

Pharmacodynamic Biomarkers for Biosimilar Development and Approval

Workshop Background

Duke-Margolis Center for Health Policy | 2-Day Virtual Public Workshop

September 20, 2021 | 10:00 am – 2:30 pm ET

September 21, 2021 | 10:00 am – 2:30 pm ET

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The Duke-Margolis Center for Health Policy is collaborating with the U.S. Food and Drug Administration (FDA) to host a two-day virtual public workshop entitled “Pharmacodynamic Biomarkers for Biosimilar Development and Approval” on September 20 – 21, 2021. This virtual public workshop is a forum for regulators, biopharmaceutical developers, and academic researchers to discuss the current and future role of pharmacodynamic (PD) biomarkers in improving the efficiency of biosimilar product development and approval.

This document summarizes information from a perspective article written by FDA authors (1), FDA guidance documents related to biosimilars and biomarkers (2,3), and the FDA’s ongoing applied regulatory science activities to inform policy regarding PD biomarkers for biosimilar development. This document is intended to facilitate scientific discussion at the September 2021 virtual public workshop and is not official guidance from the FDA.

Introduction

To ensure U.S. patients realize the public health benefit of a robust, competitive market for biosimilar products, the 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 currently conducting research to inform the agency's thinking on critical aspects of the use of pharmacodynamic (PD) biomarkers to demonstrate biosimilarity, which can either streamline or eliminate the need for comparative clinical studies with efficacy endpoints.

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an FDA-approved reference product. The enactment of the Biologics Price Competition and Innovation Act of 2009 added the 351(k) Biologics License Application (BLA) pathway to the Public Health Service Act, which established an abbreviated approval pathway for the licensure of biosimilar and interchangeable biological products. FDA recommends that sponsors use a stepwise approach to developing the data and information needed to support a demonstration of biosimilarity (2,3):

- The stepwise approach should start with extensive structural and functional characterization of both the proposed product and the reference product.
- The sponsor should then consider the role of animal data in providing additional support for demonstrating biosimilarity.
- The sponsor should then 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 after completing the prior steps, the sponsor should then consider what additional clinical data may be needed to adequately address that uncertainty. This has often been addressed by conducting comparative clinical studies with efficacy endpoints.

Use of Pharmacodynamic Biomarkers in Approved Biosimilar Development Programs

As noted above and outlined in FDA guidance documents, biosimilars may be approved based on PK and PD biomarker data without a comparative clinical efficacy study (2,3). Reliance on PK and PD biomarker data allows for shorter and less costly clinical studies that can often be conducted in healthy participants. And beneficially, evaluating PK and PD similarity to detect differences between a proposed biosimilar and its reference product may be more sensitive than evaluating clinical efficacy endpoint(s), should differences exist. As an example, a quantitative analysis showed that the PD biomarker, area under effect-time curve of absolute neutrophil count, is a more sensitive endpoint than the clinical efficacy endpoint of duration of severe neutropenia (4).

While PK similarity has been evaluated in every FDA-approved biosimilar to date, as of July 31, 2021 only eight out of 30 approved biosimilars have included PD similarity data to support demonstrations of no clinically meaningful differences between proposed biosimilar products and reference products (in other words, filgrastim-aafi, filgrastim-sndz, pegfilgrastim-jmdb, pegfilgrastim-cbqv, pegfilgrastim-apgf, pegfilgrastim-bmez, epoetin alfa-epbx, and insulin glargine-yfgn). 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; 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 (5). Biosimilar development programs can use PD biomarker data obtained from PD similarity studies to address residual uncertainties and/or detect clinically meaningful differences between a proposed biosimilar and its reference product. **Because the purpose of a biosimilar development program is to demonstrate similarity 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 a requirement.** Furthermore, PD biomarkers that reflect the mechanism of action of the biological product have the potential to be more sensitive endpoints for detecting clinically meaningful differences between two products. This provides opportunities for biomarkers that were used as secondary and exploratory endpoints in new drug development programs to play important roles in 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.

