REAGAN-UDALL FOUNDATION for the Food and Drug Administration

Biosimilar User Fee Act Regulatory Science Accelerator

Biosimilar Roundtables Summary Report

April 2025

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

ABOUT THE REAGAN-UDALL FOUNDATION FOR THE FDA

The Reagan-Udall Foundation for the FDA (Foundation) is an independent 501(c)(3) created by Congress to advance regulatory science to help the U.S. Food and Drug Administration do more to protect and promote the public's health. The Foundation manages a suite of programs that assist the FDA in engaging with external stakeholders to facilitate evidence generation, improve public understanding of the FDA, and deliver more accessible health information to the public.

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The Reagan-Udall Foundation for the FDA (the Foundation), in collaboration with the FDA's Center for Drug Evaluation and Research (CDER), hosted a series of closed-door virtual roundtable discussions with developers of biosimilar biologic products (biosimilars). This report outlines the key themes and possible research priorities discussed during the sessions, which CDER can consider alongside input from other stakeholder engagement efforts as it considers next steps for the BsUFA III Regulatory Science Pilot Program. This report is not intended to convey official US FDA policy.

Background

Biologic products (biologics) are a class of drugs that are frequently produced using a living system, such as a microorganism (e.g., yeast, bacteria), plant cell, or animal cell and tend to be large molecules with complex structures.[1,2] Examples of biologics include monoclonal antibodies and fusion proteins.

A biosimilar is "a biologic that is highly similar to another biologic that is already FDA-approved (known as the original biologic)."[3] An approved biosimilar does not differ clinically from the original biologic and matches the original in terms of dose, dosage form, route of administration and potential side effects.[4]

The Biologics Price Competition and Innovation Act of 2009 (BPCIA) was enacted as part of the Affordable Care Act to create a regulatory pathway for the approval of biosimilar and interchangeable biologic products. Its goals were to promote competition, reduce healthcare costs, and ensure access to biologic medicines while maintaining high standards for safety, efficacy, and quality.[5]

The Biosimilar User Fee Amendments of 2022 (BsUFA III) was then enacted as part of the FDA Reauthorization Act of 2022, to continue funding the FDA's biosimilar program through user fees paid by biosimilar developers. This program supports the timely review of biosimilar applications, enhancing competition and access to biologic medicines. The reauthorization for fiscal years (FY) 2023-2027 continues to

