical products.

The document aims at presenting the overarching principles of regulatory reliance in the field of oversight of medical products and the use of reliance as a tool for enhancing efficiency of regulatory oversight.

This document is intended to provide high-level guidance, definitions, key concepts and considerations in order 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.

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 and other health products), addressing all regulatory functions as defined in the GBT spanning the full life cycle of a medical product - namely registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspection, laboratory testing, clinical trials oversight, and NRA lot release (3).

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.

The concept of reliance can cover all types of medical products and regulatory activities. Special consideration could be given to using reliance approaches for medical products addressing priority diseases with unmet medical needs, medical products to be used in public health emergencies or during shortages as well as for orphan medical products.

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 good regulatory practices document (1), 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 6.2.4 Risk-based approach*). 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 of regulatory systems implies a high degree of 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 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 “levels of 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 (ISO) or pharmacopoeial standards) and guidelines (e.g. International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) or PIC/S guidelines).

mutual recognition agreement. According to a definition issued by the Organisation for Economic Co-operation and Development (OECD), mutual recognition agreements are “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” (9).

recognition. The acceptance of the regulatory decision of another regulator or 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 or a trusted institution such as WHO prequalification (WHO PQ) being relied upon by another regulatory authority.

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 including or excluding a common legal framework. The common framework must at least ensure equivalence between the members in terms of regulatory requirements, practices and quality assurance policies. The system or regional body, where it exists, may have enforcement powers to ensure compliance with the common regulatory framework.

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.

sameness of product. For the purpose of this document, the 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). All relevant aspects applicable to drugs, medical devices and in vitro diagnostics have to be considered in order 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 active pharmaceutical ingredient suppliers, 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 (for the purpose of this document, manufacturer also means marketing authorization holder) and the relying NRA in determining the merit 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) (10).

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 good practices 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.

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 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 (e.g. the different modules for quality, nonclinical and clinical data can be assigned to different NRAs for review). 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.

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 using reliance approaches.

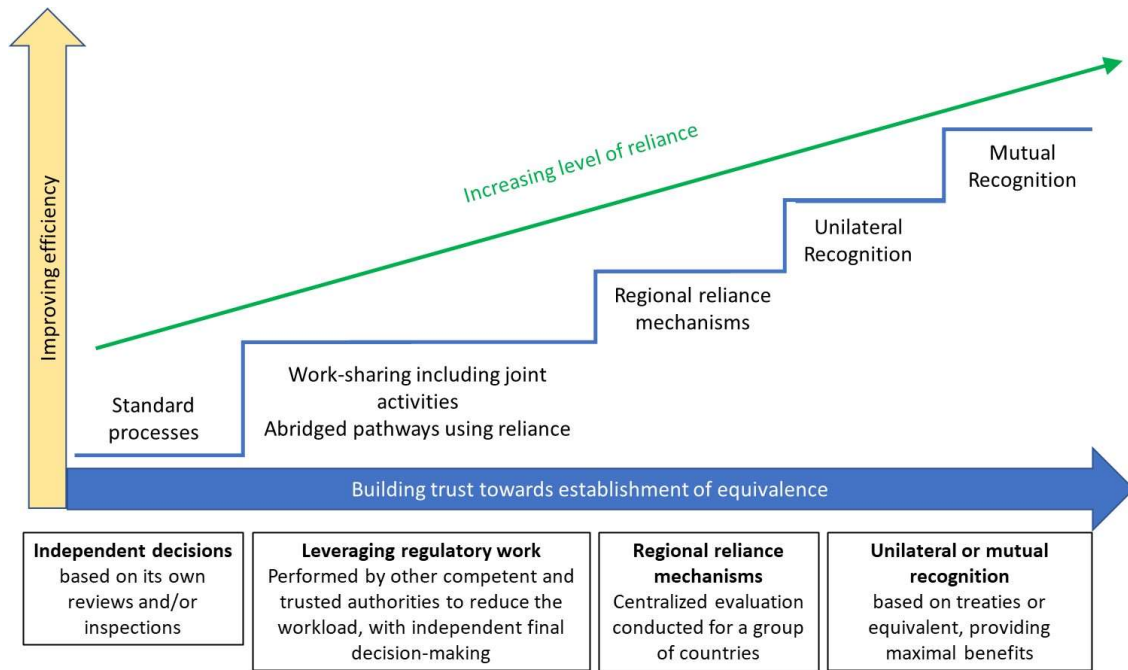
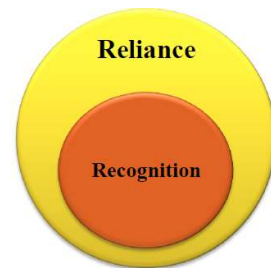


