FDA Clarifies Clinical Pharmacology Studies to Support Biosimilarity

The US Food and Drug Administration (FDA) recommends taking a progressive, "stepwise" approach when developing data needed to demonstrate biosimilarity, advice the agency underscores in final industry guidance released in December 2016. Clinical pharmacology studies form part of the approach, as they can help to reduce "residual uncertainty" about differences between the reference product and the proposed biosimilar, and establish whether those differences impact the biosimilar's safety and effectiveness.

As noted in *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product*, the degree of residual uncertainty at each step determines the need for additional studies. The final guidance is intended to advise sponsors of proposed biosimilars on the design of clinical pharmacology studies that can support FDA approval, and on the use of data derived from such studies. Comparative analytical data form the foundation for a biosimilar development programme, but clinical pharmacology studies build on that foundation and "normally" are critical to demonstrating biosimilarity.

The new guidance finalises a May 2014 draft document by the same name. Changes evident in the final version "are not substantive," according to an FDA notice in the December 29, 2016 *Federal Register*.

The final guidance identifies issues to consider when using clinical pharmacology studies to support biosimilarity claims (e.g., assessing exposure/response, the integrity of various bioanalytical methods used in pharmacokinetic [PK] and pharmacodynamic [PD] studies), addresses how to develop clinical pharmacology data (e.g., study design, dose selection), and advocates the appropriate use of simulation tools to design studies and analyse data. The following highlights several of the agency's recommendations.

Reference products – Clinical pharmacology studies conducted to demonstrate a product's biosimilarity and support its US regulatory approval typically involve direct comparisons of the proposed biosimilar with a US-licensed reference product. However, sponsors may be able to justify using a non-US-licensed comparator product "in certain studies" to support the demonstration of biosimilarity to a US-licensed reference product. Data from the sponsor should provide scientific justification and establish "an acceptable bridge" to the US-licensed reference.

PD Biomarkers – To measure PD response, use a single or composite biomarker that demonstrates the characteristics of the product's target effects. When choosing the PD biomarker(s), consider five characteristics:

- Time of onset of change in the biomarker relative to dosing and, when dosing is discontinued, time of its return to baseline.
- The dynamic range of the biomarker over the exposure range to the biological product.
- The sensitivity of the biomarker to differences between the proposed biosimilar and the reference product.
- The relevance of the biomarker to the drug's mechanism of action.
- The analytical validity of the PD biomarker assay.

If PD biomarkers are not sufficiently sensitive or specific to detect clinically meaningful differences, the FDA advises using the derived PK parameters as the primary basis for evaluating similarity, and using the PD biomarkers to augment PK data.

FDA Assessments of Analytical Quality and Similarity

The sponsor should conduct "extensive and robust" comparative structural and functional studies (e.g., bioassays, binding assays, studies of enzyme kinetics) to evaluate whether the proposed biosimilar and its reference product are highly similar. FDA assessments of such studies may assert:

- **Insufficient analytical similarity.** Further development through the 351(k) pathway is not recommended, although the FDA may suggest actions to minimise or eliminate differences.
- **Analytical similarity** with residual uncertainty. Additional information, analytical data, or other studies are required to determine whether observed analytical differences fall within an acceptable range.
- **Tentative analytical similarity.** Results to date of comparative analytical characterisation "permit high confidence" in the similarity of the products. It may now be appropriate for the sponsor to conduct targeted and selective animal and/or clinical studies to resolve residual uncertainty.
- **Fingerprint-like analytical similarity.** The results of "extremely sensitive," integrated, multi-parameter approaches allow "very high-level" confidence in analytical similarity. Taking a more targeted, selective approach to animal and/or clinical studies to resolve residual uncertainty would be appropriate.

Bioanalytical Methods to Evaluate PK and PD Properties

The FDA identifies three types of assays "of particular importance" for biosimilar product development: ligand binding assays, concentration and activity assays, and PD assays.

Safety and Immunogenicity

Sponsors should collect and evaluate safety and immunogenicity data from clinical pharmacology studies. Immunogenicity assessments should include relevant, non-immunocompromised patient populations. When incorporating safety and immunogenicity measurements in clinical pharmacology studies, sponsors should consult publicly available information about the reference product's safety and immunogenicity profile. For example, in cases where a reference product carries a known risk of immune-mediated toxicity, a sponsor should develop relevant antibody assays in advance to enable "real-time" assessments of immunogenicity.

Study Designs for Evaluating Clinical PK and PK Similarity

The FDA stresses that two study designs are particularly relevant when evaluating clinical PK and PD similarity: crossover designs and parallel study designs.

- The agency prefers a single-dose, randomised, crossover study for assessments of PK similarity, and recommends the crossover design if a product has a short half-life, a rapid PD response, and if immunogenicity incidence is expected to be low. For assessments of PD similarity, a multiple-dose crossover study "may be appropriate" if the PD effect is delayed (i.e., does not parallel the PK profile of the single dose). When using a crossover design, consider when immunogenicity appears and

disappears, and how it relates to the washout period.

- The FDA considers the parallel group design appropriate for products with a long half-life or where repeated exposure causes increased immune response (which can affect assessments of PK and/or PD similarity). The parallel group design is also appropriate "for diseases that exhibit time-related changes" linked to drug exposure.