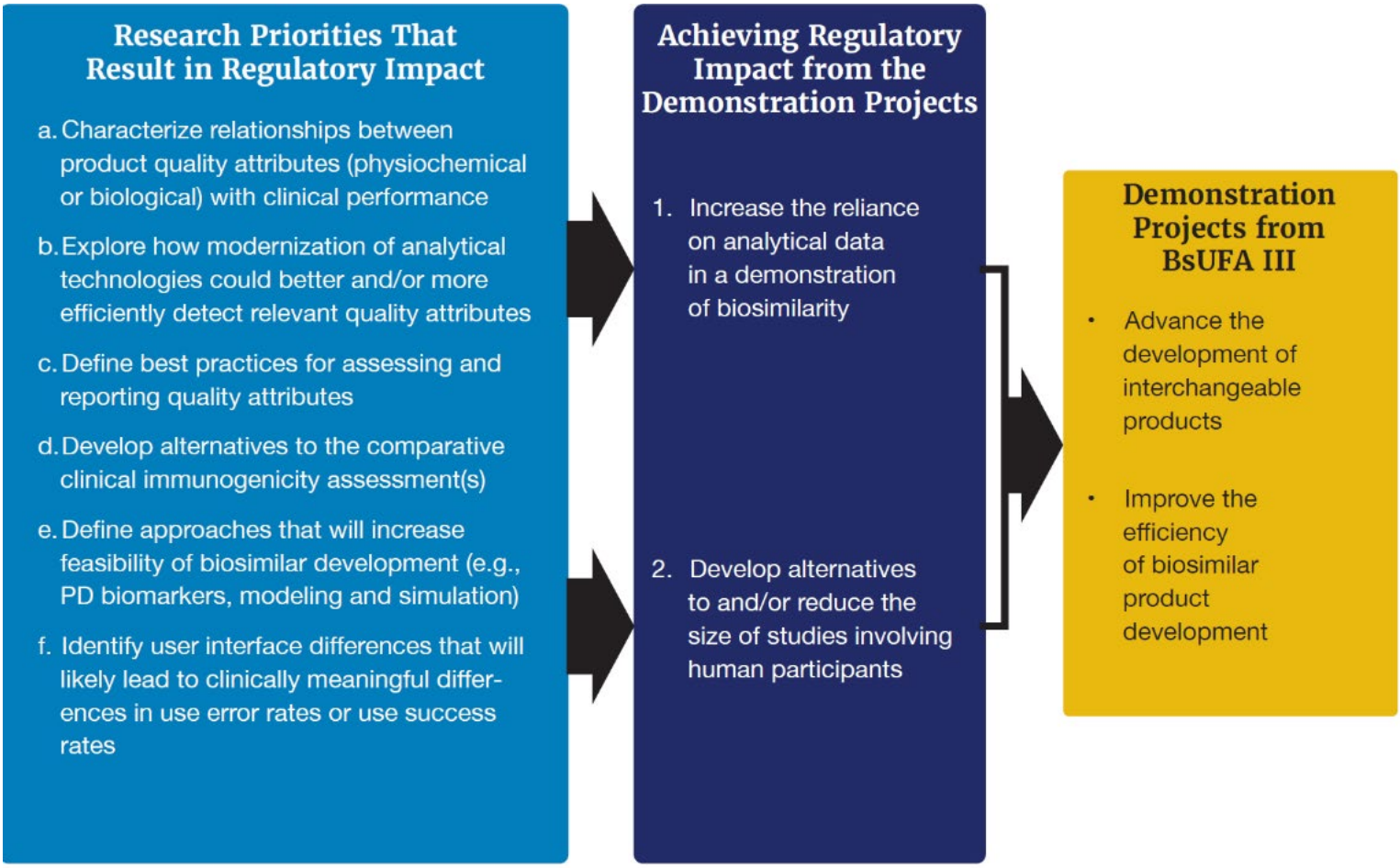
[1] Center for Drug Evaluation and Research (CDER). Overview for Health Care Professionals. www.FDA.gov. Published December 13, 2022. Accessed January 16, 2025. https://www.fda.gov/drugs/biosimilars/overview-health-care-professionals#What%20is%20a%20biological%20product
[2] U.S. Food and Drug Administration. Biosimilar and Interchangeable Biologics: More Treatment Choices. www.FDA.gov. Published July 28, 2021. Accessed December 18, 2024. https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices
[3] Ibid.
[4] Center for Drug Evaluation and Research (CDER). Biosimilars Basics for Patients. www.FDA.gov. Published 2024. Accessed January 16, 2025. https://www.fda.gov/drugs/biosimilars/biosimilars-basics-patients
[5] Pub. L. No. 111-148, §§ 7001 through 7003, which amended section 351 of the Public Health Service Act, 42 U.S.C. § 262.

support the development of safe, effective, and interchangeable biosimilars and reinforces the FDA's commitment to supporting a robust biosimilar market, driving innovation, competition, and affordability.[6,7]

BsUFA III includes a Regulatory Science Research Pilot Program (Figure 1) aimed at enhancing the development and approval of biosimilar and interchangeable biological products. In January 2024, the FDA released revised research priorities for this program, focusing on two main objectives: 1) Increasing reliance on analytical data in demonstrating biosimilarity, and 2) developing alternatives to and/or reducing the size of studies involving human participants.[8] Publicly available deliverables include a progress report and workshop by October 31, 2025, a final outcomes report by September 30, 2027, and a strategy document outlining actions to support biosimilar development within 12 months of project completion. Community and industry contributors played a critical role in shaping the FDA's biosimilar regulatory research priorities. The FDA developed these priorities through internal expertise and refined them based on stakeholder feedback. Ongoing stakeholder input is encouraged to address scientific and regulatory challenges, enhance decision-making, and support biosimilar development.