Figure 1: Key concepts of reliance

6.2.1 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 formalized approach to reliance whereby one regulatory authority recognizes 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 binding legal provisions.

Figure 2: Recognition versus Reliance

6.2.2 Unilateral vs. mutual reliance/recognition

Reliance and recognition can be unilateral, for example, when a country chooses to rely on or formally recognize the assessment from another country unilaterally and without reciprocity. In other cases, mutual reliance or recognition 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 of regulatory systems is normally a prerequisite to mutual reliance or recognition.

6.2.3 Life cycle approach

The concept of reliance for regulatory oversight of medical products should be applied across the full life cycle of medical products and all regulatory functions (*see 5. Scope*). While reliance approaches are widely used for the initial authorization of medical products, it is equally important to consider the use of reliance for vigilance and other post-authorization activities given the substantial regulatory resources required for evaluating safety and post-approval changes over the product life cycle. Reviewing post-approval changes to a product approved by a different authority may present some challenges. Therefore, if an NRA has relied upon another NRA's assessment for its initial approval, there is a strong benefit for similar reliance measures for post-approval changes and vigilance activities. This also avoids the situation of different changes being accepted in the originating and receiving countries over time.

6.2.4 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, and opportunities for reliance. Using marketing authorization as an example, one could envisage four different approaches and levels of reliance involving an increasing degree of additional assessment by the relying NRA:

- i. Verification of sameness of the product to ensure that the medical product is the same as the one that has been assessed by the reference regulatory authority (*see 8.1e Sameness of the product in different jurisdictions*).

- ii. Confirmation 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, 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, concomitantly used medicines 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 justification should be provided by the Applicant.
- iii. Abridged assessment of the quality, safety and efficacy/performance data taking into account information in the assessment reports of the reference regulatory authority.
- iv. 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.

Regardless of the approach, the expectation is that reduced timelines compared to standard timelines are applied when using reliance.

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

6.2.5 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. In some regional reliance mechanisms, the regional decision is binding on the member states (e.g., EU processes). In others, the regional decisions are recommendations that member states take into consideration when making their national regulatory decisions (e.g. Southern African Development Community (SADC) collaborative procedure (ZAZIBONA, which stands for Zambia, Zimbabwe, Botswana and Namibia), 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 and activities, an NRA should consider possible approaches in the context of the needs and characteristics of the national health and regulatory system. The decision to practice 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 their own 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 in-country 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).

7.1 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, either to increase or build capacity when they have the requisite expertise in house, but just not enough of it to perform their regulatory work as efficiently as they would like. Other NRAs use reliance to increase expertise to which they otherwise would not have local access to. Indeed, reliance is relevant for all resource settings, representing an increasingly important mechanism for improving regulatory efficiency.

7.2 Sovereignty of decision-making

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

7.3 Transparency

Transparency is a key enabler to adopting new, more efficient ways of conducting regulatory operations, both locally and internationally. NRAs should be transparent 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. NRAs should engage with all stakeholders including industry to ensure the appropriateness and awareness of the reliance processes. Furthermore, NRAs should conduct transparent regulatory operations and decision-making, not only as a fundamental principle of GRP, 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 regulatory oversight through the publishing and sharing of regulatory information. NRAs seeking to act as reference agencies are encouraged to issue public assessment reports in a common language documenting their regulatory decisions. Relying NRAs should use these reports where available as the primary source to inform assessment. If no public assessment reports are available or when additional information of a confidential nature is required, the manufacturer should provide such assessment report. If the relying NRA insists to obtain the non-public assessment reports from the reference agency, those reports may be provided by the reference agency with the consent of the manufacturer, if needed.