FDA guidance describes five characteristics for PD biomarkers (Figure 1) to assist sponsors planning to use PD biomarkers as a component of a biosimilar development program (3).

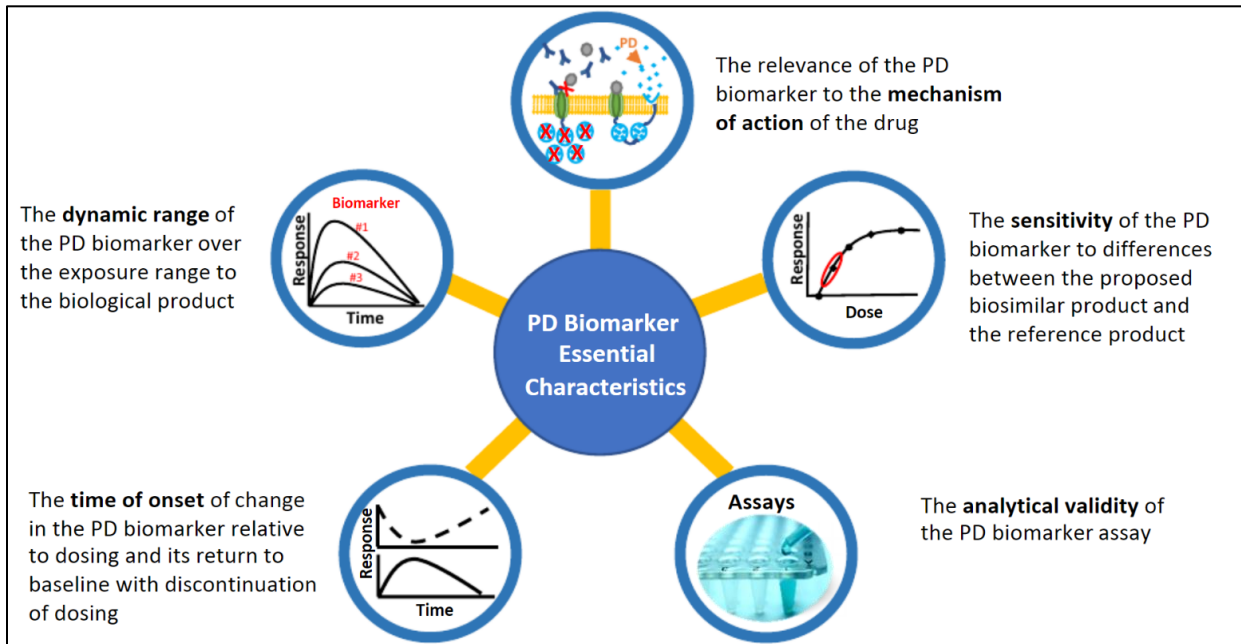


Figure 1. Five essential characteristics of a PD (pharmacodynamic) biomarker for biosimilars (adapted from Li, et al. (4))

Data to demonstrate biomarker suitability for a biosimilar development program can be generated for a single scientifically appropriate PD biomarker or more than one PD biomarker (3). 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 that describe the clinical studies 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 PD biomarker pilot study to fill information gaps. 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 (4,6-10).

Table 1: Potential Evidence to Address the Five Characteristics of 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
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
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 (for example, the time of onset, duration of response, and return to baseline)
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 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
The analytical validity of the PD biomarker assay	Data demonstrating the accuracy, precision, specificity, sensitivity, and reproducibility of the PD biomarker assay

The following sections outline specific considerations for determining the suitability of a PD biomarker and conducting pilot studies to address limited information about candidate PD biomarkers, as needed.

PD Biomarker Characteristic: 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)

As noted previously and outlined in FDA guidance documents, there is no requirement for a PD biomarker to be a surrogate endpoint for clinical efficacy outcomes (2,3). Furthermore, characterizing the relationship between a PD biomarker and clinical outcomes is not one of the above mentioned five characteristics. However, assessing the relevance of the PD biomarker to the mechanism of action of the drug is one of the 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 that are 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. While 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 efficacy study.