[6] Center for Drug Evaluation and Research (CDER). Biosimilar User Fee Amendments. www.FDA.gov. Published October 3, 2023. https://www.fda.gov/industry/fda-user-fee-programs/biosimilar-user-fee-amendments
[7] Text - H.R.6833 - 117th Congress (2021-2022): Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023. (2022, September 30). https://www.congress.gov/bill/117th-congress/house-bill/6833/text
[8] U.S. Food and Drug Administration. BsUFA III Regulatory Research Pilot Program: Revised Research Priorities | FDA. www.FDA.gov. Published 2024. https://www.fda.gov/media/175799/download?attachment

Figure 1. Structure of the BsUFA III Regulatory Research Pilot Program



Rationale and Methods

The IQVIA Institute's report, "Biosimilars in the United States: 2023–2027," highlighted that biosimilar development is being driven by smaller companies. According to the IQVIA report, "21% of the biosimilar products in the pipeline are being developed by large pharma companies (those with more than $10Bn in global sales). The remaining 79% are being developed by smaller companies with varying degrees of biologic or biosimilar development experience." To ensure stakeholder engagement for the Pilot Program captures a diverse range of perspectives, we adapted the accelerator model used during the COVID-19 pandemic, leveraging its success in fostering candid and nuanced feedback.[9,10]

Participant Selection

An open invitation was posted on the Foundation's website, allowing companies to express their interest in joining the roundtable series. Additionally, the Foundation identified and selected industry participants from development programs that had not previously engaged with the FDA Regulatory Science Research Pilot Program. Companies representing a broad spectrum of experience in biosimilar development were considered, however, due to limited space, not all interested developers could be accommodated. The final selection ensured a wide representation of biosimilar development experience was present. Each company designated two participants to attend per roundtable, enabling the inclusion of colleagues with diverse expertise relevant to the specific topics discussed. However, individuals involved in pending FDA product development meetings, applications, or actions were not eligible to participate in any session of the series. Roundtable participants are listed in Appendix A.

Roundtables

The Foundation conducted a series of five virtual roundtable discussions. Discussions were organized along themes and key questions developed in conjunction with CDER staff. The purpose of these roundtables was to explore emerging areas of regulatory science with FDA as a silent observer to gather insights, views, and perspectives to which FDA staff might not otherwise be exposed. Sessions aimed to address emerging areas of regulatory science and foster active dialogue with

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[9] Office of the Commissioner. Generating Actionable Insights from Real World Data - The COVID-19 Evi. www.FDA.gov. Published 2021. https://www.fda.gov/science-research/fda-science-forum/generating-actionable-insights-real-world-data-covid-19-evidence-accelerator

[10] Reagan-Udall Foundation for the FDA. COVID-19 Evidence Accelerator Discussion at the FDA Foundation's 2021 Annual Public Meeting. www.YouTube.com. Published May 25, 2021. https://www.youtube.com/watch?v=f77QdgDmlgo

biosimilar developers, with a particular focus on amplifying the voices of developers who may have not yet been heard.

Roundtable Key Findings

Discussion questions and emergent themes from the roundtable conversations are provided below. These questions were posed to roundtable participants to stimulate discussion in areas of focus important to the Regulatory Science Research Pilot Program. The discussion themes are a summary of the discussion between the biosimilar developers and the Foundation moderator, highlighting the challenges and concerns expressed by the roundtable participants. FDA participants were silent observers and did not participate in the discussion.

Roundtable #1 (August 6, 2024)
Achieving Analytical Similarity

Discussion Questions

- What are the 'pain-points' or barriers you have encountered while planning, developing and/or conducting a comparative analytical assessment?
- What do/would you need to decrease the 'pain-point' or barrier identified in the bullet above?
    - What research, if any, would be helpful to address the 'pain-point' or barrier identified in the bullet above?
    - How do you see an FDA/ BsUFA-led and User fee-funded research program supporting this research?
- What is your vision for what the CAA could look like in the future?
    - What research, if any, would support that vision?

Discussion Themes

- Challenges related to the availability of representative reference product lots and inherent variability within these products
- Identifying and prioritizing the most important product quality attributes for reference products
- Understanding and/or knowledge of the regulatory expectation of the level of precision and accuracy necessary with analytical measurements for regulatory decision making
- Availability and transparency of data on reference products

- Some participants proposed creating a publicly accessible library or compendium to house relevant data. The feasibility of a centralized standard or reference bank managed by agencies like the National Institute of Standards and Technology (NIST) was discussed to help resolve issues experienced by Biosimilar developers related to lot variability and biases.