7.4 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 including explicit provisions regarding the application of reliance do not exist, reliance may still be adopted through the interpretation of existing regulations provided that the legal framework does not explicitly 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 within a reasonable timeframe.

7.5 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, the expectation is that reliance shall be applied consistently for products/processes in the same predetermined categories.

7.6 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, managers and experts 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 local adverse event monitoring, market surveillance and control, national labelling and product information activities and for approval of locally manufactured products.

Equally, authorities being relied upon should possess and maintain competencies and operate within a robust and transparent regulatory system, underpinned by international standards and guidelines as well as good regulatory practices and a well-functioning quality management system (11). 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.

Reliance is encouraged in any settings, for example, when supported by 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.

As a principle, reliance should be based on the original assessment and not on a decision that was itself based on reliance from another assessment (i.e. no reliance on a fully relied upon outcome).

8.1 General considerations

8.1.1 Reliance anchored in a national regulatory authority strategy

In addition to having a legal basis supporting, or at least not precluding reliance approaches (*see 7. 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 high-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 to ensure that standards are being maintained, to assess whether or not objectives are being met, and to make refinements where warranted.

Implementing reliance should not negatively impact the financial sustainability of the NRA.

NRAs that are practising reliance should establish and publish a list of reference regulatory authorities together with the criteria used for identifying them. The NRA should decide and establish the criteria they want to apply for the selection of the reference regulatory authorities (e.g. application of international standards, longstanding recognition in the international community, proximity and commonality of medical products, etc.). In order to qualify reference regulatory authorities or a specific oversight of a regulatory function, an NRA may refer to an assessment performed by an independent organization (e.g. WHO Benchmarking and WLA, ISO accreditation, the Medical Device Single Audit Program (MDSAP), PIC/S, 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 strongly encouraged and the respective NRA should prospectively establish the metrics they will employ to measure the impact of using reliance in their regulatory decision-making and the timing when such an impact assessment will be undertaken. These metrics may include, for example, cost savings, efficiencies in the number of products reaching markets or time to market, a redirection of scarce resources to areas of higher regulatory risks, and so on.

8.1.2 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 engagement, willingness, 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 exposure to the reviews and decisions of the reference authority, 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 and competency framework needed to practise reliance will need to be developed in the NRA's workforce.

Senior management, reviewers, inspectors and other staff should 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 regulatory oversight.

8.1.3 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 and efficient processes and ensure the standards and criteria are transparent and well established when adopting reliance.

8.1.4 Implementing reliance needs investment of resources and time

As stated above, reliance should increase the efficiency of a regulatory system in a country and/or region. Nevertheless, the implementation of reliance approaches will first require time and investment of resources. 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.

8.1.5 “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 (*see 6.1 Definitions*) 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 essentially 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 to the exception of the additional country specific information submitted for review such as product stability data according to the stability zone. 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.

If the dossier is not submitted simultaneously to the agencies, the manufacturer should highlight any new information acquired about the product since the dossier was submitted to the reference agency with the corresponding assessment.

8.1.6 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.

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 between all stakeholders participating in regulatory reliance activities will help to create and build trust, which is the foundation of regulatory reliance.

8.1.7 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 given more importance to accelerate access to medical products needed in the context of the emergency.

8.2 Barriers

8.2.1 Lack of political will

The lack of political will and support at government level can make it difficult for NRAs to implement or facilitate 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.

8.2.2 Lack of accessible information and confidentiality of information

The lack of access to complete 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.

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. If this is not possible, the relying NRA should approach the reference regulatory authority for the non-public regulatory reports. In these cases, having arrangements between NRAs regarding the exchange of confidential information would facilitate the implementation of the reliance process.

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. The sharing of personal information may also require prior consent from the individual in order to comply with data protection regulations.

