U.S. FOOD & DRUG ADMINISTRATION

Biosimilar User Fee Act (BsUFA) III Regulatory Science Pilot Program

SUMMARY REPORT ON THE BsUFA III REGULATORY SCIENCE PILOT PROGRAM MEETING: IN-PERSON ROUNDTABLE DISCUSSIONS (OCTOBER 26, 2023)

NOVEMBER 2023

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INTRODUCTION

The following section summarizes the objectives and progress of the Biosimilar User Fee Act (BsUFA) III Regulatory Science Pilot Program, highlighting its dual aims of advancing interchangeable product development and improving the efficiency of biosimilar product development, as well as broader stakeholder engagement efforts and updates as discussed during FDA's October 2023 meeting.

On September 30, 2022, the U.S. Food and Drug Administration (FDA) reauthorized the Biosimilar User Fee Act (BsUFA) for fiscal years 2023 through 2027 (i.e., BsUFA III). The BsUFA III commitment letter includes a commitment for FDA to pilot a regulatory science program to further enhance regulatory decision making and facilitate science-based recommendations in areas foundational to biosimilar development. The BsUFA III Regulatory Science Pilot Program (herein referred to as "the program") aims to leverage FDA's purview, at the intersection of scientific advancement, public health, and regulatory policy, to identify knowledge gaps and direct research to advance biosimilar development. As such, the program has two aims, also referred to as demonstration projects: (1) advancing the development of interchangeable products, and (2) improving the efficiency of biosimilar product development. In January 2023, FDA published the draft BsUFA III Research Roadmap [1] to highlight specific scientific areas where advancement is expected to impact science-based recommendations and regulatory decision making. FDA sought feedback from patients, researchers, non-profit organizations, industry, and other stakeholders on this draft roadmap through a public docket, which was open for comment through April 5, 2023.[2]

In October 2023, FDA hosted a two-part public meeting to update and engage with stakeholders regarding the progress of the program. The first component of the meeting was a virtual webinar on October 16, 2023, where FDA staff presented updates to the research priorities detailed in a revised BsUFA III Research Roadmap based on stakeholder feedback.[3] This webinar also included presentations from internal and external awardees conducting research projects under the program. The second component was held in person at the FDA White Oak Campus on October 26, 2023, where attendees participated in roundtable discussions focused on progress, feedback, and recommendations to improve regulatory impact of the demonstration projects outlined under the program's revised research priorities.

Table 1 provides an overview of the number of registrants and attendees across the October 16 virtual webinar and the October 26 in-person roundtable discussions. The 394 webinar attendees self-identified their respective organizations from a variety of sectors within the broad biosimilar landscape (Figure 1). Of the webinar attendees, 56 individuals expressed interest in attending the in-person roundtable discussions on October 26; 25 subsequently registered and 20 attended. Not including the rapporteurs and media (i.e., The Pink Sheet), participants at the roundtable discussions included representatives from government (i.e., FDA), research (i.e., U.S. Pharmacopeia, Biologics and Biosimilars Collective Intelligence Consortium, EpiVax), consulting (i.e., VRT Pharma Consulting, Dr. Amy Mateen GMP Consulting), manufacturers (i.e., Sandoz), and other stakeholders (i.e., Biotechnology Innovation Organization, Biosimilars Forum, Association for Accessible Medicines, public citizens) (Figure 1).[4]

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[1] https://www.fda.gov/media/164751/download

[2] https://www.regulations.gov/docket/FDA-2023-N-0254

[3] https://www.fda.gov/drugs/news-events-human-drugs/bsufa-iii-regulatory-science-pilot-program-10162023

[4] The Biosimilars Collective Intelligence Consortium, EpiVax, and U.S. Pharmacopeia are awardees of the BsUFA III Regulatory Science Pilot Program.

