INTERNATIONAL GENERIC AND
BIOSIMILAR MEDICINES ASSOCIATION

Contact: David Gaugh
igba@igbamedicines.org

IGBA Reflection Paper on waiving bridging studies for biosimilar medicines applications

Summary: IGBA proposes a new international biosimilars framework allowing bridging studies to be waived in specific circumstances based on core scientific and regulatory principles established for current products.

Current biosimilar medicines framework

A biosimilar sponsor may use a non-locally-approved comparator biological product [**Foreign Reference**] to support a demonstration that their candidate biosimilar also matches the locally-approved reference biological product [**Local Reference**]. Currently, the biosimilar sponsor must establish a bridge between the Foreign Reference used during the biosimilar development and the Local Reference. Establishing the requirements for this bridge remains at the discretion of local regulators.

The graph annexed to this paper illustrates the bridging studies requested in selected countries, in addition to a complete comparability/similarity exercise conducted against the EU approved reference product. The jurisdictions have been selected based on their respective Medicines Agency's high Maturity Level and their requirement of an extensive comparability exercise to demonstrate biosimilarity.

IGBA Vision

To avoid unnecessary, and therefore unethical, clinical bridging studies, IGBA proposes that a bridge between the foreign and local reference products be established without any additional bridging studies as long as certain criteria are met. This will also help avoid the multiplication of bridging studies by different sponsors, for example, when making biosimilars to the same reference product, and therefore increase the efficiency of biosimilar development overall.

The biosimilar sponsor can establish that the Local Reference and Foreign Reference are the same using public information already available for both, and use this to minimize additional studies with the regulatory authority in the jurisdiction where the biosimilar application is made. Regulators have non-public sources of additional information that they may wish to use to confirm the veracity of the application, but this is not *a priori* necessary. No access to confidential information regarding the reference product is needed by the biosimilar sponsor.
Nonetheless, where useful, the existing US FDA, European Commission DG Santé and EMA confidentiality commitment could serve as a template for confidentiality arrangements among regulatory agencies. Such commitments to confidentiality enable the limited exchange of confidential information related to approved products between regulatory authorities. This can further support convergence of regulatory practices for all medicines. To facilitate such a harmonized science-based international regulatory framework, consistent definitions and criteria are needed across jurisdictions. IGBA is pleased to share definitions and the scientific-rationale for waiving bridging studies as well as circumstances when these studies can be waived.

Definitions for biosimilar product applications and criteria for qualifying as a Comparator Product for biosimilar applications in one or multiple jurisdictions

Definition of a Reference Product

A Reference Product is any originator product that has been approved by a Stringent Regulatory Authority (SRA)/WHO-Listed Authority (WLA) (Maturity Level 4/ML 4)[i], based on a stand-alone registration dossier. For a local biosimilar application, it is the named locally-approved Reference Biological Product **[Local Reference]** in that same jurisdiction, also used as Comparator Product for head-to-head comparability/similarity studies with the candidate biosimilar in order to show its similarity to that Reference Product in terms of quality, safety and efficacy.

Definition of a Comparator Product

A Comparator Product is a Reference Product used for head-to-head similarity/comparability studies to support the biosimilar application and approval. The specific Comparator Product can be the locally-approved Reference Product **[Local Reference**] or a non-locally-approved Reference Product [**Foreign Reference].**
If a multi-jurisdictional biosimilar development program is being undertaken, the Comparator Product must have been approved by a SRA/WHO-Listed Authority (WLA-ML 4), in order to be recognized by another jurisdiction.

*Definition of a **Global** Comparator Product*

A **Global Comparator Product** is any originator biological product, authorized by any SRA/WHO-Listed Authority (WLA ML4) **and** qualified as Comparator Product by complying with prespecified criteria (see below). It can be used for biosimilar product development to support a biosimilar application and approval in any jurisdiction around the world.

Criteria to qualify as a Comparator Product

1. The Comparator Product has been approved, based on a stand-alone registration dossier, by a Stringent Regulatory Authority («SRA») i.e. an Authority that has formally adopted and implemented the International Council for Harmonization (ICH) Guidelines as well as one which conforms with WHO Guidelines.
    a. "SRA" to be replaced in the future by "WHO-Listed Authority" (WLA) Maturity Level (ML) 4
2. The Comparator Product must have been inspected for compliance with cGMPs, cGCP, cGLPs and cGDPs.
    a. Production batches from different manufacturing sites can be used provided that products from all manufacturing sites are approved under a single application by the relevant regulatory authority, and all batches used in the comparability exercise conform to the same specifications.
3. The Comparator Product must be fully identifiable by the approved product name, pharmaceutical form and qualitative composition.
4. An evaluation report related to the Comparator Product's application should ideally be publicly available in the country of origin of the Comparator Product (e.g. the European Public Assessment Report (EPAR) issued by the EMA; the Summary Basis of Approval (SBA) issued by the FDA; the Regulatory Summary Decision (RSD) issued by Health Canada).