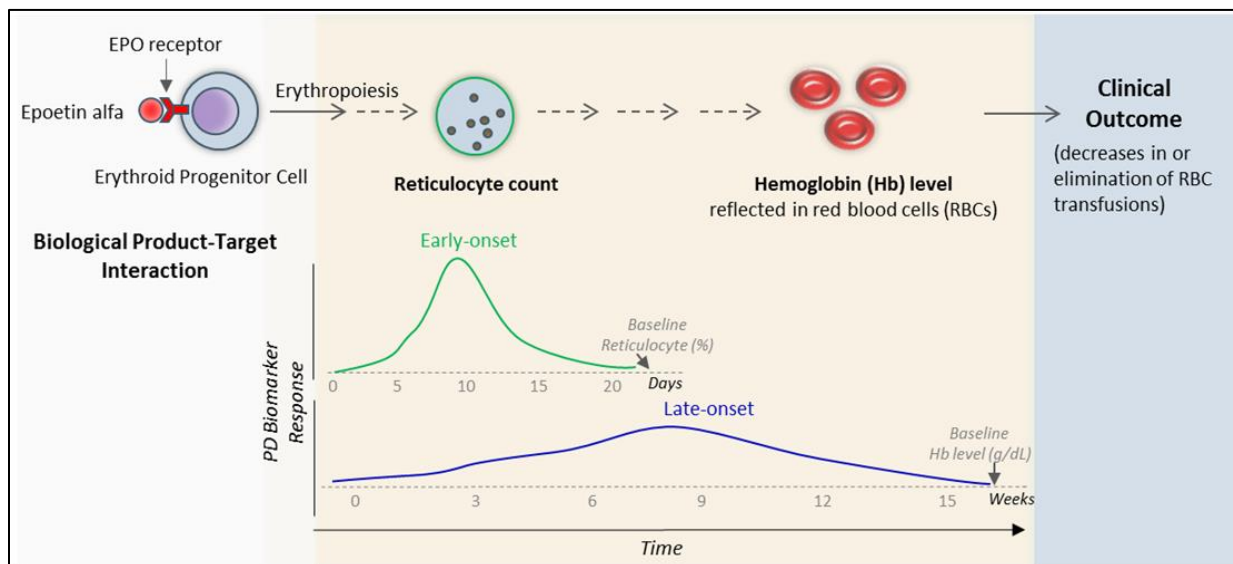


Figure 2. Mechanism of action and representative temporal profiles of PD biomarkers after epoetin alfa treatment

Some drugs have complex pharmacology with many measurable PD biomarkers (for example, immunomodulating agents for neurodegenerative disorders). When a drug exhibits complex pharmacology, identifying a single PD biomarker that reflects the mechanism of action can be challenging. However, such circumstances do not rule out establishing biosimilarity with a PD biomarker-based approach in lieu of a comparative clinical efficacy study. Evaluating whether a PD biomarker-based approach is appropriate depends on the characteristics of the PD biomarker(s) (for example, assessment of all five biomarker characteristics), assessments of multiple PD biomarker (if relevant), and the totality of evidence supporting the overall biosimilarity assessment.

PD Biomarker Characteristic: The time of onset of change in the PD biomarker relative to dosing and its return to baseline with discontinuation of dosing

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. 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. 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 that may not be observed for several days or weeks. Early-onset PD biomarkers may allow for shorter study durations (as with reticulocyte count) and may also afford higher sensitivity (as with epoetin alfa product exposure). Late-onset PD biomarkers may require longer study periods (as with hemoglobin) (Figure 2). In certain cases, inclusion of both early-onset and late-onset PD biomarkers may be appropriate to address residual uncertainties. Data included within the approved 351(k) BLA for the biosimilar epoetin alfa-epbx included both early-onset and late-onset PD biomarkers (reticulocyte count and hemoglobin, respectively). 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. Overall, 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).

