Annex 10

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

Background

WHO supports reliance on the work of other regulators as a general principle in order to make the best use of available resources and expertise. is principle allows leveraging the output of others whenever possible while placing a greater focus at national level on value-added regulatory activities that cannot be undertaken by other authorities, such as, but not limited to: vigilance, market surveillance, and oversight of local manufacturing and distribution. Reliance facilitates timely access to safe, e ective, quality-assured medical products (see section 3. Scope) and can support regulatory preparedness and response, particularly during public health emergencies.

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

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

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

Abbreviations to Annex 10

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

1. Introduction

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

results showed that regulatory reliance is broadly accepted and widely practised with regard to medical products, especially among well resourced regulatory

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

4. Glossary

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

Abridged regulatory pathways. Regulatory procedures facilitated by reliance, whereby a regulatory decision is solely or partially based on application of reliance. is usually involves some work by the national regulatory authority (NRA) that is practising reliance (see section 5.4 Risk-based approach). It is expected that use of reliance in these pathways will save resources and time as compared with standard pathways, while ensuring that the standards of regulatory oversight are maintained.

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

Equivalence of regulatory systems. Implies strong similarity between two regulatory systems, as mutually established and documented through objective evidence. Equivalence can be established using criteria and approaches such as similarity of the regulatory framework and practices, adherence to the same international standards and guidelines, experience gained in use of assessments for regulatory decision making, joint activities and exchanges of sta . It is expected that equivalent regulatory systems will result in similar standards and levels of regulatory oversight or “control”.

International standards and guidelines. For the purpose of this 7tips.5(simi)-5ap

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

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

Recognition. Acceptance of the regulatory decision of another regulator or

aspects of drugs, medical devices and in vitro diagnostics, including those related to the quality of the product and its components, should be considered to con rm that the product is the same or su ciently similar (e.g. same qualitative and quantitative composition, same strength, same pharmaceutical form, same intended use, same manufacturing process, same suppliers of active pharmaceutical ingredients, same quality of all excipients). Additionally, the results of supporting studies of safety, e cacy and quality, indications and conditions of use should be the same. e impact of potential, justi ed di erences should be assessed by the manufacturer (for the purpose of this document, manufacturer also means marketing authorization holder) and the

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

5. Key concepts

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

Key concepts of reliance

Unilateral versus mutual reliance or recognition

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

Life cycle approach

e concept of reliance for regulation of medical products should be applied throughout the life cycle of medical products and in all regulatory functions (see 3. Scmupoh(l)-3(e3(e)4(li)-3(a)a)-5(l4(ce a)9(n))11(p)7(li)13(o)-9(d)56(h)4(e)-5(9(n)4((e ex

- con rmation of the applicability of the assessment outcomes of another authority for regulatory decision making in the national context, for example, in terms of legal and regulatory settings, bene t–risk assessment, co-morbidities, unmet medical needs, risk management plans and any quality-related speci cities such as climatic zones for product stability. In case of di erences, such as in target population, epidemiology and other features of the disease, medicines used concomitantly and other factors that can substantially a ect the bene t–risk pro le of a medicine, as well as quality parameters, especially in relation to the stability under di erent climatic conditions, appropriate evidence should be provided by the manufacturer.
- abridged assessment of data on quality, safety and e cacy or performance, taking into account information in the assessment reports of the reference regulatory authority; and
- joint assessment or work-sharing between two or more regulatory authorities. is may take various forms, including a primary review by one authority followed by a joint assessment session to nalize the report and comments or distribution of the modules (quality, non-clinical and safety or e cacy) between the authorities.

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

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

Regional reliance mechanisms

In some regions, medical products can be assessed centrally in a regional regulatory system. In some regional reliance mechanisms, the regional decision is binding on the member states (e.g. European Union). In others, regional decisions are recommendations that member states take into consideration when making national regulatory decisions (e.g. the Southern African Development Community collaborative procedure ZAZIBONA [Zambia, Zimbabwe, Botswana and Namibia; initial participants in the Southern African Development Community collaborative procedure for joint assessment of medicines], the Gulf Health Council and the Caribbean Regulatory System).