We invite WHO to publish, together with SRAs, a list of originator biological products which can be considered as global comparator products. This could form the basis for further development of the WHO's prequalification program for biosimilars, aiming at increasing access to essential biological medicines, and thereby supporting the 2030 goal of Universal Healthcare Coverage (UHC).

Rationale for the Global Comparator Product approach

Great efforts have been made over decades to harmonize the development of originator products worldwide. Such sharing of primary data expedites development and access to essential medicines.[ii]

One clinical data base for global registration of the originator biological product

Providing substantial evidence, created by compiling information that is already public in one readily accessible place (for example, an online clinical data base) would be valuable. This would indicate that all versions of the originator product irrespective of where they are sourced can be used as the Comparator Product in any jurisdiction. This will include both local and foreign-sourced reference, each having been approved in each jurisdiction based on essentially the same original data, including clinical safety and effectiveness/efficacy data[iii]. The data package does not need to be identical but simply overlap (given that different jurisdictions may have additional requirements for the originator approval).

Any manufacturing changes to these Reference Products over time will have been approved following a stepwise comparability exercise as described in the ICH Q5E guideline. This ensures that the safety and efficacy are maintained between the pre- and post-changed product. This is also reflected by the label/product information, which does not change after the manufacturing change (albeit possibly revised for other reasons such as the addition of an indication or observation of an adverse event). Further *"The comparability approach has successfully been applied for more than 2 decades in hundreds of manufacturing changes. When comparability has been demonstrated, the new version can be introduced to the market without informing prescribers, pharmacists or patients ".*[iv]

Finally, "*the fact that a biosimilar is usually expected to be licensed in multiple jurisdictions, in each case as similar to the local reference product, confirms that minor analytical differences between versions of reference biologics are typically inconsequential for clinical outcomes and licensing."*[v]

The Same Pivotal Clinical Data Supporting the Approvals of Six Biologics in Multiple Jurisdictions

Biologic	**Trade Name**	**Sponsor**	**Countries in which First Approvals Were Based on the Same Studies***	**Studies Submitted for First Approvals in More Than One Country**	**Indications Studied**
Infliximab	Remicade	Janssen	US, EU, Canada, Australia	T16, T21	Crohn's disease
Etanercept	Enbrel	Amgen	US, EU, Canada, Australia	16.009, 16.014	Rheumatoid arthritis
Adalimumab	Humira	AbbVie	US, EU, Canada, Australia	DE009, DE011, DE019, DE031	Rheumatoid arthritis
Pegfilgrastim	Neulasta	Amgen	US, EU, Canada, Australia	980226, 990749	Febrile neutropenia in treatment of non-myeloid cancers
Bevacizumab	Avastin	Genentech/ Roche	US, EU, Canada, Australia	AVF2107g, AVF0780g	Metastatic colon cancer
Ranibizumab	Lucentis	Genentech	US, EU, Canada, Australia	FVF2598g, FVF2587g, FVF3192g	Age-related macular degeneration

**This is not necessarily a comprehensive list of the countries in which these studies were submitted for licensure of the product.*

Reproduced with permission of the authors[vi] *of* A "Global Reference" Comparator for Biosimilar Development[vii]

Repeated bridging studies are unethical because they do not contribute additional scientific value
Clinical studies bridging between a Local Reference and a Foreign Reference will not provide new information, as such they expose human subjects to unnecessary, and consequently unethical, clinical trials.[viii] e.g. a 3-way human PK-comparison, as needed by U.S. FDA, can expose subjects to potent medicines that often carry side-effects.

Waiving bridging studies supports increased patient access
Bridging studies add substantial costs and time to biosimilar development. "*These costs are not trivial in absolute terms and, due to the multiplier effect of required repetition by each biosimilar sponsor, their collective costs are substantial*".[ix] A 3-way comparison (e.g. Biosimilar vs US-approved Reference Product vs EU-approved Reference Product) typically requires 40-80 additional subjects, which adds €1-3 m additional cost while having no impact on the safety profile of the biosimilar product.[x] Sourcing originator biological products is also becoming increasingly difficult and complex[xi] and constitutes a substantial part of the development costs. Often multiple batches are needed with different shelf-lives, which are difficult to source, especially in smaller markets. Waiving unnecessary bridging studies supports true global development, reduces development and approval times and thereby improves patient access and affordability for health systems overall.