- Need for clear guidance on critical quality attributes (CQAs) and acceptable variability
  - A balance between flexibility and clarity in regulatory requirements is sought. Challenges exist in determining which tests are essential given limited inventory of the reference product and varying methodologies, highlighting the need for clearer direction on testing requirements.

Roundtable #2 (August 27, 2024) Leveraging Analytics to Inform Remainder of Biosimilar Development

Discussion Questions

- How do you determine that your product is highly analytically similar to the reference product?
  - In this thought process, what steps/methods are particularly challenging?
- How early in your development do you use analytics in selecting a biosimilar candidate?
  - Where do you get the expertise to start designing your development program?
- How can the FDA provide better information on selecting the tests needed to identify differences between a proposed biosimilar and its reference product?
- Might any of that information be supported with a regulatory science research project facilitated by FDA, such as those under BSUFA regulator science program?
  - Given the nature of research, how can we ensure that the research projects would be relevant and valuable 2-3 years after initiation?

Discussion Themes

- Determining the level of analytical similarity should be required, especially when using biological assays with low precision

- Improving the accuracy and precision of both cell-based assays and physicochemical methods in analytical similarity assessments is essential. In particular, understanding factors that impact bioassay precision is critical for biosimilar development and developers need clear expectations from the FDA.
- The sufficiency of literature-based arguments versus extensive data generation for regulatory requirements
- Complexity of the comparative analytical assessment increases for emerging drug classes, such as antibody-drug conjugates (ADCs), requiring analysis of components like the antibody, payload, and linker
    - Advanced analytical techniques may be needed, and FDA guidance on method selection and CQAs for emerging drug classes like ADCs and hyaluronidase-based products would be helpful.

Roundtable #3 (September 18, 2024)
Achieving Pharmacokinetic (PK) Similarity

Discussion Questions

- What are the challenges or barriers you have encountered while planning, developing, conducting, and/or analyzing a PK similarity assessment study?
    - What do/would you need to decrease the challenges or barriers identified in the question above?
    - What research, if any, would be helpful to address the challenges or barriers identified above?
- How do you decide when a biosimilar candidate is 'similar enough' to proceed to a PK study or other clinical study?
- Are there any situations where you consider a PK similarity study would not be needed as part of demonstrating similarity? If so, please describe.

Discussion Themes

- Challenges when including patients in pharmacokinetic (PK) studies versus healthy volunteers
    - For example, dropouts increase as the number of required PK samples increase because patients are more likely to miss visits solely for PK sampling (i.e., not tied to a healthcare follow-up visit). Also, requiring PK samples at steady state can extend the PK similarity study follow-up from weeks to months when studying drugs with long half-lives.

- Modeling and simulation can be used to optimize PK sampling and minimize PK visits while still having the required precision and sensitivity for the PK parameters being measured. Digital clones may be useful for conditions with a small sampling pool. Modeling is subject to bias, which should be considered if used in place of PK sampling in humans.
- The possibility of waiving PK similarity studies in the following situations was stated:
  - When the drug is administered locally and when there is no systemic exposure (e.g., intravitreal application)
  - When a pharmacodynamic (PD) biomarker could serve potentially as surrogate endpoint instead of conventional clinical efficacy endpoints

Roundtable #4 (October 8, 2024) Leveraging Pharmacokinetics (PK) and/or Pharmacodynamics (PD) to Inform Remainder of Biosimilar Development

Discussion Questions

- What are the opportunities, if any, to make PK studies more efficient?
- What opportunities are there, if any, to leverage the PK similarity assessments to reduce the size of or need for subsequent clinical studies conducted as part of biosimilar development?
- In what situations in a biosimilar development program would you consider incorporating PD similarity assessments?
- What research, if any, would be helpful to clarify these opportunities for more efficient biosimilar development?

Discussion Themes

- There is a need for clarity and guidance around the following:
  - Understanding when pursuing a PD biomarker is useful,
  - Methods to improve PK study efficiency, for example, when there are no known gender effects on PK established by the reference listed drug established, and
  - PK studies are a valuable tool to evaluate immunogenicity.

- A synthesized FDA manuscript highlighting precedents for PK/PD biomarker use would be valuable for reducing uncertainty in biosimilarity assessments for the developer.