6. Principles of good reliance practices

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

e following principles are meant to complement and extend the basic principles of GRP. ey are based on the principles presented in the concept note and recommendations on regulatory reliance principles of PAHO and the

Competence

Implementation of reliance approaches requires that NRAs have the necessary competence for critical decision-making. Introduction of the reliance approach usually requires the involvement of senior regulatory sta , managers and experts who are competent to make the best use of foreign information in the local context. NRAs should maintain the appropriate scienti c expertise of their sta for activities in which they do not apply reliance, such as monitoring local

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

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

WHO encourages NRAs to monitor and evaluate the impact of regulatory reliance, including its bene ts, in their country and region and to share their experiences with other regulatory authorities. When possible, the impact should be measured speci cally, and the NRA should establish the metrics they will use to measure the impact of using reliance in regulatory decision-making and the time for conducting the assessment. e metrics may include costs saved, e ciency in the number of products reaching the market or time to market, and redirection of scarce resources to areas of higher regulatory risk. NRAs should consider methods for sharing best practices and experience in establishing reliance arrangements in international forums for regulation of medical products

Senior management, reviewers, inspectors and other sta should build con dence and trust in the work done by other NRAs or trusted authorities. is will take time and require a change in the culture of the relying NRA. e experience of regulatory authorities and systems that already practise reliance should be leveraged to promote acceptance and avoid pitfalls. Trust should also be built with the public, health care professionals and the industry by assuring them that reliance o ers more e cient regulatory oversight.

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

The role of industry

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

Review and discussion of pilot programs to quickly adapt and improve guidance will be key to bene t from key learnings and improve implementation. Collaboration and dialogue among all stakeholders participating in regulatory reliance activities will help to create and build trust, which is the foundation of regulatory reliance. Transparent publication of an NRA's reliance framework and strategies, including the metrics used and bene ts achieved, will encourage industry to support and promote the reliance approach.

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

Sensitive, non-public information in unredacted assessment or inspection reports can also be shared between regulatory authorities upon

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

Convergence and harmonization

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

Di erences in standards and practices, however, do not prevent one authority from relying on another, particularly when the relying authority has limited capacity and expertise. e system on which an NRA relies should be at least equivalent to or superior to the standards it applies. As a matter of good practice, NRAs should rely on assessments or decisions from reference regulatory authorities that apply international standards and guidelines.

7.3.3 Information-sharing and dialogue among regulators

Information-sharing is an essential part of reliance, and NRAs are encouraged to share information and good practices with other NRAs. Increasing dialogue among regulators is seen in the growing number of international initiatives such as the International Pharmaceutical Regulators Programme and in networks for sharing regulatory information and work such as the Pan American Network for Drug Regulatory Harmonization, the Southeast Asia Regulatory Network, regulatory networks in the Regional Economic Communities under the African Medicines Regulatory Harmonisatly oataticaue(o)24(a)9(r)-6wT1a.c(a)3(s)12(n a)(n)4(c 3(a

Appendix 1

Examples of use of reliance

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

A1. Clinical trials

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

Union Medicines for all) (*4*

Work-sharing

e Australia–Canada–Singapore–Switzerland United Kingdom ACCESS Consortium (*10*) was formed in 2007 by "like-minded" medium-sized regulatory authorities to promote work sharing for greater regulatory collaboration and alignment of regulatory requirements. e ACCESS Consortium explores opportunities to share information and work in areas such as biosimilar products, complementary medicines, generic medicines, new prescription medicines, medical devices and information technology. e Consortium capitalizes on each country's strengths, addresses gaps in science, knowledge and expertise and leverages resources to expedite risk assessment, while

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

A3. Post-approval changes

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

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

A4. Testing and lot release

Network of O cial Medicines Control Laboratories

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

Lot release and quality monitoring of vaccines and other biological products

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

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

A5. Pharmacovigilance

Exchanges and sharing of data are critical in pharmacovigilance. More than

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

A8. Examples of public health emergencies

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

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

References to Appendix 1