Table 1: Registration and Attendance for Virtual Webinar and In-Person Roundtable Discussions

Event	Registrants	Participants[5]
Virtual Webinar (October 16, 2023)	873	394
In-Person Roundtable Discussions (October 26, 2023)	25	20

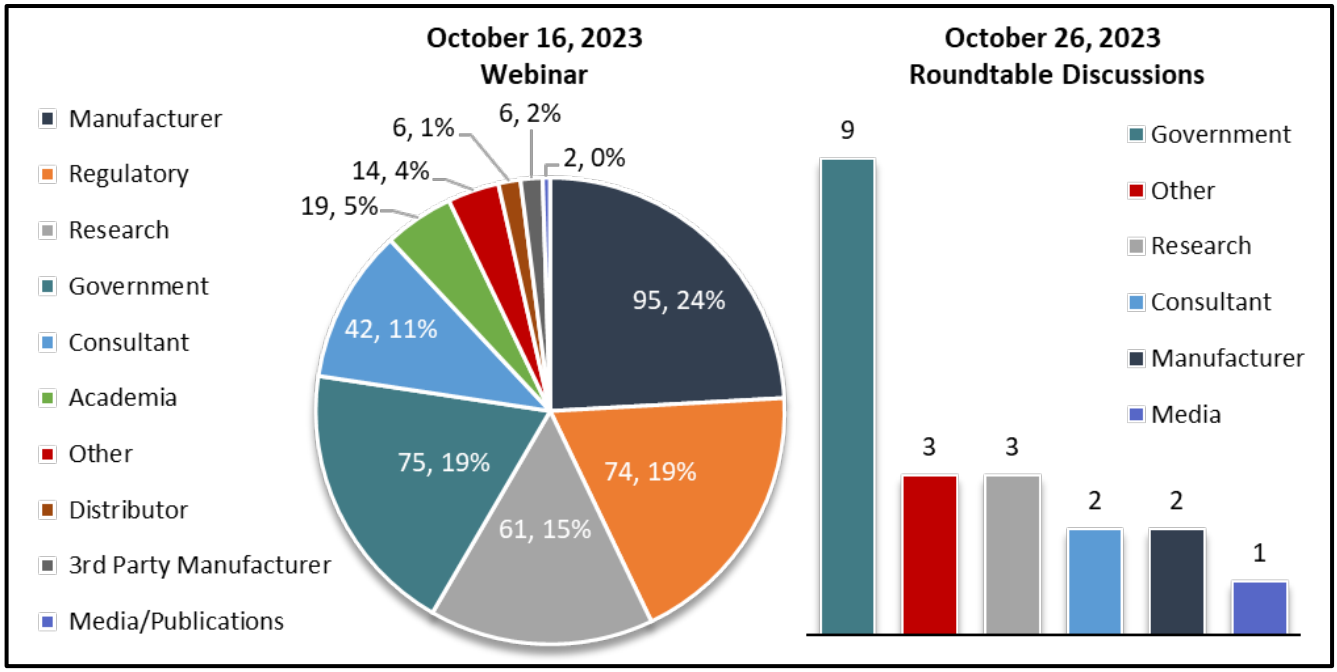

Figure 1. Attendee Representation at Virtual Webinar and In-Person Roundtable Discussions

The following sections provide two summaries related to the October 26 in-person roundtable discussions: (1) a summary of discussions, and (2) a summary of feedback received via survey following the roundtable discussions. The summary of the discussions is organized based on research priority and grouped by the two scientific areas for regulatory impact that FDA has deemed essential for achieving the program's demonstration projects, namely "Increasing the reliance of a demonstration of biosimilarity on analytical data" and "Develop alternatives to and/or reduce the size of studies involving human subjects," (Figure 2).

[5] In addition to the participants included in Table 1, one FDA attendee and three additional attendees from Booz Allen Hamilton served as rapporteurs for roundtable discussions. One media representative (The Pink Sheet) was in attendance during opening remarks and meeting conclusions but did not participate in roundtable discussions.