Dose Selection – Sponsors should choose the most sensitive dose, able to detect and evaluate differences in the PK and PD profiles of the products. While the approved dose of the reference product may be the right choice for a study conducted in a patient population, if PD is to be measured or if the study is to be conducted in healthy subjects, the FDA typically advises using "a lower dose on the steep part of the exposure-response curve." The final guidance describes additional situations in which an alternative dose (e.g., a range of doses) may be useful or appropriate. When appropriate, sponsors should use PD biomarkers to assess PK/PD similarity.

PK Measures – Sponsors should obtain all PK measures for both the proposed biosimilar and the reference, including measures of peak concentration (C^{max}) and total area under the curve (AUC) in a relevant biological fluid. The guidance addresses how to calculate these measures in various types of studies, and clarifies the situations in which they are considered primary, co-primary, and secondary endpoints.

PD Measures – The FDA notes that, "in certain circumstances," clinical PK and PD data demonstrating similar exposure and response between a proposed biosimilar and its reference may be enough to assess the presence of clinically meaningful differences; an assessment of immunogenicity is still necessary, however. The biosimilarity assessment should be based on similarity in PD; when the PD measure has a "wide dynamic range," the biomarker used should reflect the mechanism of drug action. Comparisons of PD biomarker(s) should be based on determinations of area under the effect curve (AUEC).

Statistical Comparisons of PK and PD Results to Assess Product Similarity

The FDA advises taking an average-equivalence statistical approach when comparing PK and PD parameters for both replicate and non-replicate design studies. This entails calculating a 90% confidence interval (CI) for the ratio between the geometric means of the parameters of the proposed biosimilar and the reference product. The calculated CI should fall within an acceptable limit; according to the FDA, 80–125% is a suitable starting point. Sponsors proposing other limits should justify them to the FDA.

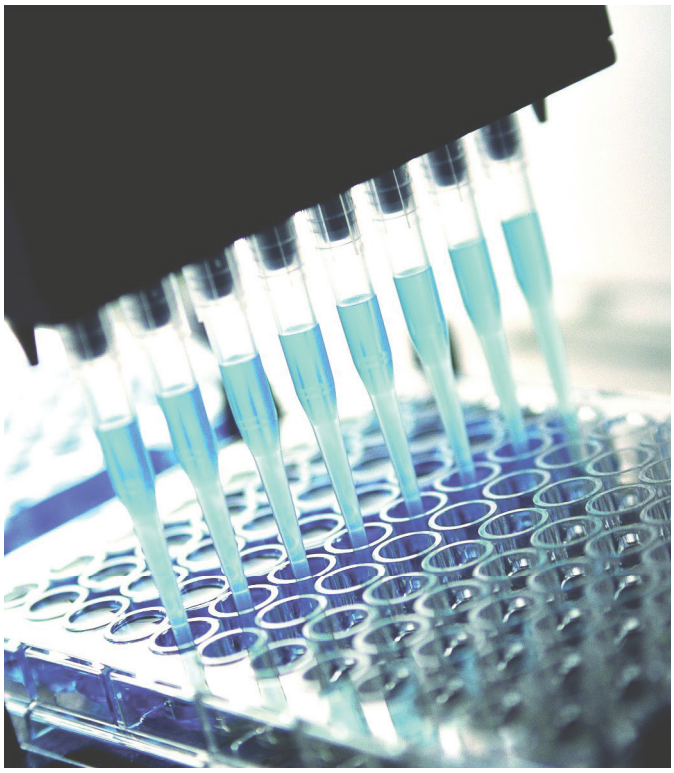
Defining "Biosimilar"

As defined by section 351(k) of the Public Health Service (PHS) Act, a biosimilar product is highly similar to its reference product, "notwithstanding minor differences in clinically inactive components." That is, while minor differences between the biosimilar and its reference are allowed, they must not be "clinically meaningful" in terms of safety, purity, and potency.

Such allowable differences distinguish biosimilars from generics, which are bioequivalent (i.e., identical) to their brand-name drug products: they have the same active ingredient, as well as the same dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. Drugs typically are manufactured via chemical processes. Biologics are produced in living organisms and cannot be copied identically.

Section 351(k) also outlines the FDA's abbreviated pathway for licensing biosimilar products. Demonstrations of biosimilarity typically rely on data from analytical, animal, and clinical studies, including assessments of immunogenicity, PK, and PD. To date the FDA has approved four biosimilars:

- Zarxio (filgrastim-sndz), by Sandoz Inc, a biosimilar to Neupogen (filgrastim), by Amgen Inc; on March 3, 2015.
- Inflectra (infliximab-dyyb), by Celltrion, Inc, a biosimilar to Remicade (infliximab), by Janssen Biotech, Inc; on April 5, 2016.
- Erelzi (etanercept-szzs), by Sandoz Inc, a biosimilar to Enbrel (etancercept), by Amgen, Inc; on August 30, 2016.
- Amjevita (adalimumab-atto), by Amgen Inc, a biosimilar to Humira (adalimumab), by AbbVie Inc; on September 23, 2016.



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