PD Biomarker Characteristic: The dynamic range of the PD biomarker over the exposure range to the biological product

Understanding dynamic range information (for example, dose-response, exposure-response) for a PD biomarker helps determine dosing that may or may not result in a measurable and differentiable PD effect. As outlined in the FDA biosimilarity clinical pharmacology guidance (3), PD biomarkers with a large dynamic range over the range of drug concentrations observed in PK evaluation are recommended. When dose- or exposure-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. To accurately determine the dynamic range of the PD biomarker response, it is important to consider the performance range of the assay for measuring the PD biomarker. Modeling dose-response data can help to illustrate the dose-response relationship, identify the sensitive dose range, and justify dose selection, for example, by illustrating that doses along the plateau of the dose-response curve are not selected (Figure 3). Factors to consider while selecting a dose to study in a PD similarity study may include the variability of the PD biomarker, the study population (healthy participants 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 similarity and PD similarity can be assessed together in a single clinical study, particularly when the same dose and population is acceptable for those evaluations.

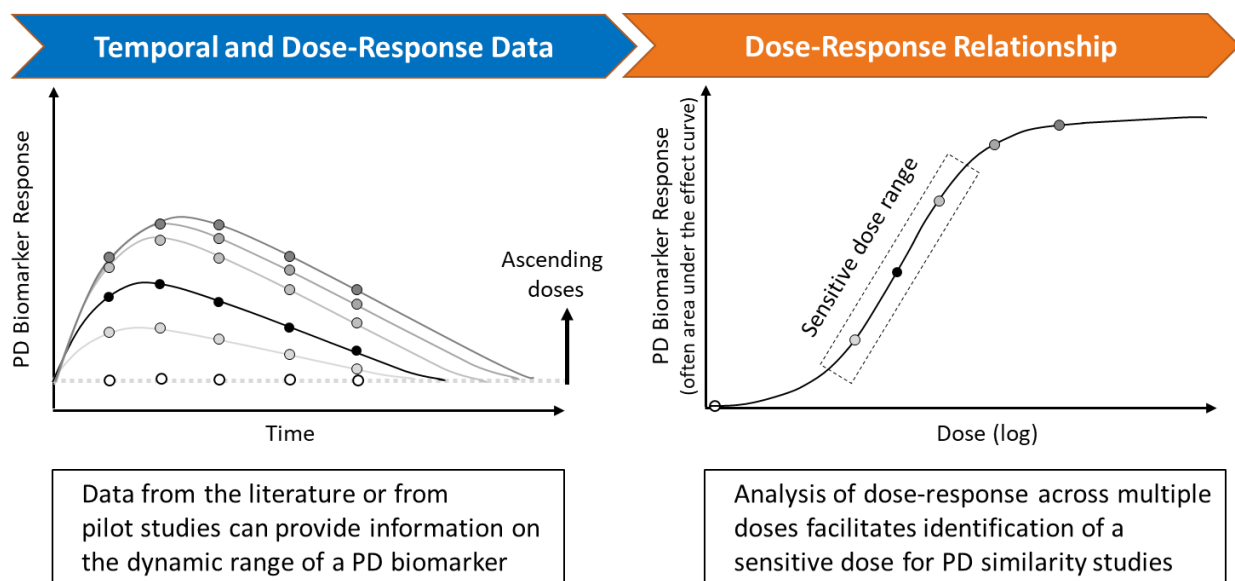


Figure 3. Example temporal and dose-response data for a PD biomarker to inform identification of a sensitive dose

PD Biomarker Characteristic: The sensitivity of the PD biomarker to differences between the proposed biosimilar product and the reference product

A suitable PD biomarker should be sensitive enough to address residual uncertainties to support a conclusion that there are no clinically meaningful differences between a proposed biosimilar product and its reference product. The sensitivity of the PD biomarker in the context of a PD similarity study may be affected by other factors, such as participant variabilities, the selected dose, and the dose-response relationship. Therefore, it is important to select a dose that is sensitive enough to detect differences in the PD biomarker and a study population that will minimize variability. A dose that is not on the plateau of the dose-response curve is generally considered sensitive when PD responses are measured (Figure 3).