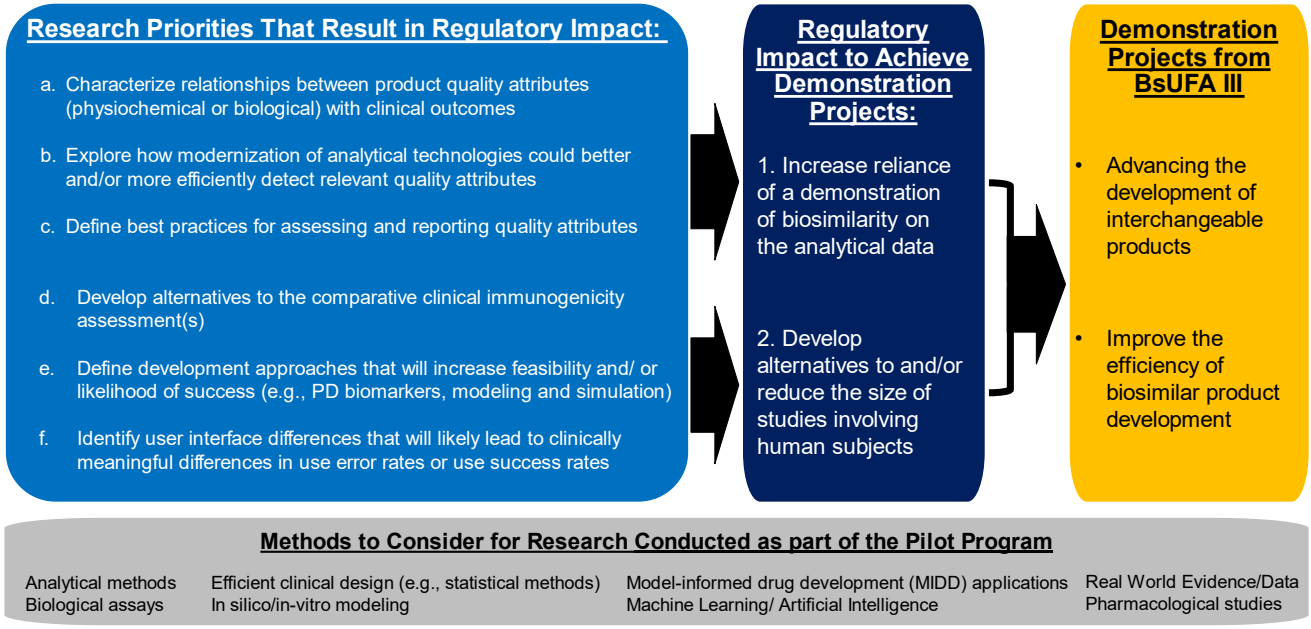

Figure 2. Research Outcome and Regulatory Impact Reporting Structure of the BsUFA III Regulatory Science Pilot Program

SUMMARY OF IN-PERSON ROUNDTABLE DISCUSSIONS

The following section provides a summary of roundtable discussions held during the October 26 in-person roundtable discussions. These discussions are organized based on revised research priorities presented during the October 16 virtual webinar.[6]

The in-person roundtable discussions were divided into two sessions, each focusing on feedback on one of the scientific areas for regulatory impact and its respective research priorities. The goals and questions for consideration outlined in Table 2 served as the basis for all roundtable discussions. Participants at each roundtable engaged in discussions on each regulatory impact for 30 minutes, followed by a 15-minute large-group discussion, during which each roundtable presented the key topics and main ideas identified during the conversations.

Of note, discussions were an open dialogue and did not always follow the order of the research priorities. The summary text below has been integrated for ease of the reader and notes when the text representing a discussion point is organized out of order of the actual discussion. Additionally, nothing in this document should be considered, in whole or in part, as being statements of policy or recommendation by FDA.