Information sharing and collaboration amongst regulators is steadily increasing
A number of National Regulatory Authorities (NRAs) have established confidentiality agreements and/or have set up channels, clusters and fora to share regulatory practices and information on medicinal products (e.g., Biosimilars Cluster EMA/FDA/HC/PMDA driven toward attaining scientific alignment[xii], International Pharmaceutical Regulators Programme/IPRP[xiii], United States FDA-European Commission DG Santé/EMA Confidentiality Commitment[xiv], ACSS Consortium/Australia, Canada, Switzerland and Singapore[xv], WHO-International Conference of Drug Regulatory Authorities/ICDRA[xvi], WHO Pilot Prequalification Procedure for Biotherapeutic Products: trastuzumab and rituximab[xvii].

Another important information sharing tool already being adopted is the ISO Identification of Medicinal Products (IDMP) standards.[xviii] ISO IDMP is a worldwide system for internationally harmonized data definitions to establish unique identifiers for medicinal products to be used during their entire life-cycle. These standards, originally developed by ICH, establish a lasting international framework which allows the exchange of information on medicinal products in a robust, consistent and reliable manner. They also support interoperability across regulatory and healthcare communities. The ISO IDMP standards for the identification of medicinal products are currently implemented in a phased program, based on the four domains of master data in pharmaceutical regulatory processes: substance, product, organization and referential (SPOR) data. While implementation worldwide is at various stages, these developments will further support the exchange of information on medicinal products in a robust, consistent and reliable

manner between agencies and demonstrate that there is no legal impediment to sharing information on products between agencies.

Circumstances where bridging studies between the locally-approved Reference Product (Local Reference) and the non-locally-approved Reference Product (Foreign Reference) can be waived

Bridging studies can be waived when the non-locally approved Reference Product (Foreign Reference)

- meets the definition of a Comparator Product;
- contains a version of the same active pharmaceutical ingredient (API), and has the same pharmaceutical form and same route of administration as the Local Reference;
- has the same composition of excipients as the locally-approved reference product (Local Reference), or, if the qualitative compositions of excipients are different, the sponsor provides a justification showing the excipients have been assessed and are not expected o impact clinical efficacy and safety;
- was approved in the respective jurisdiction based on essentially the same original data package as the locally-approved reference product (Local Reference) as demonstrated via evidence in the public domain;
- subsequent manufacturing changes were regulated according to ICH Q5E principles to ensure that the clinical properties remain unchanged.

IGBA's reflection paper is broadly based on the scientific and regulatory case made in the Webster/Woollett publication "A Global Reference Comparator for Biosimilar Development". This is the first publication to put forward a coherent basis for selecting a comparator product that does not require conducting new bridging studies. We invite those interested to read this reflection paper in conjunction with the Webster-Woollett publication.

IGBA looks forward to discussing implementation of this Global Comparator Product framework with key stakeholders, and to optimizing its application. Additionally we will be developing a similar framework, tailored to generic and generic products with complex pharmaceutical forms.

Date: 13 September 2018

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. The IGBA is at the forefront of preserving sustainable competition within our industries, by stimulating competitiveness and innovation in the pharmaceutical sector; thereby, ensuring millions of patients around the world have access to high quality, pro-competitive medicines. For more details see the IGBA website at: www.igbamedicines.org

INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

[i] New terminology and concept presented by WHO at the WHO Pre-ICDRA meeting in Dublin 3-4 September 2018.

[ii] Christopher J. Webster Comment to FDA docket FDA-2018-N-2689 (FDA Part 15 Biosimilars Hearing at FDA on 5Sep18), available at https://www.regulations.gov/document?D=FDA-2018-N-2689-0005

[iii] A 'Global Reference' comparator for biosimilar development, Christopher J. Webster – Gillian R- Woollett _BioDrugs_published online 19 May 2017, Volume 31, Issue 4, pp 279–286 http://link.springer.com/article/10.1007%2Fs40259-017-0227-4

[iv] Interchangeability of Biosimilars: A European Perspective; Pekka Kurki et al, BioDrugs April 2017, Volume 31, Issue 2, pp 83–91, published online January 2017 https://link.springer.com/article/10.1007/s40259-017-0210-0

[v] A 'Global Reference' comparator for biosimilar development, Christopher J. Webster – Gillian R- Woollett _BioDrugs_published online 19 May 2017, Volume 31, Issue 4, pp 279–286 http://link.springer.com/article/10.1007%2Fs40259-017-0227-4