As described in the FDA biosimilarity clinical pharmacology guidance (3), a study in healthy participants may offer more sensitivity to detect differences between products than a study in patients because healthy participants have fewer confounding factors (such as comorbidities and concomitant medications) that may influence baseline PD measurement and PD responses upon product exposure. However, in certain cases PD similarity studies can only be conducted in patients (for example, when a PD response can only be detected in the patient population).

When determining a PD biomarker’s suitability, it is important to consider factors that may contribute to intra-individual variability (for example, diurnal variability or fasting state) and inter-individual variability (for example, body weight). Enrolling a population expected to result in limited variability among PD biomarker responses can decrease the sample size required of a PD similarity study that can sensitively detect potential differences between products.

PD Biomarker Characteristic: The analytical validity of the PD biomarker assay

Because the reliability of PD biomarker data depends on the quality of the PD biomarker assay, 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 (11). 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 (3). The following attributes may be evaluated to demonstrate bioanalytical assay validity:

- Selectivity and specificity of an assay to quantitatively measure an intended analyte (such as a PD biomarker) and the factors that might interfere with such measurements, including the endogenous levels expected to be present in the matrix used to prepare the calibration standards and quality control samples
- When applicable, the suitability of the recombinant/synthetic version of the biomarker used in the preparation of the calibration standards and the quality control samples, including but not limited to the evaluation of binding kinetics with the assay reagents
- Intra- and inter-assay accuracy and precision
- Dynamic range (the range in measurements that provide reliable data) and sensitivity (determination of the lower limit of quantitation and the upper limit of quantitation of an assay)
- Reliability of the assay data, including determination of the impact that sample collection, handling, and storage might have on the data quality

As outlined in the FDA’s Bioanalytical Method Validation guidance (11), 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 when the assay is used to support regulatory decision-making. Nonetheless, the reliability of data from the pilot study will depend on the quality and performance of the assay used to measure the PD biomarker, and poor assay performance could impact the reliability of conclusions that result from analyzing the data. Although an assay’s performance characteristics might differ depending on the specific biomarker attributes (for example, stimulatory or inhibitory, free versus bound forms, total versus 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 within some of the PD biomarker considerations above, modeling and simulation tools can be useful when designing a PK and/or PD similarity study, for example, by informing 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. As outlined in the

FDA’s biosimilarity clinical pharmacology guidance (3), sponsors should use an average equivalence statistical approach to compare PK and PD parameters. 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 an acceptable limit. The guidance states that an appropriate starting point for an acceptable limit for the confidence interval of the ratio is 80 to 125 percent; however, sponsors can propose other limits if justified. If information exists that links a PD biomarker to clinical endpoints, modeling and simulation can be used to justify alternative limits for PD similarity (Figure 4).