[6] https://www.fda.gov/drugs/news-events-human-drugs/bsufa-iii-regulatory-science-pilot-program-10162023

Table 2. Goals for All Roundtable Discussions and Questions for Consideration

Goals for Roundtable Discussions	Questions for Consideration
Provide feedback on the updated research priorities	How do the updated priorities address the challenges you face during biosimilar development?
Identify additional regulatory or knowledge gaps not captured by the updated priorities	What additional challenges and barriers in biosimilar development and regulation could be addressed by regulatory science research?
Specifically define immediate or direct regulatory impact for the BsUFA III Regulatory Science Pilot Program	Given the U.S. 351(k) statutory requirements today, what change/information/approach would directly or immediately impact your job for the better?

Regulatory Impact 1: Increasing the reliance of a demonstration of biosimilarity on analytical data

Updated Research Priorities for Regulatory Impact 1: Increasing the reliance of a demonstration of biosimilarity on analytical data
a. Characterize relationships between product quality attributes (physiochemical or biological) with clinical outcomes
b. Explore how modernization of analytical technologies could better and/or more efficiently detect relevant quality attributes
c. Define best practices for assessing and reporting quality attributes

a. Characterize relationships between product quality attributes (physiochemical or biological) with clinical outcomes

Participants broadly agreed that characterizing the relationship between product quality attributes (PQAs) and clinical performance is the foundation for increasing the reliance on analytical data for the demonstration of biosimilarity. Participants also noted there is already a robust set of underutilized information available that could help to establish relationships between PQAs and biological functions and elucidating these relationships will provide more sensitive measures to detect differences than traditional clinical endpoints. Thus, participants noted that any research in this area should aim to correlate analytical assays with biological function. Additionally, participants indicated that analytical assays performance must be able to detect relevant differences in PQAs (e.g., mannose content) to account for differences in biological function.

An underutilized resource is information from post-approval manufacturing changes and the data submitted by sponsors to support those changes over the development history of a reference product (e.g., monoclonal antibodies that have been on the market for decades), particular in context of more recent analytical advancements. If a particular PQA was used to justify manufacturing changes over the life cycle of a reference product (i.e., as analytical technologies improved) and the information is publicly available, this could be leveraged for the comparative analytical assessment in 351(k) biologics license application (BLA) data packages.

For reference products where there is a lack of clinical experience and/or data available (e.g., recently licensed products or products for rare disease(s)), establishing clear and measurable correlations of analytical data with biological function or clinical performance remains challenging due to unknown relevance of model systems to human physiology. Participants discussed the potential value of bioassays, animal models, and computational modeling. Any research in this area should aim to increase confidence in bioassays for the purpose of correlating analytical data with clinical performance and should not be product specific.

b. Explore how modernization of analytical technologies could better and/or more efficiently detect relevant quality attributes[7]

Participants indicated that the modernization of analytical technologies to detect relevant PQAs more efficiently is an important priority for the program. Several participants noted that improvements to analytical methods would likely not be specific or limited to biosimilars. However, efforts should focus on both modernization of existing analytical technologies as well as the development of new technologies that can support biosimilar development. Participants also noted that it is becoming more common for analytical technologies to extend across multiple companies or contract organizations than for one developer to acquire expertise in all the analytical methods needed in the assessment of a proposed biosimilar. Some companies offer analytical methodologies as part of their services or capabilities, and larger biosimilar developers are beginning to contract with them to perform analytical studies. Participants highlighted that additional publicly available information would broadly benefit and increase efficiency of biosimilar development.

Participants highlighted that research is needed in manufacturing science to understand how manufacturing process development and controls impact product quality given that most biosimilar development program failures occur due to manufacturing issues. Participants further noted that if an identified analytical difference has unknown relevance to clinical performance and is due to manufacturing process-related impurities, it may be more efficient to modify the manufacturing process rather than elucidating any potential differences in immunogenicity or safety using a nonclinical and/or clinical study. However, other participants expressed concern over the lack of analytical method sensitivity to detect either process or product-related impurities and expressed a need for development of novel approaches to detect variations in impurities.

