



INTERNATIONAL GENERIC AND
BIOSIMILAR MEDICINES ASSOCIATION

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July 16, 2018

The Honorable Alex M. Azar II
Secretary
U.S. Department of Health and Human Services
200 Independence Ave. SW, Room 600E
Washington, DC 20201

**RE: HHS Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs [RIN 0991-ZA49]
IGBA submission**

Dear Secretary Azar,

The International Generic and Biosimilar Medicines Association (IGBA)ⁱ representing member associations from the USA (AAM), Canada (CGPA), South Africa (GBMSA), India (IPA), Jordan (JAPM), Japan (JGA), Europe (Medicines for Europe) and Taiwan (TGPA), as well as associate member associations from Australia (GBMA), Brazil (ProGenericos), Mexico (AMEGI) and Saudi Arabia (NCPI), very much welcomes the U.S. Food and Drug Administration (FDA) prioritizing ongoing efforts to improve the efficiency of the biosimilar and interchangeable product development and approval process as well as highly appreciates the development of new policies to improve the availability, competitiveness and adoption of biosimilars as affordable alternatives to originator (reference) biological products. We thank you for providing us with the opportunity to comment via this consultation and wish to comment on the chapter of “Development and Review Challenges”, which is a key focus of IGBA. We believe that seeking to improve access to quality medicines worldwide and to promote the quality, safety and efficacy of generic and biosimilar medicines is of utmost importance.

Development and Review Challenges

What specific types of information resources or development tools would be most effective in reducing the development costs for biosimilar and interchangeable products?



For full details on each association see the respective website

Some efficiency gains were achieved when the FDA included in its guidelineⁱⁱ the possibility of accepting some development data for biosimilars generated with reference (comparator) product versions licensed outside their own jurisdiction, provided the reference (comparator) product is authorized in a jurisdiction with similar high scientific and regulatory standards (e.g. EMA/EU) and appropriate bridging data are provided. Biosimilar sponsors are required to justify the relevance of the comparative data and establish an acceptable bridge to the US-licensed reference product.ⁱⁱⁱ However, bridging studies are at the discretion of the FDA.

Today, we invite the FDA to revisit their position and waive the requirement for bridging studies. This constitutes an important and effective development tool in reducing the development costs for biosimilars and interchangeable products, will increase competition and hence improve access to these live-saving innovative treatments.

The expected financial costs of comparator bridging studies for each jurisdiction vary between sources, but are estimated to be within a range of several hundred thousand to 1-2 million US dollars, depending on the requirement for clinical studies.^{iv} As an example, a 3-way comparison (e.g. Biosimilar vs US -licensed reference product vs EU-authorized reference product) typically requires 40-80 additional subjects in a clinical pharmacology study, which adds \$1-3 m additional cost^v. Due to the multiplier effect of required repetition by each biosimilar applicant and, more importantly, for the same US-licensed reference product, their collective costs are substantial. In addition, these bridging studies do not bring any added scientific value, nor increase the safety profile of the biosimilar product or the safety of the patient. Clinical bridging studies between the non-US sourced comparator and the US reference product potentially also exposes subjects to unnecessary, and therefore unethical, clinical trials.

The bridge between the US-licensed reference product version and the non-US reference (comparator) product version can indeed be established by the applicant in most cases without bridging studies, while remaining within the regulatory biosimilars framework. We consequently invite the FDA to develop, together with industry, a new regulatory framework by adopting the concept of global comparator product and allowing the waiving of bridging studies. IGBA is pleased hereby to share its approach.