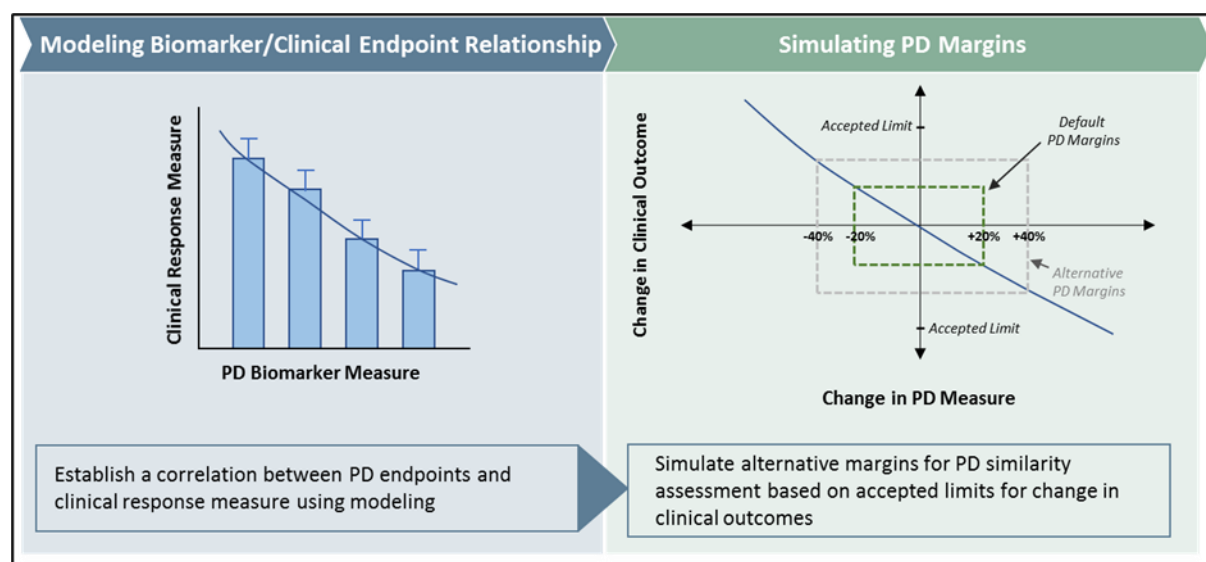


Figure 4. Example application of modeling and simulation to support selection of a PD biomarker and margins for a PD similarity study

The FDA’s biosimilarity clinical pharmacology guidance (3) also comments on how sponsors can conduct a PK and/or PD similarity study between the proposed biosimilar and its reference product with multiple dose levels when a clear dose-response relationship is observed. Under such circumstances, PK/PD parameters such as the half maximal effective concentration (EC_{50}), the maximum PD response (E_{max}), and the slope of the concentration-effect relationship can be evaluated for similarity. If sponsors consider such an approach, it is recommended that they discuss their approach with the FDA in advance.

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 (12), 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 (12), 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 agency's expectations for the use of PD biomarkers to support a demonstration of biosimilarity. As a part of this action plan, the FDA has conducted three pilot PK/PD biomarker clinical pharmacology studies, each with two marketed originator biologics with the same mechanism of action. The different studies cover products with the following PD biomarker characteristics:

- PD biomarker reflecting the mechanism of action of and used as a surrogate endpoint for the reference products over long-term follow-up in patients
- PD biomarker reflecting the mechanism of action but not used as a surrogate endpoint for approval of the reference product
- PD biomarker within a pharmacologic/biologic pathway where binding of the drug to its receptor initiates a complex signaling system; thus, it is difficult to determine the precise mechanism of action

These pilot studies were designed to collect intensive PK and PD biomarker data at different dose levels for each of the six drugs studied, enabling the evaluation of different PD biomarkers and model-based approaches for analyzing data. As discussed in FDA guidance (2,3), 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 PD biomarker identification for biologic products without candidate PD biomarkers. In addition to pre-specified primary and secondary PD biomarkers of interest, the FDA is assessing the utility of large-scale proteomic methods and other technologies for this purpose. The following summarizes the outcome measures of the three pilot studies:

Primary Outcome Measures

1. The values and variability of standard PD metrics (area under the effect curve [AUEC] and maximal difference at a single time-point) for a primary pre-specified PD biomarker at multiple doses (3 or 4, depending on study) for each drug

Secondary Outcome Measures

1. The values and variability of standard PD metrics (AUEC and maximal difference at a single time-point) for a secondary pre-specified PD biomarker (in 2 of the 3 studies) at multiple doses for each drug
2. The values and variability of pharmacokinetic characteristics (maximum concentration and area under the curve of free drug concentration) at multiple doses for each drug
3. PK/PD model parameters after combining data from multiple doses

Exploratory Outcome Measures

1. Plasma proteomics (differential expression of circulating proteins)
2. Plasma small RNA transcriptomics (differential expression of circulating small RNAs)

Data from these studies is 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 pre-specified biomarkers, these studies will contextualize the utility of omics technologies to identify and characterize biomarkers that could be used for a PD similarity assessment. Initial data from the FDA pilot studies will be presented and discussed at the workshop, focusing on how the study results inform general methodological best practices for PD biomarker identification and characterization for the context of using PD biomarkers in biosimilarity studies.

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. While 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 endpoint(s). This includes utilizing PD biomarkers that were not used as surrogate endpoints 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.

Acknowledgements

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