Roundtable #5 (October 30, 2024)
Conducting Immunogenicity Risk Assessments and Evaluation

Discussion Questions

- What are the nonclinical immunogenicity assays/models, if any, that you use for selection of a biosimilar candidate?
- How do these nonclinical immunogenicity assays/models inform, if at all, the design of subsequent clinical studies in your biosimilar development programs?
- If regulatory expectations changed regarding clinical immunogenicity (e.g., considering a nonclinical study in lieu of a clinical immunogenicity study), would you be more likely to (try to) employ nonclinical methods in your development program?*
    - How would you approach validating any nonclinical immunogenicity assay to inform its utility for immunogenicity risk assessment?
    - What scientific knowledge/information is needed, if any, for nonclinical immunogenicity assays/models to make biosimilar development more efficient?
        - What research would provide that knowledge or information?
- What other approaches/strategies/tools that could help resolve concerns about immunogenicity in biosimilar development?
    - What research would support development of these approach/ strategies/ tools?

* This question is posed as hypothetical and is intended for discussion purposes only. It does not reflect any change, or contemplated change, in current regulatory expectations.

Discussion Themes

- There was concern about whether non-clinical in vitro assays for immunogenicity (in-vitro assays) can serve as reliable surrogates for clinical outcomes, especially regarding adaptive and innate immune responses.
- In vitro assay sensitivity was emphasized as crucial for meaningful immunogenicity evaluation. The discussion emphasized the need for in vitro

assays that are not only scientifically robust but also capable of detecting subtle yet clinically significant immune responses.

- In-silico tools and bioinformatics, such as sequence-based epitope mapping and proteome fingerprinting, can supplement in-vitro assays. These tools are valuable for identifying immunogenicity risk early in development but require integration with analytical similarity and bioanalytical data to enhance predictive accuracy.
- Discussion highlighted to which extent PK studies play a key role in assessing immunogenicity, in particular, whether single-dose PK studies are sufficient to assess immunogenicity.
- Participants proposed the design of in-vitro assays targeting known epitopes and the integration of analytical similarity and bioanalytical data to enhance sensitivity, specificity, and predictive accuracy for biosimilars and the reference product.

Final Poll: Key Findings

Following the roundtable series, a brief poll (Appendix B) was conducted. Participant companies were asked to identify the top challenges facing their biosimilar development programs based on the roundtable discussion and prioritize issues for the BsUFA Regulatory Science Program to address.

Nine of the ten companies that participated in the roundtables responded to the poll. The top challenges identified by programs are listed in Table 1. Respondents deemed clarity on critical quality attributes (CQAs) as the highest priority item for the BsUFA Regulatory Science Program to address.

Table 1: Top Challenges Identified by Roundtable Participants

1. Availability and variability of reference product lots
2. Lack of clarity on CQAs, acceptable variability, and essential analytical methods
3. Limited access to comprehensive and transparent data on reference products
4. High rates of dropouts due to long follow-up times in patient sampling in PK similarity studies
5. Integrating immunogenicity into PK studies
6. Lack of guidance on method selection and CQAs for emerging drug classes like ADCs

A key theme that emerged from the roundtable discussions was the suggestion that the FDA provide a synthesized overview of its experience with reference products and biosimilar application reviews in the public domain. To gather input on this, participants were asked to identify which topic would be most helpful for the FDA to synthesize. The results of this poll are summarized in Table 2, highlighting the priority topics identified by respondents. Table 2 lists the topics identified by poll respondents.