Lastly, participants strongly emphasized that, when using a non-US comparator, shifting to a three-way analytical bridging approach would mitigate the need for time-consuming and expensive three-way pharmacokinetic (PK) bridging studies. Participants further asked about the scientific or research gaps, if any, that needed to be addressed for FDA to shift to a three-way analytical bridge-only approach.

c. Define best practices for assessing and reporting quality attributes

During roundtable discussions, participants indicated that defining best practices for assessing and reporting quality attributes should be considered a priority for streamlining biosimilar development. One main discussion theme was a need to identify a common way of reporting product quality data in 351(k) BLAs since different sponsors often submit varying quality attribute descriptors and data. For example, glycosylation can be reported in different ways. Participants emphasized a need to establish reporting criteria for (1) PQAs, (2) the number of analytical methods, (3) the number of reference product and biosimilar candidate batches at each manufacturing stage (e.g., process development, good manufacturing practices (GMP), commercial scale), and (4) statistical design. Regarding number three, due to challenges in procuring reference product batches and the numerous batches required for analytical studies, participants questioned whether it would be possible to generate more confidence using smaller and/or fewer batches. Participants highlighted that establishing a common data reporting structure might facilitate review and expedite regulatory decision making by creating consistency in BLA submissions.

Given that multiple companies conduct analytical assessments across the biosimilar landscape, another discussion topic was creating benchmarks for certain analytical methods by setting standards for assay capabilities (e.g., common separation technology; common nonclinical methods to assess immunogenicity).

Lastly, participants indicated a need to create generalizable consensus standards on the relationships between PQAs and clinical performance (as outlined in priority a) to reduce barriers for sponsors to enter the biosimilar

[7] Part of the summary text here was discussed during the time allotted for priority d but was moved to priority b for ease of the reader.

development space. These consensus standards should include the nature of quality attributes, their context of use, and criteria for measurement of the quality attributes.

Regulatory Impact 2: Develop alternatives to and/or reduce the size of studies involving human subjects

Updated Research Priorities for Regulatory Impact 2: Develop alternatives to and/or reduce the size of studies involving human subjects
d. Develop alternatives to the comparative clinical immunogenicity assessment(s)
e. Define development approaches that will increase feasibility and/or likelihood of successful biosimilar development
f. Identify user interface differences that will likely lead to difference in use error rates or use success rates in the context of pharmacy substitution

d. Develop alternatives to the comparative clinical immunogenicity assessment(s)[8]

Participants agreed that developing alternatives for comparative clinical immunogenicity assessments should be a research priority and were eager to consider a future state when comparative clinical immunogenicity will no longer be needed as part of the biosimilar development process. During the discussions, participants considered difficulties in determining when a comparative clinical immunogenicity assessment is needed in part due to not understanding the impact of analytical differences, if any are identified, on safety between the biosimilar and reference product.

As potential approach to address the challenges described above, participants discussed that a starting point should always be a robust immunogenicity risk assessment of the biosimilar candidate that includes what is known about the immunogenicity profile of the reference product. For example, comparative clinical immunogenicity assessments could be maintained for biosimilar candidates to reference products that pose a high risk for immunogenicity (e.g., live saving products that have therapeutic endogenous counterpart with non-redundant function). Conversely, these clinical assessments may not be needed for biosimilars candidates to reference products with low immunogenicity risk because a clinical assessment would not be sensitive enough to detect a difference, if any. Participants also highlighted that advancement of analytic technologies can result in detecting PQAs of the reference product that were not observed during the original development and not evaluated during early reference product manufacturing changes.

Ideally analytical data from nonclinical immunogenicity assessments would also help determine whether a clinical immunogenicity assessment may be needed. However, participants highlighted challenges around how predictive the results of nonclinical immunogenicity assessments are to clinical immunogenicity as well as the threshold for differences in assay results observed that may indicate a possible difference in clinical safety.