Criteria allowing the waiving of bridging studies under defined circumstances

a) Definition of a comparator product

A comparator product is a reference biotherapeutic product used for head-to-head similarity/comparability studies with the biosimilar candidate to show similarity in terms of quality, safety and efficacy.^{vi}

b) Criteria to qualify as a comparator product

- The comparator product must have been authorized by a Stringent Regulatory Authority (SRA) i.e. *“in a jurisdiction that has a well-established regulatory framework and principles, as well as considerable experience of evaluation of the biotherapeutic products and post-marketing surveillance activities”^{vii}* (i.e. former ICH countries, called currently Stringent Regulatory Authorities by the World Health Organisation^{viii}). This means that the comparator product should be from *“a jurisdiction that has formally adopted International Council for Harmonization (ICH) guidelines. This criterion ensures that any comparability studies that have been conducted to support manufacturing changes of the reference have been conducted according to an internationally accepted process and standard, and that the reviewing authority is experienced in operating this standard”^{ix}*

- FDA may want to consider establishing a list of Regulatory Authorities meeting these criteria and for this purpose.
- The comparator product should have been approved according to international ICH standards with a complete registration dossier.
- 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).
- The comparator product must be fully identifiable by the approved product name, pharmaceutical form and qualitative composition.

c) Circumstances where bridging studies between the US-licensed Reference Product and the chosen Comparator Product can be waived

The comparator product

- must meet the criteria of the comparator product as described above;
- must have the same concentration of active pharmaceutical ingredient (API) as the US-licensed reference product;
- must have the same pharmaceutical form and route of administration as the US-licensed reference product (relevant for the biosimilar application)
- must have the same qualitative composition of excipients as the US-licensed reference product;
 - if the qualitative compositions of excipients are different, a justification should be provided ensuring that they have been assessed and are not expected to impact clinical efficacy and safety;
- was approved in the respective jurisdiction based on essentially the same original data package as the US licensed-reference product, including clinical safety and effectiveness data, and additionally 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.

d) Confidentiality arrangements between regulatory agencies provide a framework for cross-checking product information and making bridging studies obsolete in most cases

The existing US FDA, European Commission DG Santé and EMA confidentiality arrangements could serve as a template for confidentiality agreements with other regulatory agencies, falling within the scope of this framework. Such a confidentiality commitment allows for the exchange of confidential information related to licensed products as part of regulatory and scientific processes.

To avoid unethical clinical bridging studies, as well as the multiplication of bridging studies in general by several sponsors for the same reference product, FDA and EMA now have an established and highly confidential avenue to cross check information provided by the applicant regarding the comparator and the local reference product. By doing so, the FDA and the EMA will be able to confirm the veracity of this information

The updated statements of authority and confidentiality commitment from the United States Food and Drug Administration not to publicly disclose non-public information shared by the European Commission's Director General for Health and Food Safety and the European Medicines Agency, and vice versa, are clear regarding the possibility of exchanging information on licensed products.



- FDA is authorized under 21 C.F.R. § 20.89 to disclose non-public information to the European Commission's Directorate General SANTE and to the EMA regarding FDA-regulated drugs, including pre-and post-market activities, as appropriate, as part of cooperative law enforcement or cooperative regulatory activities.^x
 - Equally, the European Commission's Directorate-General SANTE and the EMA are authorized to disclose non-public information to the United States Food and Drug Administration (FDA) regarding EU-regulated drugs, including pre-and post-market activities, as appropriate, as part of cooperative law enforcement or cooperative regulatory activities.^{xi}
- e) **ISO Identification of Medicinal Product (IDMP) standards have been developed to allow the exchange of information between international agencies**

The ISO Identification of Medicinal Product (IDMP) standards are being implemented in the United States and in the EU with the aim of establishing a lasting international framework which allows the exchange of medicinal product information in a robust and reliable manner and which supports interoperability across regulatory and healthcare communities. Cross-checking information related to licensed products provided by the applicants will be increasingly facilitated via the IDMP route.

Clinical trials in biosimilar development

Another important and very efficient tool to reduce biosimilar development costs relates to large clinical trials which are very cost-intensive and nearly prohibitive for many biosimilar developers. We invite the FDA, in consultation with industry, to develop conditions under which biosimilar developments for monoclonal antibodies can be carried out without randomized comparative efficacy and safety trials. Purchasing the reference product required for those comparative studies alone may reach 50-70 million dollars and represents a major burden for biosimilar developers.^{xii} Innovative development concepts are the only means to maintain the sustainability of the development of biosimilars and this industry. IGBA is in the process of developing a Reflection Paper on clinical trials in biosimilar development and will share with the FDA and the EMA.

A global development framework for generic and complex generics


Generic and complex generics were also on the agenda of the June 2018 bilateral regulatory dialogue meeting in Brussels between the European Commission, the European Medicines Agency and the US Food and Drug Administration. « *The opportunity was taken to better understand the fundamentals of legal, regulatory and scientific requirements for approving generic and hybrid applications on both sides and to identify possible ways of streamlining the scientific requirements for such approvals with a particular focus on complex generics (FDA) and hybrids (EU)* ». ^{xiii} It is not uncommon for these products to require clinical endpoint studies to demonstrate their clinical equivalence, or that bioequivalence studies need to be performed in patient populations, which leads to longer and more expensive development processes. The sourcing of the comparator product can also be challenging in some cases. We consequently invite FDA to consider a global development approach to generics and to complex generics developments. Complex generics entail certain challenges during their development, as pointed out by Commissioner Gottlieb^{xiv}.

Conclusion

The waiving of bridging studies would be in line with the FDA's strong engagement in robust regulatory and scientific discussions to support global development of biosimilars. This revisited approach towards biosimilar approvals would also pave the road for the concept of **Global Comparator Product** and **true global development**. It also fits perfectly into the framework of the reinforced EU/US collaboration on medicines, expressed during the EC, EMA and FDA 2018 bilateral regulatory dialogue meeting in Brussels, on 18 and 19 June, which aims to advance scientific and regulatory excellence worldwide.^{xv}

Regarding biosimilars, IGBA will follow-up within the coming weeks with FDA and EMA separately regarding a detailed rationale for such a revisited global development framework as well as share an internal mapping of the bridging requirements by key agencies around the world.

Sincerely,



David R. Gaugh
Chair
International Generic and Biosimilar Medicines Association (IGBA)

About IGBA

The International Generic and Biosimilar Medicines Association (IGBA) was founded to strengthen cooperation between associations representing manufacturers of generic medicines from around the world. The IGBA is at the forefront of preserving sustainable competition within our industry, 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.

ⁱ IGBA website accessible via <https://www.igbamedicines.org/>

ⁱⁱ FDA Guidance for Industry "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009". Accessed: June 25, 2018. Available at: <https://bit.ly/2vll60y>.

ⁱⁱⁱ Dr. Steve Kozlowski/FDA, GPhA Fall Technical Conference October 2012

^{iv} A "Global Reference" Comparator for biosimilar development – Christopher Webster, Gillian Woollett; BioDrugs-published online: 19 May 2017 <https://bit.ly/2Cn4g3H>

^v Dr. Sigrid Balsler, "A global reference product for biosimilar development"; WHO workshop on biosimilars; 5 July 2017

^{vii} WHO SBP guidelines <https://bit.ly/2oU099B>

^{viii} WHO/SBPQ&A/Draft/Dec 2017

^{ix} WHO Guidance Document 15 February 2017 Clarification with respect to a Stringent Regulatory Organisation as applicable to the Stringent Regulatory Authority (SRA) Guideline

^x A "Global Reference" Comparator for biosimilar development – Christopher Webster, Gillian Woollett; BioDrugs-published online: 19 May 2017 <https://bit.ly/2Cn4g3H>

^{xi} FDA to EMA and DG Santé, Confidentiality Commitment <https://bit.ly/2IE12D9> ; accessed on 28 June 2018

^{xii} EMA website-United States-Confidentiality arrangement <https://bit.ly/2N1mTRv>; accessed on 28 June 2018

^{xiii} A biosimilar sponsor's calculation (on file)

^{xv} EMA website: Reinforced EU/US collaboration on medicines <https://bit.ly/2yzZLq6>; accessed on 28 June 2018