Points to consider on:

THE IMPORTANCE OF **"SAMENESS OF PRODUCT"** IN THE CONTEXT OF REGULATORY RELIANCE

by IFPMA

INTRODUCTION

WHO's Good Reliance Practice guideline was adopted in April 2021 to support and promote a more efficient approach to medicines and health products oversight. Available resources can be leveraged more efficiently through greater collaboration between National regulatory authorities (NRAs) regionally and internationally, thereby improving and expediting access to quality compliant, effective and safe medical products.

According to the WHO[1], reliance can only be practiced if "the medical product being assessed is essentially the same as the one submitted to the reference NRA". In defining sameness WHO states that "…sameness of product means that two products have identical essential characteristics (i.e. the product being submitted to the relying NRA and the product approved by the reference NRA should be essentially the same). All relevant aspects of drugs, medical devices and in vitro diagnostics, including those related to the quality of the product and its components, should be considered to confirm that the product is the same or sufficiently similar (e.g. same qualitative and quantitative composition, same strength, same pharmaceutical form, same intended use, same manufacturing process, same suppliers of active pharmaceutical ingredients, same quality of all excipients). Additionally, the results of supporting studies of safety, efficacy and quality, indications and conditions of use should be the same".

IFPMA believes that mutual trust between all parties is the foundation of reliance. Transparency is a key principle for good regulatory practice and fundamental to reliance. A mutual understanding of product sameness for reliance purposes is critical. The purpose of this document is to explain how multinational companies (MNCs) are developing innovative products under ICH guidelines to ensure sameness in product quality supplied to all geographies.[2] We want to provide assurance that MNCs supply products of the same quality to all countries and do not provide different "versions" of product quality to different countries.

COMMON MISCONCEPTIONS

Sameness of product **does not mean** identical manufacturing sites or suppliers

- MNCs produce products to the same high-quality standards because they operate under a global quality system (e.g., internationally recognized quality system like ISO 13485) that ensures products are produced to the same high-quality standard, no matter what jurisdiction they will be shipped to. In line with ICH Q10, the pharmaceutical quality system (PQS) requires manufacturers to monitor and control product quality throughout the different stages of the product life cycle and the system is regularly inspected by NRAs from PIC/S member countries. A robust product quality monitoring and change management system assures that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate and improvement opportunities are identified and evaluated. The PQS is not influenced by the jurisdiction receiving the product.
- MNCs are responsible for supplying high quality medicinal products globally. More than one manufacturing site is often used to ensure uninterrupted supply of medicinal products. All manufacturing sites in the supply chain will manufacture in conformance with the approved manufacturing processes and operate under essentially the same quality system which is designed to ensure consistent manufacturing and quality of the products. Company's PQS set rules and requirements for product transfers (intra and inter-company) to assure equivalent product quality also when manufactured at different sites (e.g., WHO guidelines on transfer of technology, Annex 7). All starting materials, raw materials, excipients and primary packaging used in the manufacturing process are qualified under the company established quality system. And this quality system is subject to inspection by various NRAs.
- For biotherapeutics, any manufacturing process changes are qualified/validated, and product comparability is established through scientific analysis specific to the product and process . These data ensure that the same high-quality product is being produced and distributed, independent of the manufacturing site or the jurisdiction receiving the product.[3] For all products, the manufacturing process and respective controls will be performed in accordance with the approved manufacturing authorization.

Sameness of product **does not mean** identical dossiers or documentation

Global harmonization of dossier structure and content is a work in progress. MNCs prepare dossiers that contain the results from supporting quality, safety, and efficacy studies, in accordance with the regulatory requirements of a region or individual country. Documentation differences between reference and relying countries, especially related to the level of details provided reflect the differences in regulations between jurisdictions but do not indicate a difference in product quality. Therefore, differences of documentation should not preclude from using reliance approaches. For more information on this, please refer to the annex.

Sameness of product **does not mean** identical indications or conditions of use globally

Even if the same indications or conditions of use are claimed in different countries, the approved indications are often dictated by the country priorities, settings and healthcare frameworks, which lead to different approved indications or conditions of use. Therefore, not all indications approved by the reference country might be submitted in the target country due to public health, commercial or patent reasons.

> "More than one manufacturing site is often used to ensure uninterrupted supply of medicinal products. All manufacturing sites in the supply chain will manufacture in conformance with the approved manufacturing processes and **operate under essentially the same quality system**."

HOW CAN MNCs ESTABLISH "SAMENESS OF PRODUCT"?

MNCs must have a process in place under their PQS to ensure that the product has equivalent efficacy, safety and quality.

Principles described in ICH guidance can ensure that any changes are evaluated scientifically in a manner appropriate to the product type. The quality assurance department(s) of the MNC is responsible for the global PQS and this ensures there has been an appropriate assessment of the impact of potential differences on the product quality, safety and efficacy. A signed declaration of sameness of product can be provided to the NRA including justifications for any potential differences.