[8] Part of the summary text here was discussed during the time allotted for priority b but was moved to priority d for ease of the reader.

e. Define development approaches that will increase feasibility and/or likelihood of successful biosimilar development[9]

During the discussions, participants indicated that identifying and creating approaches to enable successful biosimilar development is an important area of research. Given that this priority area is intentionally worded very broadly, ideas and additional details on the approaches of interest and clarification on expectations from FDA would be helpful (e.g., benchmarks and expected milestones for PQAs), particularly focused on the approaches that will reduce the need for clinical assessments that are not product specific (e.g., comparative clinical efficacy studies). Of note, FDA indicated that there is an emerging technology program in which FDA engages with sponsors early in development to discuss novel technology and confirm that the resulting analytical data are robust, can be validated, and meets regulatory expectations.[10]

The development of pharmacodynamic (PD) biomarkers is not required for successful biosimilar development, and if a PD biomarker has not already been established, participants highlighted that a biosimilar developer is not incentivized to invest resources to develop one. A developer is more likely to suspend a biosimilar product program rather than invest in the process of identifying and developing a PD biomarker. Any related research should clarify when PD biomarkers would be appropriately used in lieu of comparative efficacy study.

However, participants also noted that comparative clinical efficacy studies are often not informative for resolving uncertainty around a biosimilar candidate's clinical performance, so if a PD biomarker is being used in lieu of a comparative clinical efficacy study, the value add of the PD biomarker is not immediately clear. Additionally, participants noted that a proposed product is highly similar through multiple independent approaches (i.e., orthogonal analytics), then a PD biomarker should not be needed. Similarly, in situations where there might be variations in charge or certain other attributes, but strong biological characterization and PK data are available, data from a PD biomarker also should not be needed.

f. Identify user interface differences that will likely lead to difference in use error rates or use success rates in the context of pharmacy substitution

Participants agreed that it is important to conduct research to understand how the substitution of a biosimilar for a reference product at the pharmacy level that involves a device change could lead to differences in error rates or success rates. Specifically, there is a need to better understand the role of human factors, patient priorities, and perceptions of product safety when a device change occurs with a substituted drug-device combination. Information about differences in the devices or delivery could include the shape of the injector, the number of steps required for injection, the number of doses delivered, and which physical characteristics or aspects pf clinical performance, if any, could be altered.

Participants also highlighted the flexibility to differentiate a biosimilar product from the reference product through novel biosimilar device development without compromising clinical performance and that patent protections sometimes necessitate the development of a novel biosimilar device. Additionally, the application of statistical methodology to clinical human factor studies is extremely time- and cost-intensive and incentivizing developers not to innovate.

[9] There was additional discussion about the role of clinical data in biosimilar adoption as some physicians have reported challenges in patient adoption of biosimilar use and view clinical studies to provide additional assurance of safety and efficacy to patients. FDA is aware that there is an educational need among providers and has been working to address this gap through the development of educational and training materials for use in healthcare degree program curricula. These discussions are out of scope of the BsUFA III Regulatory Science Pilot Program and are not included in this integrated summary. Please see the following URL for additional information: https://www.fda.gov/drugs/biosimilars/curriculum-materials-health-care-degree-programs-biosimilars

[10] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program

SUMMARY OF PARTICIPANT FEEDBACK ON IN-PERSON ROUNDTABLE DISCUSSIONS

The following section provides a summary of the participant feedback survey results that were collected following the October 26 in-person roundtable discussions.

Following the in-person roundtable discussions, the 20 participants were invited to provide their feedback on the event through an online survey. The survey included three questions that gauged how informative the roundtable discussions were and the participants' preference for similar in-person events in the future. Twelve of the 20 participants (60%) responded to the survey. Most participants found the meeting to be very informative and all participants would be in favor of similar in-person events. Table 3 shows the questions posed to the participants, the available response options, and the survey results.

