INTERNATIONAL GENERIC AND
BIOSIMILAR MEDICINES ASSOCIATION

IGBA position on Streamlined Development

Position:

Today's regulatory science supports the development of biosimilars based on analytical (physicochemical and functional) data and a clinical pharmacokinetic study (which includes safety and immunogenicity data) alone. Clinical comparative efficacy studies using conventional efficacy and/or pharmacodynamic endpoints are much less sensitive to detect meaningful differences between a candidate biosimilar and the reference product, hence they do not provide additional regulatorily-relevant information.

This position, to forego the mandate to conduct routine comparative clinical efficacy studies, is in principle applicable to all well-characterized biosimilars. Such an approach is consistent with the established regulatory science.

When the reference product is known to be the same across jurisdictions (for example, because it was approved in each jurisdiction based on the same pivotal clinical studies) and when evidence to support this is publicly available, there should be no requirement for studies to be repeated with locally sourced reference material.

This position fits within the revisions to the WHO Guideline, and would support global access and affordability to quality, safe, and effective biosimilars.

Rationale:

1. Regulatory science today enables streamlined biosimilar development. Analytical studies complemented by clinical pharmacokinetic studies are much more sensitive to detect differences between a candidate biosimilar and a reference product than comparative efficacy studies using conventional or pharmacodynamic endpoints.
2. The experience with biosimilar development and regulatory assessments in highly regulated markets has shown that demonstrating efficacy in clinical comparative efficacy studies has not been predictive of an approval of biosimilars.
3. The concern that in the absence of comparative efficacy and safety results, a biosimilar candidate might be inappropriately approved based on evidence from quality and clinical PK studies only is not supported by latest data.

It should be an obligation to avoid exposing human subjects to clinical studies which do not contribute to regulatory decision making.

How is comparable efficacy ensured?

Outline of argument

- Three “safety nets” ensure comparable efficacy related to the active pharmaceutical ingredient: 1. Physicochemical comparison, 2. Binding assays, 3. Cell-based bioassays (where relevant for Mechanism of Action)
- These assays are done with high precision and accuracy, and they are much more sensitive than clinical endpoints to detect meaningful clinical differences between a candidate biosimilar and its reference product’. Robust analytical data, obtained with state of the art and orthogonal methods is a routine requirement already today and is an established and reliable basis for regulatory decision making for all biologics.
- Differences in physicochemical quality attributes can also be readily assessed through functional characterization (i.e. binding assays and cell-based bioassays)
- Clinical PK study ensures evaluation of comparable drug absorption and distribution, which is essential for comparable efficacy.

Experience with biosimilar development and evaluation has been examined, and the evidence shows that demonstrating efficacy in clinical comparative efficacy studies has not been predictive of an approval of biosimilars in highly regulated markets..

How is comparable safety ensured?

Outline of argument:

- Biologics-related safety is associated with on-target effects, which are a consequence of the high specificity with which recombinant biotherapeutics interact with physiological targets (e.g. target, receptors)
- Comparable pharmacological activity translates into comparable biologic-related safety.
- Process-related safety is ensured by today’s pharmaceutical quality standards for biologics (e.g. limits for contaminants, toxic process reagents, safety of excipients, leachates and extractables)
- Safety and immunogenicity data obtained in clinical PK studies has typically been confirmed in subsequent clinical efficacy studies.
- A clinical pharmacokinetic study provides additional confirmatory clinical safety and immunogenicity data and is an extra assurance for registration, over and above the robust analytical comparability data routinely required .
- Experience with biosimilar development and evaluation shows that robust demonstration of analytical comparability is predictive of comparable efficacy, safety, and immunogenicity.

How is comparable immunogenicity ensured?

Outline of argumentation:

- Comparable immunogenicity depends upon the identical amino acid sequence, such that the biosimilar presents the same T-cell epitopes (binding sites) as the reference product.,
- Impact of differing formulations and/or excipients on immunogenicity can be readily evaluated by a risk assessment and in a comparative clinical PK study.
- Control of risk factors which may potentially increase unwanted product related immunogenicity, such as aggregates or non-human glycans (e.g. alfa-Gal motiv) are ensured by today’s quality norms.
- Comparative clinical pharmacokinetic study is also designed to provide additional similarity data of the immunogenicity profiles of candidate biosimilar and reference product, through assessment of incidence and titre of anti-drug antibodies (including neutralizing antibodies).

In which cases might an additional clinical study be warranted?

Outline of argumentation

- In cases of a new indication, posology, or route of administration, which does not exist for the reference product.

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.

References

Experience with biosimilar development and regulatory assessments in highly regulated markets is summarized in the following publications:

- Kirsch-Stefan et al. BioDrugs 37, 855–871 (2023). https://doi.org/10.1007/s40259-023-00631-4
- Guillen et al. Clin Pharmacol Ther, 2023;113, 108-123. https://doi.org/10.1002/cpt.2785
- Bielsky et al. Drug Discov. 2020;25, 1910-1918 doi: https://doi.org/10.1016/j.drudis.2020.09.006
- Schiestl et al. BioDrugs 2020;34, 97–306; https://doi.org/10.1007/s40259-020-00422-1
- Cohen et al BioDrugs 2023; Future Evolution of Biosimilar Development by Application of Current Science and Available Evidence: The Developer's Perspective. https://doi.org/10.1007/s40259-023-00619-0

The latest study by Kirsch Stefan et al reviewed marketing applications for 33 monoclonal antibodies and 3 antibody derived fusion proteins evaluated by EMA up to November 2022. The data source included public EPARs and confidential Day 120 assessment reports. Additionally, the authors performed a detailed analysis of analytical biosimilarity data and clinical comparability data of 4 rituximab and 7 trastuzumab biosimilars (which add to the previous analysis of 5 bevacizumab and 7 adalimumab biosimilars). The authors concluded that:

- "In the regulatory assessment of 33 mAbs and three fusion proteins evaluated by EMA, we found no instance where seemingly negative clinical data, including failed efficacy trials, led to a negative overall decision."
- "In the analysis of quality and clinical packages of trastuzumab and rituximab biosimilar candidates, in no cases were clinical trial data necessary to resolve residual uncertainties regarding the quality part."
- "The concern that, in the absence of comparative efficacy and safety results, a biosimilar candidate might be inappropriately approved based on quality data only is not supported by our findings. The analytical and biological results can be considered predictive for the clinical performance of the biosimilar candidates."
- "We conclude that a sufficiently robust analytical/functional similarity package, together with a PK trial capturing data on safety and immunogenicity would be sufficient for the purpose of regulatory decision making for biosimilar mAbs and fusion proteins."

Relevant literature on safety and immunogenicity

- Kurki et al. BioDrugs 31, 83–91 (2017). https://doi.org/10.1007/s40259-017-0210-0
- Kurki et al. Drugs 81, 1881–1896 (2021). https://doi.org/10.1007/s40265-021-01601-2