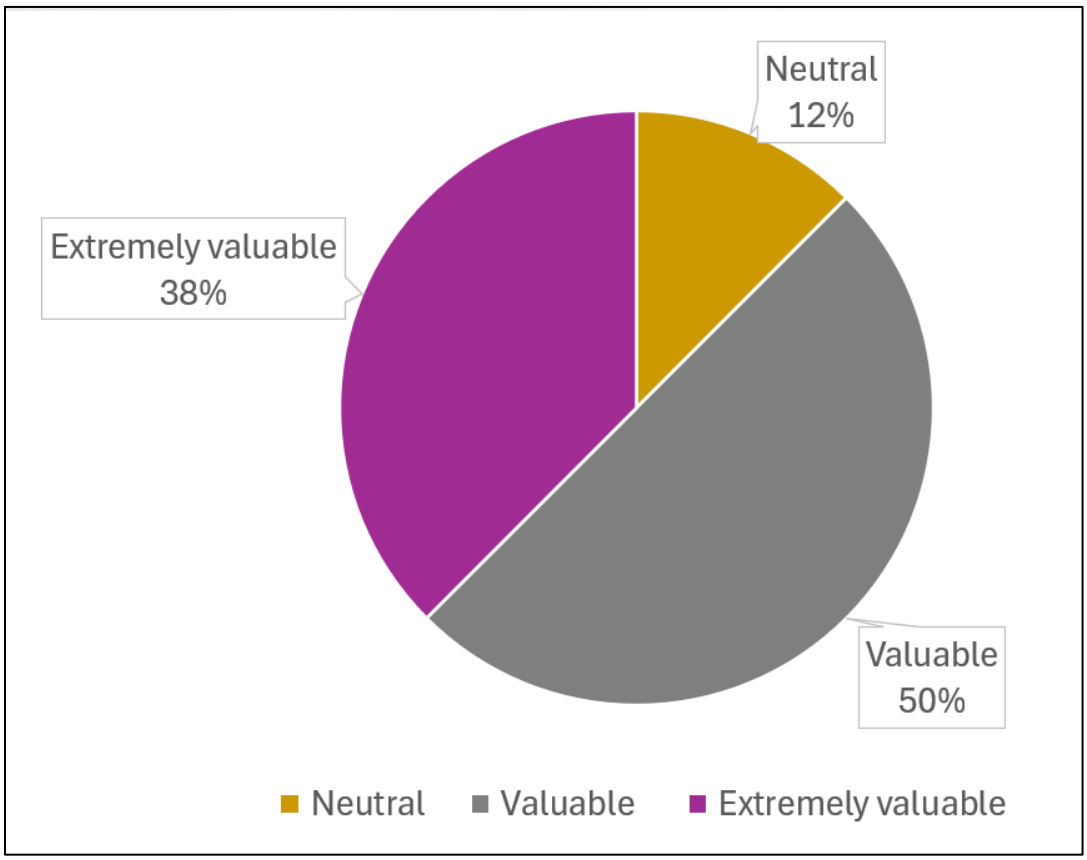
Table 2: Topics Related to Biosimilar Development Identified for FDA to Synthesize and Describe their Experience

- Usage of non-US reference products in the biosimilarity assessment, including clinical studies. For example, a comprehensive comparative study can be done by FDA which evaluates quality attributes of a reference product marketed in the US and EU.
- PK and Immunogenicity data from reference products
- Catalogue of impurities that are associated with safety concerns, based on reference products (and/or) the biosimilar application review experience
- Product class-specific guidance documents to give clarity on common CQAs
- Recommendations on the considerations for the selection & evaluation of CQAs for the future biosimilar development with, if possible, case studies of both succeeded and failed molecules
- Further insight on CQA and most relevant and suitable methods for comparative analytical assessment (CAA)
- Impact of CQA on a product's efficacy and safety; specifically, whether there is a difference in the expectation of the impact among IgG1, IgG2, and IgG4
- An explanation of immunogenicity as presented in the different FDA guidances: an unwanted immune response triggered by the drug and how the key point is similarity in terms of their clinical impact
- Whether a one-dose PK similarity study in healthy volunteers is sufficient to evaluate immunogenicity between the biosimilar product and low-risk protein reference product
- It would be helpful if FDA could publish their experience on the extent of which analytical, clinical PK and comparative efficacy data contributed to the regulatory decision making on whether a proposed biosimilar could be approved.

Overall, participants found the roundtable series highly valuable (Figure 2). They appreciated the opportunity to exchange information and ideas, gain a better understanding of industry concerns and perspectives, and receive helpful insights

into approaches and key considerations. The discussions provided a platform for addressing technical and scientific challenges in biosimilar development alongside industry peers.

Figure 2. Value of Roundtable Engagement



The participants reported that the series was well-organized and fostered active engagement. Suggestions for future improvements for subsequent roundtables, if any, included increasing participation from biosimilar developers and manufacturers with approved or marketed products in the US and expanding topics to include emerging classes of medications, such as ADCs, CAR-T therapies, and mRNA therapies. Additionally, participants expressed interest in further exploring the FDA's and industry experts' perspectives on the use of in vitro bioassays as clinical surrogates for predicting efficacy and immunogenicity, similar to their application in peptides.