Given the sensitivity of such non-public information, NRAs may require that confidentiality agreements be signed which govern the exchange, management and disclosure of such information in order to ensure that the confidential nature of the information is protected by relying NRA. Such information should always be exchanged using secure channels or information-sharing platforms.

8.2.3 Other considerations

Additional barriers can include issues around language such as lack of common language or translation difficulties/cost, differences in country-specific regulatory requirements and evidentiary standards, the lack of regulatory alignment of product risk-classifications and inconsistent practices regarding product modifications in the area of 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 competencies 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

8.3.1 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 is developed through 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 throughout the entire organization, which thereafter leads to the effective use of reliance in regulatory work. Trust can be built in phases, starting with the exchange of assessment reports, and moving to work-sharing or joint assessments in a stepwise approach. Regulatory authorities may also consider using applications of lower risk (*see 6.2.4 Risk-based approach*) to initiate reliance processes.

8.3.2 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 implementation of the ICH Common Technical Document (CTD) and the electronic CTD (eCTD) as a common format for regulatory submissions around the globe is just one example how harmonization can facilitate and enable reliance.

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.

8.3.3 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), International Coalition of Medicines Regulatory Authorities (ICMRA) and so on, which are great facilitators for reliance.

Scientific and technical events, such as ICH and ICDRA conferences, are also platforms that promote the dissemination of regulatory information and support building knowledge and trust among NRAs.

As already mentioned, the sharing of confidential information should always occur through secure channels or via secure platforms. Investment in the respective IT infrastructure is therefore important to enable reliance.

8.3.4 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 Asia-Pacific Economic Cooperation (APEC), ASEAN, the Caribbean Community and Common Market (CARICOM), the EU, the Eurasian Economic Union, Gulf Cooperation Council (GCC), Pacific Alliance (PA), the RECs in Africa, or the Southern Common Market (MERCOSUR).

8.3.5 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 of regulatory operations in the oversight of medical products. It allows NRAs to make the best

use of resources, build expertise and capacity, increase the quality of regulatory decisions, reduce duplication of effort and, ultimately, promote timely 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 regulatory oversight based on constructive regional and international collaboration, one that will also facilitate and promote convergence and the use of common international guidelines and standards, as well as ensure access to medical products to patients worldwide with more predictable and faster approvals.

Reliance does not represent a less stringent form of regulatory oversight 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 by NRAs 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 account when implementing regulatory reliance frameworks or strategies. Effective implementation of reliance will benefit not only NRAs but also patients, healthcare providers and industry.

While reliance may be viewed as a particularly useful strategy for low-resourced regulatory authorities, it is equally relevant for well-resourced NRAs. Reliance is an approach to be used by all NRAs and, as such, should become an integral part of regulatory operations.

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 (GRoLP) 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 (12) and via the African Vaccine Regulatory Forum (AVAREF) (13). By assessing clinical trial applications together, NRAs and, in some cases, ethics 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 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 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 (14).

b) Marketing authorization

Abridged regulatory pathways using reliance for initial marketing authorization

Several procedures are available through stringent regulatory authorities (SRAs) (e.g. EMA, Health Canada (HC), the Pharmaceuticals and Medical Devices Agency (PMDA), Swissmedic, U.S. FDA) or the World Health Organization Prequalification (WHO PQ) Programme in order to enable the use of an abridged regulatory pathway by the relying NRAs.

Among those procedures, the EU Article 58, also referred to as European Union Medicines for all (EU-M4 all) (15), the Swissmedic Marketing Authorisation for Global Health Products (MAGHP) (16) procedures and the WHO Collaborative Registration Procedure (CRP) (1) 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 and scientific advice 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.

The WHO Certificate of a pharmaceutical product (CPP) is also being used as a reliance tool, in lieu of full of partial assessment for marketing authorization (18). If a CPP is provided, it is being used in lieu of a full or partial review and assessment is accelerated. Such procedures currently exist in Benin, Bolivia, Bolivia, Cameroon, Congo, Cuba, Curacao, Guinea, Haiti, Hong Kong and Honduras.