[vi] Gillian R. Woollett, MA, D.Phil *(corresponding author)*
Senior Vice President, FDA Regulatory Strategy and Policy
Avalere Inc, 1350 Connecticut Avenue, NW, Suite 900, Washington, DC 20036, USA
Email: gwoollett@avalere.com; Telephone: +1 (202) 207-1320

[vii] A 'Global Reference' comparator for biosimilar development, Christopher J. Webster – Gillian R- Woollett _BioDrugs_published online 19 May 2017, Volume 31, Issue 4, pp 279–286 http://link.springer.com/article/10.1007%2Fs40259-017-0227-4

[viii] Christopher J. Webster, Gillian R. Woollett (2018) Comment http://link.springer.com/article/10.1007/s40259-018-0297-y on "The End of Phase 3 Clinical Trials in Biosimilars Development?" by Xavier Frapaise https://doi.org/10.1007/s40259-018-0287-0

[ix] A 'Global Reference' comparator for biosimilar development, Christopher J. Webster – Gillian R- Woollett _BioDrugs_published online 19 May 2017, Volume 31, Issue 4, pp 279–286 http://link.springer.com/article/10.1007%2Fs40259-017-0227-4

[x] Sigrid Balser-Presentation "A Global Reference Product for Biosimilar Development"-WHO workshop, Copenhagen, July 5, 2017 (presentation on file)

[xi] Keynote Address by Commissioner Gottlieb to the 2018 FDLI Annual Conference, Mar 3, 2018, https://www.fda.gov/NewsEvents/Speeches/ucm606541.htm

[xii] Biosimilars cluster https://bit.ly/2MnrlZn

[xiii] IPRP website https://www.igdrp.com/

[xiv] FDA-EMA-DG Sante Confidentiality Commitment https://bit.ly/2lE12D9

[xv] ACSS website https://bit.ly/2QjTsLX

[xvi] International Conference of Drug Regulatory Authorities (ICDRA) https://bit.ly/1h5Y0i2

[xvii] WHO pilot procedure for prequalification of biotherapeutic products: rituximab and trastuzumab https://bit.ly/2Qnhy8P

[xviii] ISO Identification of Medicinal Products (IDMP) standards

Bridging studies required for a submission as a biosimilar product in selected countries[1] in addition to a complete comparability exercise conducted against the EU RP

complete comparability exercise against EU-authorized reference product	+ US [3]	+ JP [3]	+ CH [3]	+ AU [3]	+ SK [3]	+ TW [3]
Clinical: 2-way efficacy & safety study, EU vs biosimilar	Clinical: add. obligations (transition study for chronic indications; switching for nterchangeability	Clinical package includes either 1) sub-group analysis with JP subjects				
PK/PD: 2-way study: EU vs. Biosimilar (potentially 3-way required if bridging to US-licensed product in efficacy and safety study is requested)	PK/PD: 3-way: EU vs.US vs. Biosimilar	2) PK studies with JP subjects vs. JP reference product 3) PK studies with JP subjects vs authorized foreign reference product				
In-vivo[2]: 2-way: EU vs. biosimilar Includes: PK/PD, Toxicity, Efficacy, local tolerance, tissue cross reactivity						
In vitro: 2-way: EU vs. biosimilar Includes: approximately 10 functional assays, i.e. binding (e.g. target binding, receptor binding), mode-of-action (e.g. ADCC, CDC, apoptosis)	3-way: EU vs. US vs. Biosimilar	customized package including additional comparability against the local JP reference product	EU package plus comparability against CH reference product	EU package plus comparability against AU reference product	EU package plus comparability against SK reference product	EU package plus comparability agains TW reference product
Physico-chemical: 2-way: EU vs. biosimilar Includes: 30-60 quality attributes like primary structure, higher order structure, size variants, charge heterogeneity (e.g. C- and N-terminal), post-translational modifications (e.g. glycosylation, glycation, oxidation, deamination), comparative stability, forced degradation studies	3-way: EU vs. US vs. Biosimilar	customized package including additional comparability studies against the local JP reference product	EU package plus comparability against CH reference product	EU package plus comparability against AU reference prod	EU package plus comparability against SK reference product	EU package plus comparability against TW reference product

[1] = *Jurisdictions selected on the basis of their Agency's requirement of a comprehensive comparability exercise.*
[2] = *in vivo animal studies are becoming significantly less relevant for biosimilars and are expected to be considered unethical in the near future*
[3] = *sizes of the boxes represent the relative additional work needed to bridge to the requirements of thespecific region EU: European Union; US: United States; JP: Japan; CA: Canada; CH: Switzerland; AU, Australia; SK: South Korea; TW: Taiwan*

IGBA
INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION