Pharmacodynamic Biomarkers Evidentiary Considerations for Biosimilar Development and Approval

David G. Strauss1,*, Yow-Ming Wang2, Jeffry Florian1 and Issam Zineh3

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from a US Food and Drug Administration (FDA)-approved reference product. The development and approval of biosimilars is critical to enhancing the availability of safe, effective, and affordable treatment options for patients. Utilization of pharmacodynamic (PD) biomarkers can help streamline biosimilar development programs as the current process can be costly and time-consuming. Whereas PD biomarkers have not been prominently used across biosimilar approvals to date, moving forward, there is ample opportunity to increase the use of PD biomarkers in biosimilar development programs in place of comparative clinical studies with efficacy end point(s). This includes utilizing PD biomarkers that were not used as surrogate end points in approval of reference products. This mini-review summarizes how PD biomarkers have been used in biosimilar development programs to date and then discusses evidentiary considerations for PD biomarkers. In addition, study design considerations for clinical pharmacokinetic and PD assessment of proposed biosimilars are discussed. This included conducting three clinical studies to address information gaps about PD biomarkers for biosimilars and inform general methodological best practices. In summary, enhancing our understanding of key evidentiary considerations and optimal study designs for incorporating PD biomarkers in the evaluation of proposed biosimilars can help bring more treatment options to patients faster.

To promote a robust, competitive market for biological products, the US Food and Drug Administration (FDA) is focused on improving the efficiency of biosimilar development and approvals. Because comparative clinical studies can be costly and time-consuming, the FDA is conducting research to inform the FDA’s thinking regarding use of pharmacodynamic (PD) biomarkers to demonstrate biosimilarity, which can either streamline or eliminate the need for comparative clinical studies with efficacy end points.

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an FDA-approved reference product. An abbreviated approval pathway for biosimilars and interchangeable biological products was established with the enactment of the Biologics Price Competition and Innovation Act of 2009, which added the 351(k) Biologics License Application (BLA) pathway to the Public Health Service Act. The FDA recommends that sponsors should evaluate the extent to which there is residual uncertainty about biosimilarity of the proposed product and generate data and information, such as those outlined below to address that uncertainty1,2:

- Comparative analytical assessments should include extensive structural and functional characterization of both the proposed product and the reference product.
- The sponsor should consider the role of animal data in providing additional support for demonstrating biosimilarity.
- The sponsor should conduct comparative human pharmacokinetic (PK) and PD studies (if there is a relevant PD measure(s)) and compare the clinical immunogenicity of the two products in an appropriate study population.
- If there is residual uncertainty about biosimilarity, additional clinical data may be needed to adequately address that uncertainty. This has often been addressed by conducting comparative clinical studies with efficacy end points.

USE OF PHARMACODYNAMIC BIOMARKERS IN APPROVED BIOSIMILAR DEVELOPMENT PROGRAMS

As outlined in the FDA biosimilar guidance documents1,2, biosimilars may be approved based on PK and PD similarity studies without a comparative clinical study in patients. Reliance on PK and
MINI-REVIEW

PD similarity data allows for shorter and less costly clinical studies that can often be conducted in healthy participants. Additionally, evaluating PK and PD similarity to detect differences between a proposed biosimilar and its reference product may be more sensitive than evaluating clinical efficacy end point(s), should differences exist. As an example, a quantitative analysis showed the PD biomarker, the area under effect-time curve of absolute neutrophil count, is a more sensitive end point than the clinical efficacy end point of duration of severe neutropenia.3

Although PK similarity has been evaluated in every FDA-approved biosimilar with systemic exposure to date, as of June 2022, only 11 of 36 approved biosimilars have included PD similarity data to support demonstration of no clinically meaningful differences between proposed biosimilar products and reference products (specifically, 3 filgrastim biosimilars, 4 pegfilgrastim biosimilars, 2 insulin glargine biosimilars, and 1 epoetin biosimilar). Notably, these products all had well-characterized PD biomarkers (absolute neutrophil count for filgrastim products and pegfilgrastim products; CD34+ cells for filgrastim products; reticulocyte count and hemoglobin level for epoetin alfa products; and glucose infusion rate for insulin glargine products).

CONSIDERATIONS FOR PD BIOMARKER ASSESSMENT AND PK AND PD SIMILARITY STUDY DESIGN

Criteria for PD biomarkers intended to support a demonstration of biosimilarity are inherently different from criteria for surrogate biomarkers used to support new drug approvals.4 Because the purpose of a biosimilar development program is to demonstrate similarity to the reference product and not to independently establish the safety and effectiveness of a biosimilar product, a correlation between the PD biomarker and clinical outcomes, while beneficial, is not required.1,2 This provides opportunities for biomarkers that were used as secondary and exploratory end points in new drug development programs to inform biosimilar programs. There is also an opportunity to identify new PD biomarkers or fill information gaps on existing biomarkers to facilitate the use of PD biomarker data in clinical pharmacology studies in lieu of comparative clinical efficacy studies to support a demonstration of biosimilarity. Although the focus of this paper is selecting and using PD biomarkers for demonstration of biosimilarity, similar principles could be applied to demonstrating interchangeability.

The FDA guidance describes five characteristics for PD biomarkers (Figure 1) to assist sponsors planning to use PD biomarkers as components of a biosimilar development program.2 PD similarity data to demonstrate no clinically meaningful differences in a biosimilar development program can be based on a single scientifically appropriate PD biomarker or more than one PD biomarker.2 Data to demonstrate biomarker suitability may be obtained from regulatory documents for the reference product and other approved biosimilar products (for example, product labels and review documents available at Drugs@FDA). Data to demonstrate PD biomarker suitability may also be obtained from peer-reviewed publications, including systematic reviews, research articles, clinical case studies, and reports on the use of real-world data and could include data for products with similar mechanism(s) of action as the reference product. As outlined in Table 1, such data can facilitate candidate PD biomarker selection, provide data to address the five characteristics of a PD biomarker and, if needed, inform the design of a pilot study to fill information gaps about the PD biomarker. Modeling and simulation using dose- or exposure-response data may provide information on dose–response relationships, sensitive dose ranges, variability in PD biomarker responses, and sensitivity of study populations with respect to PD biomarker responses.3,5–9

Figure 1 Five essential characteristics of a PD biomarker for biosimilars (adapted from Li et al.3). PD, pharmacodynamic
MINI-REVIEW

PD biomarker characteristic #1: The relevance of the PD biomarker to the mechanism of action of the drug (to the extent that the mechanism of action is known for the reference product)

Whereas the FDA biosimilar guidances outline a PD biomarker is not required to be a surrogate end point or have an established relationship with clinical efficacy outcomes, assessing the relevance of the PD biomarker to the drug’s mechanism of action is one of the five characteristics. As seen in Figure 2, epoetin alfa engages with the erythropoietin (EPO) receptor on erythroid progenitor cells (target engagement), which initiates erythropoiesis leading to an increase in reticulocyte count (PD biomarker 1), which subsequently results in an increased red blood cell count and hemoglobin concentration (PD biomarker 2). The increased hemoglobin concentration then decreases or eliminates the need for red blood cell transfusions and the adverse sequela of anemia (clinical outcomes). Both reticulocyte count and hemoglobin concentration are PD biomarkers relevant to the mechanism of action of the reference product and were considered acceptable biomarker(s) for PD similarity evaluation in the FDA review and approval of epoetin alfa-epbx. Although target engagement at the EPO receptor is the critical first step for epoetin alfa’s intended pharmacologic effect, target engagement by itself has generally not been considered an adequate PD biomarker that would obviate the need for a comparative clinical study in patients.

Table 1 Potential evidence to address the five characteristics for a PD biomarker to be used in PD similarity studies

| Characteristics of a PD biomarker, as outlined in FDA biosimilarity clinical pharmacology guidance | Potential evidence to address each characteristic |
|---|---|
| #1: The relevance of the PD biomarker to the mechanism of action of the drug (to the extent that the mechanism of action is known for the reference product) | Data demonstrating the relevance of a PD biomarker (and the pharmacological effect it illustrates) to all or some of a product’s known mechanisms of action |
| #2: The time of onset of change in the PD biomarker relative to dosing and its return to baseline with discontinuation of dosing | Data demonstrating the full PD biomarker response profile that includes the time of onset, duration of response, and the time of return to baseline. |
| #3: The dynamic range of the PD biomarker over the exposure range of the biological product | PD response data obtained from a range of doses that characterize the range of PD biomarker responses to demonstrate dynamic range, dose dependence, and magnitude of response. The PD responses associated with the range of concentrations in observed PK profile are appropriately captured. |
| #4: The sensitivity of the PD biomarker to differences between the proposed biosimilar product and the reference product | Dose–response relationship data to determine the sensitive dose range, and estimate the variability in PD biomarker response |
| #5: The analytical validity of the PD biomarker assay | Data demonstrating the accuracy, precision, specificity, sensitivity, and reproducibility of the PD biomarker assay |

FDA, US Food and Drug Administration; PD, pharmacodynamic; PK, pharmacokinetic.

*Such data can come from clinical investigations, published literature, and/or modeling and simulation.

Figure 2 Mechanism of action and representative temporal profiles of PD biomarkers after epoetin alfa treatment. EPO, erythropoietin, PD, pharmacodynamic.
Some drugs have complex pharmacology with many measurable PD biomarkers (for example, immunomodulating agents for neurogenerative disorders). When a drug exhibits complex pharmacology, identifying a single PD biomarker that reflects the mechanism of action can be challenging. In such cases, it may be appropriate to use a panel of PD biomarkers to contribute to the totality of evidence in supporting the overall biosimilarity assessment.

**PD biomarker characteristic #2: The time of onset of change in the PD biomarker relative to dosing and its return to baseline with discontinuation of dosing**

A well-characterized temporal response profile captures the time of onset of the PD biomarker response relative to dosing and its return to baseline upon discontinuation of dosing, in addition to the magnitude of change over time that is associated with the temporal PK profile (Figure 3). PD biomarkers may exhibit an early onset, with an initial PD response measured over hours or days, or a late onset, with an initial PD response observed after several days or weeks. Early-onset PD biomarkers may allow for shorter study durations and may also afford higher sensitivity (as with reticulocyte count). Late-onset PD biomarkers may require longer study periods (as with hemoglobin). In certain cases, inclusion of both early- and late-onset PD biomarkers may be appropriate to demonstrate no clinically meaningful differences. Data included within the approved 351(k) BLA for the biosimilar epoetin alfa-epbx included both early- and late-onset PD biomarkers (reticulocyte count and hemoglobin, respectively; Figure 2). Of note, the PD similarity assessment with hemoglobin was only assessed until 30 days after initiation of dosing. In this case, the FDA review did not consider it necessary to follow the hemoglobin concentration until the late-onset biomarker returned to baseline after discontinuation of dosing. It is not a general requirement to include both early- and late-onset PD biomarkers, and biosimilar applications can rely on PD similarity data from a single PD biomarker for approval (for example, absolute neutrophil count for pegfilgrastim biosimilars). Overall, designing an effective PD similarity study depends on understanding the temporal response profiles of candidate PD biomarker(s) to inform study duration and the timing and frequency of PD biomarker measurements.

**PD biomarker characteristic #3: The dynamic range of the PD biomarker over the exposure range to the biological product**

PD biomarkers with a large dynamic range over the range of drug concentrations observed in PK evaluation allow for evaluation of the dose–response relationship to inform the PD similarity study dose selection. When dose–response data are limited or not available for a proposed PD biomarker, a pilot study examining multiple dose levels can be conducted to establish or better define the dose–response relationship. Alternatively, published data that may include clinical investigations or PK/PD models for the reference product provide another means of evaluating dose–response. Modeling dose–response data can help illustrate the dose–response relationship, identify the sensitive dose range, and justify dose selection, for example, by illustrating that proposed doses are not on the plateau of the dose–response curve (Figure 3). Factors to consider while selecting a dose to study in a PD similarity study may include the variability of the PD biomarker data, the study population (healthy subjects or patients), safety concerns, study duration, and sensitivity of the dose to identify potential differences in the PD biomarker response between the proposed biosimilar and reference product. In many cases, PK and PD similarity can be assessed together in a single clinical study, particularly when the same dose and population is acceptable for those evaluations. Understanding dynamic range information (for example, dose–response and exposure-response) for a PD biomarker helps determine dosing that may or may not result in a measurable and differentiable PD effect.

Figure 3 Example temporal and dose–response data for a PD biomarker to inform identification of a sensitive dose. PD, pharmacodynamic
The reliability of PD biomarker data depends on the quality of the PD biomarker assay; as such, it is important to demonstrate the bioanalytical validity of PD biomarker assays. Evidentiary standards for bioanalytical assay validation are outlined in the FDA's Bioanalytical Method Validation Guidance. In addition, the FDA’s biosimilarity clinical pharmacology guidance states that a PD biomarker assay is expected to be accurate, precise, specific, sensitive, and reproducible. Whereas the FDA’s guidance mentioned that the approach used for drug assays should be the starting point for validation of biomarker assays, the guidance also clarifies the FDA realizes that some characteristics may not apply or that different considerations may need to be addressed. It is essential to develop scientifically sound approaches to demonstrate the validity of bioanalytical methods appropriate for the technologies used to measure the PD biomarker levels.

A fit-for-purpose approach may be applied when demonstrating the analytical validity of a bioanalytical method according to the stage of product development. For example, a PD biomarker assay used in pilot studies to select candidate PD biomarkers may not require full validation, but full validation is needed if the assay is used to support regulatory decision making. Nonetheless, assay quality and performance are important considerations when analyzing PD biomarker data from pilot studies because poor assay performance can impact design of a subsequent PD similarity study. Although an assay’s performance characteristics might differ depending on the specific biomarker attributes (for example, stimulatory or inhibitory, free vs. bound forms, and total vs. active forms), a suitable PD biomarker assay will be sensitive and specific in quantifying the PD biomarker response with low variability and yield a wide dynamic range.

**Additional considerations: Statistical analysis and utility of modeling and simulation**

As discussed above, modeling and simulation tools can be useful when designing a PK and/or PD similarity study, for example, by characterizing the dose–response relationship to support the selection of a dose that is sensitive to detect potential differences between the proposed biosimilar and reference product. In addition, the assessment of PK and PD similarity of a proposed biosimilar and its reference product is based on statistical evaluation. The FDA’s biosimilarity clinical pharmacology guidance recommends using an average equivalence statistical approach to compare PK and PD parameters between two products. This involves calculating a 90% confidence interval for the ratio between the geometric means of the parameters of the proposed biosimilar and its reference product. To establish PK or PD similarity, the calculated confidence interval should fall within a prespecified acceptable limit. According to the guidance, an appropriate starting point for an acceptable limit for the confidence interval of the ratio is 80–125%; however, other limits may be proposed if scientifically justified. If information exists that links a PD biomarker to clinical end points, modeling and simulation can be used to justify alternative limits for PD similarity (Figure 4).

**CURRENT FDA ACTION ON PD BIOMARKER ASSESSMENT FOR BIOSIMILAR DEVELOPMENT**

To support the development of biosimilars and to increase scientific and regulatory clarity for the biosimilar development community, the FDA released its Biosimilars Action Plan in July 2018, which included the key action to create information resources and development tools that can assist biosimilar sponsors in developing high quality biosimilar and interchangeable products using state-of-the-art techniques. Under the Biosimilars Action Plan, the FDA has been conducting applied research to advance the science around PD biomarkers for biosimilars and inform evidentiary strategies and criteria to bring greater clarity to the FDA’s expectations for the use of PD biomarkers to support a demonstration of biosimilarity. As a part of this action plan, the FDA conducted three clinical pharmacology studies, each with two marketed originator biologics with the same mechanism of action and its reference product. To establish PK or PD similarity, the geometric means of the parameters of the proposed biosimilar and its reference product. To establish PK or PD similarity, the calculated confidence interval should fall within a prespecified acceptable limit. According to the guidance, an appropriate starting point for an acceptable limit for the confidence interval of the ratio is 80–125%; however, other limits may be proposed if scientifically justified. If information exists that links a PD biomarker to clinical end points, modeling and simulation can be used to justify alternative limits for PD similarity (Figure 4).

These studies were designed to collect intensive PK and PD biomarker data at several dose levels for each of the six drugs studied, enabling the evaluation of PD biomarkers and model-based approaches for analyzing data to assess dose–response relationship. These studies exceeded typical pilot study designs in terms of number of dose levels, subjects studied, and samples collected to ensure sufficient information would be available to evaluate different analysis methods and novel methods for PD biomarker identification.
As discussed in the FDA guidance, PD biomarker(s) used to measure PD responses can be single PD biomarkers or composites of multiple relevant PD biomarkers that effectively demonstrate the characteristics of a product’s target effects. Using broader panels of PD biomarkers capturing multiple pharmacological effects of the product may provide additional value, in particular for identifying candidate PD biomarkers for biologic products where potential PD biomarkers may not be evident from the development program of reference product. In addition to analyses focusing on known PD biomarkers of interest, the FDA is assessing the utility of proteomic methods and other technologies for this purpose.