WHAT ELSE CAN BE DONE TO BUILD TRUST AND ENSURE MUTUAL UNDERSTANDING?

When filing an application through a reliance-based pathway, MNCs would be ready to have a preliminary exchange of information with the concerned NRA to clarify why reliance can be used in that particular case and address any concerns regarding product sameness.

A cover letter can then be attached to the application, highlighting any differences of concern to the NRA (e.g., different manufacturing sites) and a justification for why such differences have no impact on the quality, efficacy and safety of the physical product.

We would support workshops and educational sessions to better explain the ICH product quality standards managed under the PQS. We can contribute with practical insights and case studies on how MNCs apply the "sameness" definition and supply the same quality of product to all countries.

In addition, reduction of additional national requirements and further work towards global harmonization and recognition of regulatory requirements and quality standards, such as WHO, ICH, ISO, IDMP2, and PIC/S plays an important role in aligning clinical study results and working towards a more uniform dossier content.

As a long-term aspiration, the Global Pharmaceutical Quality Knowledge Management system as proposed by ICMRA[4] can be a step in the right direction towards facilitating reliance and identification of the same product across global countries.

1 WHO, 2021, 55th report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, TRS 1033, Annex 10

2 There could be exceptions based on destination country specifications due to climatic zone conditions and how products are stored

3 Biotechnological/Biological Products: demonstration of comparability does not necessarily mean that the quality attributes are identical, but that they are highly similar, and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product (ICH Q5E). ICH Q5E applies to pre and post manufacturing changes being made by the same MAH.

4 ICMRA (2021), Pharmaceutical Quality Knowledge Management System Statement

FREQUENTLY ASKED QUESTIONS

1. Why do companies use different manufacturing sites?

MNCs need flexibility to manage complex supply chains and volumes of production around the world. To ensure sufficient supply and resilient supply chains, MNCs need to manufacture products in multiple facilities using multiple suppliers.

2. Are companies supplying different quality of product to some countries?

MNCs manufacture all products that are supplied globally under the same global product quality system (PQS). Although products manufactured from different sites cannot scientifically claim to be identical, there is a comparable and consistent control strategy (as defined by Q8(R2)) that ensures the same safety, efficacy and performance of the product, irrespective of where it is supplied. Registrations and post-approval changes are approved by NRAs and PQS is regularly inspected by the NRAs during GMP inspections. This ensures the same product quality regardless of the manufacturing site or any differences in indications or documentation.

3. How can companies provide assurance that the physical product is the same as assessed by the reference NRA?

The impact of potential product differences is assessed by the MNC within its quality assurance department who is responsible for the company global pharmaceutical quality system (PQS). A confirmation of sameness of product quality can be provided and any product differences shall be highlighted and justified.

4. What should NRAs do if there are different manufacturing sites from that of the reference country and these sites have not been inspected by the reference country?

Any differences between the different manufacturing sites have to be justified and properly documented (e.g. comparability data need to be submitted for biotherapeutics). For sites which have not been inspected by the reference NRA, the manufacturer will provide a CPP from another competent NRA or GMP certificate issued by another PIC/s member country.

5. Why are companies providing different dossier versions to different countries?

Dossier requirements have evolved in different jurisdictions over several years. The dossiers submitted have been constantly adapted to comply with these evolving requirements ("right first-time approach"). Furthermore, dossiers are usually updated with the most recent stability, clinical safety, and/or other information depending on their timepoint of submission (which may differ from a country to another). There can also be divergence due to NRA requests (e.g., information requested to assess the control strategy) that arise during review.

This explains why dossiers submitted to different NRAs might be presenting different levels of details but contain essentially the same information, based on the same set of studies. While convergence is not necessary for reliance, establishment of common set of dossier requirements and recognition of international standards is key to facilitate reliance.

Therefore, we remain committed to helping with global dossier harmonization and promote harmonization of technical standards.

6. Are there any examples of quality dossier differences that might occur which have no impact on the product quality?

- Differences in stability data due to differences in climate zone
- Different tablet images (e.g., different markings, shapes)
- Different sites registered in the reference country due to supply arrangement
- Excipient information included in the dossier rather than filing DMF in reference country
- Various levels of GMP information requested

7. What differences in clinical data may still exist due to differing public health needs in the countries?

For example, there may be a difference in the number of indications sought and/or how these are expressed, (first line, second line etc.) in the label compared to the reference product. The reference country could have registered indications XXX and YYY, but the target country may only be registering indication YYY. This would not preclude the application of reliance since the data support registration of indication YYY.

8. What differences are expected and acceptable in terms of product labeling and instructions for use?

For various reasons, certain jurisdictions may require country specific labeling. This does not mean the product itself is different – it simply means the labeling has been customized for a particular jurisdiction. Jurisdiction-specific labeling should not negate the use of reliance. If there are differences that significantly affect the safety and quality of the product, the manufacturer can include those differences and the NRA or recognized institution can decide on the extent to which reliance can be applied.