Summary

The series of private virtual roundtables, hosted by the Foundation in collaboration with FDA CDER, introduced a novel approach to stakeholder engagement under BsUFA. These roundtables convened biosimilar developers with varying levels of experience, offering a platform for sharing diverse perspectives on challenges encountered within the biosimilar development landscape. Participants outlined the obstacles they face and shared suggestions on how the BsUFA III Regulatory Science Pilot Program could support their development programs. In turn, FDA representatives gained valuable insights into the unique challenges faced by biosimilar developers, particularly smaller companies.

The Foundation and FDA thank the roundtable participants for their ongoing engagement and candid feedback. We appreciate the experiences and insight shared during the project.

Appendices

Appendix A: Roundtable Participants

Aigal, Darshan
Fuentes, Rudy
Ghosalkar, Jeevan
Henneberg, Jens
Hull, Wade
Jagatheesan, Annalakshmi
Jin, Xiaofang
King-Smith, Dominic
Lahori, Mohammedazam
Li, Ywan-Feng
Lin, Ae-Ning
Ma, Chih-Yuan
Mangale, Mayuri
McDowell, William
Mocny, Jeffrey
Newsam, John
Pan, Yi-Hsuan
Poetzl, Johann
Radulovic, Vanja
Samiwala, Esmail
Schiestl, Martin
Schöndorfer, Georg
Schulze, Tina
Sharma, Nidhi
Sridhar, SB
Stevenson, Joanne
Vaithiyalingam, Siva
Vogg, Barbara
von Richter, Oliver
Yan, Haoheng (Sandy)
Zhou, Liang

Appendix B: Poll Questions

1. **The following are a list of challenges that were raised during the roundtable discussions. Please select your three top challenges:**
   - ❑ Sensitivity of assays for detecting immune responses
   - ❑ Reliability of non-clinical in-vitro assays as clinical surrogates
   - ❑ Determining when to use Pharmacodynamic (PD) biomarkers evaluating the similarity between a biosimilar and its reference product
   - ❑ Integrating immunogenicity into Pharmacokinetic (PK) studies
   - ❑ Criteria for waiving PK when not linked to systemic action
   - ❑ Bias in model-based analyses
   - ❑ Dropouts and long follow-up times in patient sampling
   - ❑ Pharmacokinetic (PK) studies in patients vs. healthy volunteers
   - ❑ Understanding factors that impact assay precision of analytical tests
   - ❑ Guidance on test (method) selection and CQAs for emerging drug classes like ADCs
   - ❑ Defining the level of biosimilarity for low-precision assays
   - ❑ Ensuring precision and accuracy to minimize bias of analytical tests
   - ❑ Clarity on Critical Quality Attributes (CQAs), acceptable variability, and essential tests
   - ❑ Limited access to comprehensive and transparent data on reference products
   - ❑ Availability and variability of reference product lots
2. **Biosimilar developer user fee funds are utilized to support research initiatives that enhance regulatory science. Based on the top three scientific challenges you identified in the previous question, which one would you prioritize for the BsUFA Regulatory Science Program to try to address?**
3. **One key theme that emerged from these discussions is that it would be helpful for FDA to synthesize/describe their experience with reference products and biosimilar application review in the public domain. What topic(s) would be most helpful for FDA to synthesize?**
4. **On a scale of 1 to 5, how valuable did you find this engagement? (1 being not valuable at all, 5 being extremely valuable) What suggestions do you have for improving future engagements?**
   - ❑ 1 - Not valuable at all
   - ❑ 2 - Somewhat valuable
   - ❑ 3 - Neutral
   - ❑ 4 - Valuable
   - ❑ 5 - Extremely valuable

Appendix C: FDA Observers

Baldassari, Laura
Florian, Jeffry
Gutierrez Lugo, Maria
Kozlowski, Steven
Lacana, Emanuela
Maxfield, Kimberly
Pedras-Vasconcelos, Joao
Puig, Montserrat
Ridge, Sarah
Rubio, Jennifer
Solorzano, Darlese
Sun, Qin
Welsh, Joel
Yim, Sarah