Data from these studies are expected to address information gaps about the five essential characteristics of a PD biomarker for biosimilars and inform general methodological best practices across other biological products for pilot study design and PD biomarker analysis. In addition to characterizing the values and variability of standard PD metrics and model parameters of prespecified biomarkers, these studies aim to contextualize the utility of omics technologies to identify and characterize biomarkers that could be used for a PD similarity assessment. The three primary results papers and a separate proteomics analysis are reported separately in this journal.13–15

SUMMARY

The development and approval of biosimilars is critical to enhancing the availability of safe, effective, and affordable treatment options for patients. Utilization of PD biomarkers can help streamline biosimilar development programs as the current process can be costly and time-consuming. Whereas PD biomarkers have not been prominently used across biosimilar approvals to date, moving forward, there is ample opportunity to increase the use of PD biomarkers in biosimilar development programs in place of comparative clinical studies with efficacy end point(s). This includes utilizing PD biomarkers that were not used as surrogate end points in approval of reference products. Using PD similarity data in biosimilar development can benefit public health by bringing additional safe, effective, and affordable treatments to patients faster.

ACKNOWLEDGMENTS

This paper summarizes information from a background document included as part of the FDA/Duke-Margolis “Pharmacodynamic Biomarkers for Biosimilar Development and Approval” workshop from September 2021, the FDA guidance documents related to biosimilars and biomarkers, and the FDA’s ongoing applied regulatory science activities to inform use of PD biomarkers for biosimilar development. The authors would like to thank the staff from Booz Allen Hamilton and the FDA Office of Clinical Pharmacology and Office of Therapeutic Biologics and Biosimilars who contributed to these activities as part of their duties.

FUNDING

Funding provided by the US Food and Drug Administration.

CONFLICT OF INTEREST

As an Associate Editor for Clinical Pharmacology & Therapeutics, David Strauss was not involved in the review or decision process for this paper. All other authors declared no competing interests for this work.

DISCLAIMER

The opinions expressed in this manuscript are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.
1. US Food and Drug Administration. FDA Guidance: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product <https://www.fda.gov/media/82647/download> (2015). Accessed April 1, 2022.
2. US Food and Drug Administration. FDA Guidance: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product <https://www.fda.gov/media/88622/download> (2016). Accessed April 1, 2022.
3. Li, L. et al. Quantitative relationship between AUEC of absolute neutrophil count and duration of severe neutropenia for G-CSF in breast cancer patients. Clin Pharmacol Ther 104, 742–748 (2018).
4. US Food and Drug Administration. FDA draft guidance: Biomarker Qualification: Evidentiary Framework <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM628118.pdf> (2018). Accessed April 1, 2022.
5. Wang, Y.C. et al. Use of pharmacodynamic/response biomarkers for therapeutic biologics regulatory submissions. Biomark Med 13(10), 805–809 (2019).
6. Wang, Y.C. et al. Role of modeling and simulation in the development of novel and biosimilar therapeutic proteins. J Pharm Sci 108(1), 73–77 (2019).
7. Wang, Y. & Huang, S.M. Commentary on fit-for-purpose models for regulatory applications. J Pharm Sci 108(1), 18–20 (2019).
8. Zhu, P., Hsu, C.H., Liao, J., Xu, S., Zhang, L. & Zhou, H. Trial design and statistical considerations on the assessment of pharmacodynamic similarity. AAPS J 21(3), 47 (2019).
9. Zhu, P., Ji, P. & Wang, Y. Using clinical PK/PD studies to support No clinically meaningful differences between a proposed biosimilar and the reference product. AAPS J 20(5), 89 (2018).
10. US Food and Drug Administration. FDA Guidance: Bioanalytical Method Validation <https://www.fda.gov/media/70858/download> (2018). Accessed April 1, 2022.
11. US Food and Drug Administration. Biosimilars action plan: Balancing Innovation and Competition <https://www.fda.gov/media/114574/download> (2018). Accessed April 1, 2022.
12. Li, J. et al. Advancing biosimilar development using pharmacodynamic biomarkers in clinical pharmacology studies. Clin Pharmacol Ther 107, 40–42 (2019).
13. Sheikhy, M. et al. Considerations for use of pharmacodynamic biomarkers to support biosimilar development – (I) a randomized trial with PCSK9 inhibitors. Clin Pharmacol Ther 113, 71–79 (2023).
14. Gershuny, V. et al. Considerations for use of pharmacodynamic biomarkers to support biosimilar development – (II) a randomized trial with IL-5 antagonists. Clin Pharmacol Ther 113, 80–89 (2023).
15. Hyland, P. et al. Evaluating the utility of proteomics for the identification of circulating pharmacodynamic biomarkers of IFNβ-1a biologics. Clin Pharmacol Ther 113, 98–107 (2023).
16. Duke Margolis Center for Health Policy. Public Workshop: Pharmacodynamic Biomarkers for Biosimilar Development and Approval <https://healthpolicy.duke.edu/events/biosimilar> (2021). Accessed April 1, 2022.