INTERNATIONAL GENERIC AND
BIOSIMILAR MEDICINES ASSOCIATION

In Support of Global Comparator for Biosimilars
Waiving bridging studies concerning *local* versus *global* reference products

I. Introduction

The initial approval of a novel medicine in a country or region is usually supported by the **same quality, non-clinical and pivotal clinical study datasets** used for approval in other jurisdictions (notwithstanding additional clinical studies may be required in some countries to satisfy local regulatory demands). Moreover, for recombinant proteins, regulatory authorities adhere to the concept that the biological drug substance and product derive from a **single, approved manufacturing process**. There may be operational variations between different manufacturing sites but the quality (and hence the efficacy and safety) of the drug substance and product, based on data, must be comparable. This concept is present throughout the lifecycle of the product.
Sometimes, it is not clear to all health system stakeholders if a product approved in different jurisdictions is the same. For example, the **trade name or license holder may be different** because of co-marketing agreements.
Therefore, irrespective of the regulatory jurisdiction where approval is given and based on scientific rationale and regulatory expectations (unless data is available to confirm otherwise), **a biological product produced by the same developer and marketed around the globe** should by default be considered of comparable quality and equivalent in terms of the safety and efficacy profile.

II. How Bridging Studies Hinder Patient Access to Biosimilar Medicines

The logical consequence is that **this concept should be applicable to reference products (RPs)** when developing biosimilar medicines; that is, the biologic upon which the biosimilar is based (the RP) is the same product whether manufactured in the country/region where biosimilar authorization is being sought or in another county/region with comparable standards of GMP. The selection of the RP is a critical step in biosimilar development and unfortunately**, laws, regulations and guidelines in some jurisdictions dictate a locally approved and sourced RP for the similarity assessment**. This means analytical and, in some cases, clinical bridging studies are expected to demonstrate what is already known by the RP developer: that a local and non-local reference product are the same product. **The duplication of bridging studies is an unnecessary hindrance to biosimilar development**, and contributes to high costs of development and delays patient access to biosimilars.
It is important that **any requirement for bridging studies between local and non-local RPs is based on scientific merit** and required only in cases where data establishing their congruity is not already available to regulators. In some cases, legal and regulatory constraints limit disclosure of proprietary information, and **it should not be the responsibility of the biosimilar product manufacturer to obtain supporting information** already available to health authorities, such as comparability data supporting multiple manufacturing sites of the RP. Often, **health authorities**

are able to share information between themselves without jeopardizing confidentiality of the RP developer.

III. How Regulators Can Improve Access to Biosimilar Medicines

To avoid unnecessary, hence potentially unethical, testing of multiple reference products, **Health Authorities should clarify that bridging studies are not presumed to be required by default**, and that biosimilar sponsors will be informed upon request or as part of formal scientific advice, if bridging of local and non-local reference product is required, taking into consideration the below-mentioned criteria. In the longer term, **local Authorities should review and update their guidance on the choice of reference product and bridging requirements, t**o make clear for prospective biosimilar developers which local reference products are considered equivalent to their non-local counterparts for purposes of waiving bridging studies.

Below are proposed items for **consideration by regulatory authorities to allow waiving of bridging studies between a locally-approved and sourced Reference Product (local RP) and a foreign/non-local-sourced Reference Product (non-local RP).** There should not be any requirement to repeat analytical testing of local RP if the foreign RP meets the criteria listed below.

- The foreign RP contains a version of the same active pharmaceutical ingredient (API) as defined by international non-proprietary name (INN) and meets all other criteria listed in Section 6 of WHO biosimilar guideline (April 2022) for the reference biological product (RP).

  Notably, criteria included in the WHO biosimilar guideline (April 2022) related to RP and incorporated by reference herein includes (*non-exhaustive*):
  - The RP should be licensed based on full quality, safety, and efficacy data. Therefore, a biosimilar should not be considered as a choice for RP.
  - The same RP should be used throughout the development of the biosimilar (i.e., for the comparative quality, non-clinical, and clinical studies).
  - The RP should be licensed in a jurisdiction that has a well-established regulatory framework, as well as experience with the evaluation of biological products and post-marketing surveillance activities
  - The drug substance/drug product of the RP and the biosimilar must be shown to be similar.
  - The dosage form and route of administration of the biosimilar should be the same as that of the RP.

  The WHO biosimilar guideline (April 2022) further states that: “Traditionally, NRAs have required the use of a nationally licensed RP for the licensing of a generic medicine. In the case of biosimilars, this practice may not always be feasible nor necessary, and **several regulatory jurisdictions have allowed for the use of a non-local RP** as comparator **to enable faster development of and access to biological therapies**. **The use of an RP sourced from another jurisdiction with similar scientific and regulatory standards is therefore possible.”**

It is not only possible, it should be the default or recommended practice unless a compelling scientific rationale is provided to explain the need for a local RP.

NRAs should enter into mutual recognition agreements or other data sharing agreements that protect confidentiality while providing the legal mechanism to share relevant information.

- Usually, the non-local and local RPs have the same, or similar, excipients. In the **rare cases where the excipients are different**, in addition to fulfilling the criteria above,

additional justification is required to show that different excipient(s) do not affect quality, efficacy, and safety. The following are examples how such justification may be obtained:

- Information and/or data may be available in the public domain that confirms different formulations/excipients of foreign and local RPs are equivalent with respect to safety and efficacy.
- The approved dossier of the local RP is on file at the health authority and consultation with the relevant quality, non-clinical and clinical data should confirm that excipients used in the local RP formulation do not impact clinical efficacy and safety.
- Comparability data between local and non-local RP's, based on principles described in ICHQ5E, should be available. If this is not available, the **local health authority is encouraged to contact their counterparts who are responsible for approval of the non-local reference product (e.g. EMA or US FDA)** to request access to or confirmation of any comparability data, if the data was submitted to the counterpart health authority.

- **The manufacture of RP in different manufacturing facilities is not an automatic exclusion criterion** because if an RP manufacturer can produce the same biologic at different manufacturing sites, so can a manufacturer of a biosimilar of that biologic. If more than one manufacturing site is used, it is expected that comparability data from the originator, based on the principles described in **ICHQ5E**, is available to Health Authorities confirming that **each manufacturing site is able to manufacture product with comparable quality** and equivalent safety and efficacy profiles. It may also be possible to find information in the public arena (e.g., public assessment reports, scientific journals, clinical trial databases) that also support use of multiple manufacturing sites.

IV. Conclusion

Regulatory policy should adapt to advances in the scientific understanding of biosimilarity. It is well established that reference products in one country or region are approved based on the same data package as in other countries/regions, and are manufactured using the same process, even if at different facilities. To reduce the time and cost needed to develop and manufacture biosimilar medicines, and therefore improve patient access to biosimilar medicines globally, global health authorities should adopt policies that favor waiving bridging studies between a local RP and a non-local RP.

About IGBA

The International Generic and Biosimilar medicines Association (IGBA) strengthens cooperation between associations representing manufacturers of generic and biosimilar medicines from around the world. Adopting a patient centric approach, IGBA works to improve patients' access to quality-assured, safe and cost-effective medicines by promoting competition and enabling innovation in the pharmaceutical sector and sustainable economic contributions for all stakeholders. For more details, regarding IGBA and its member associations, see the IGBA website at: www.igbamedicines.org.