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) (19) 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 (20). 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) (21) 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, 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 together, 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 those in the Regional Economic Communities in Africa (East African Community (EAC) (22), ZAZIBONA (23) in the SADC, the Economic Community of West

African States (ECOWAS)/West African Health Organization (WAHO) (24), the Association of Southeast Asian Nations (ASEAN) Joint Assessment Coordinating Group (25), and so on.

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 and recognition (26).

c) Post-approval changes

Following the same principles as for initial marketing authorization, reliance can also be applied broadly for assessing post-approval changes already approved by NRAs considered as reference authorities. In the case of CRP, for example, the participating NRAs for prequalified products are informed by WHO of any variations approved by WHO PQ Team (17).

The Health Sciences Authority (HSA) in Singapore is applying a verification route with shortened timelines for approving post-approval quality and product label changes, which aims to enable greater leveraging of reference agencies' assessments, minimize duplication of effort and enhance process efficiency as part of HSA's on-going effort, in particular for effective life cycle management for registered therapeutic medicinal products. To qualify, the proposed changes must be identical to those approved by one of HSA's five reference agencies, accompanied by the proof of approval of that reference agency as well as the approved product label of that reference agency where applicable (27).

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) (28) 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 biologic products

Launched in 2017, the WHO-National Control Laboratory Network for Biologicals (WHO-NNB) (29) 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 collaboration and 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) (30). 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.

The EU introduced the concept of a supervisory authority for pharmacovigilance in 2012 in the Regulation 1235/2010 (31) who shall be responsible for verifying on behalf of the Union that the marketing authorization holder for the medicinal product satisfies the pharmacovigilance requirements as per EU legislation.

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 (32) with Australia, Canada, Japan, Switzerland and the United States of America (USA); ASEAN Mutual Recognition Agreement (33), etc.

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) is a non-binding, informal co-operative arrangement between regulatory authorities in the field of Good Manufacturing and Good Distribution Practices (GMP and GDP) of medicinal products for human or veterinary use, and more recently also in Good Clinical Practices (GCP) and Good Pharmacovigilance Practices (GVP) (34). It aims at facilitating cooperation and networking between competent authorities, regional and international organizations, thus increasing mutual confidence regarding inspections. PIC/S has also issued a guidance on inspection reliance, which outlines a process for the desk-top assessment of GMP compliance (35).

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 (36).

The OECD operates the Mutual Acceptance of Data system in the assessment of chemicals (including pharmaceuticals) which supports the acceptance of data, generated in any member country in accordance with OECD test guidelines and Principles of Good Laboratory Practices (GLP), in any other member country for assessment purposes relating to the protection of human health and the environment (37).

g) Examples in the field of medical devices

The use of reliance is equally prevalent in the regulation of medical devices including in vitro diagnostics. An example of this is the Medical Device Single Audit Program (MDSAP) (38) 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 United States 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.

The IMDRF has also set guidance for the exchange of information between NRAs respect to medical device safety (39). The system focuses on incidents that represent a serious public health threat that extend beyond national borders in order to inform other NRAs of such. Additionally, IMDRF outlines consistent adverse event reporting, coding, and terminology in their IMDRF terminologies for categorized Adverse Event Reporting: terms, terminology structure and codes document (40).

The above-mentioned initiative and guidance are just two examples of the work IMDRF does in the field of harmonization, convergence and reliance in the area of medical devices. Other examples are The IMDRF Optimizing Standards for Regulatory Use (41), the Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices (42) or the Competence, Training, and Conduct Requirements for Regulatory Reviewers (43).

In Singapore, medical devices and in vitro diagnostics with prior authorization through specific market authorization pathways in the United States, Europe, Canada, Australia, or Japan are eligible for abridged evaluation routes. To qualify for this, the proposed intended use must be identical to that approved in the reference country and typically documentation including proof of approval from the reference regulatory authority and summary technical documentation can be used to satisfy many supporting documentation requirements (44). Additionally, Australia will recognize registrations and certifications from Notifies bodies designated by the medical device regulators of European member states, U.S. FDA, HC, the PMDA and MDSAP auditing organizations (45).

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