Table 3: Roundtable Participant Feedback Survey Results

Question	Response Option	% of Participant Reponses (n = 12)
Q1. Overall, how informative did you find your roundtable discussion regarding your understanding of different stakeholders' perspectives on biosimilar development?	Very Informative	75.0%
	Informative	16.7%
	Minimally Informative	8.30%
Q2. Overall, how informative did you find your roundtable discussion in clarifying how you and/or your organization can contribute to the BsUFA III Regulatory Science Pilot Program?	Very Informative	58.3%
	Informative	25.0%
	Moderately Informative	8.3%
	Minimally Informative	8.3%
Q3. Would you like to see more meetings similar to the in-person roundtable discussion hosted by the BsUFA III Regulatory Science Pilot Program?	Yes	100.0%
	No	0.0%

SUMMARY TABLE OF DISCUSSION TOPICS

The following table provides a high-level snapshot of the main discussion topics from the in-person roundtable discussions held on October 26, 2023. Stakeholders can use this table as a reference when considering furthering discussions or engagements with FDA. Stakeholders are encouraged to contact the BsUFA III Regulatory Science Pilot Program at: BsUFARegSciProgram@fda.hhs.gov

Table 4. Summary of Roundtable Discussion Topics

Research Priority	General Discussion Topics
a. Characterize relationships between product quality attributes (physiochemical or biological) with clinical outcomes	• Characterizing the relationship between PQAs and clinical performance is the foundation for increasing the use of analytical data for the demonstration of biosimilarity. • For biosimilar candidates (and their reference products) with clinical and regulatory experience, post-approval manufacturing changes and data submitted that is publicly available should be able to streamline the comparative analytical assessment(s). • For biosimilar candidates (and their reference products) with a lack of clinical experience and/or data available, there is potential for bioassays, animal models, and computational modeling to correlate analytical data with biological function and/or clinical performance. Research efforts would be needed to increase the experience and confidence in these methodologies.
b. Explore how modernization of analytical technologies could better and/or more efficiently detect relevant quality attributes	• Given that it is becoming more common for certain analytical expertise technologies to be housed in contract organizations, increasing the efficiency of the comparative analytical assessment (CAA) could have an outsized impact on the efficiency of biosimilar development. • Given that many unsuccessful biosimilar development programs fail at the manufacturing stage, research efforts should focus on understanding the impact of manufacturing changes on product quality. • If FDA has identified any scientific or research gaps that, when filled, would lead to paradigm shift to a three-way analytical bridge-only approach when using a non-US comparator, this should be a research priority.
c. Define best practices for assessing and reporting quality attributes	• There is a need to establish reporting criteria for (1) PQAs, (2) the number of analytical methods, (3) the number of reference product and biosimilar candidate batches at each manufacturing stage (e.g., process development, GMP, commercial scale), and (4) statistical design. • Creating benchmarks for certain analytical methods by setting standards of assay capability could increase review consistency and expedite regulatory decision making. • As a follow up to priority a, there needs to be generalizable consensus of standards for the relationship between quality attributes and clinical performance.

Research Priority	General Discussion Topics

d. Develop alternatives to the comparative clinical immunogenicity assessment(s)	• An alternative process to the default clinical immunogenicity assessment could be:
	  ○ Conducting a robust immunogenicity risk assessment of the biosimilar candidate that includes what is known about immunogenicity profile of the reference product.
	  ○ Leveraging nonclinical immunogenicity data to de-risk, focus and/or inform the clinical assessment.
	  ○ Defining when low(er) risk products may not need a comparative immunogenicity assessment beyond the CAA unless there is a specific difference identified with unknown relevance.
	• Further research is needed to interpret the differences in results from in-vitro assays that could indicate a possible difference in the safety profile between the biosimilar and reference product.

e. Define development approaches that will increase feasibility and/or likelihood of successful biosimilar development	• This priority area is intentionally worded very broadly to promote creativity, but ideas and additional details on the approaches of interest and clarification on expectations would be helpful. • The role of PD biomarkers in biosimilar development is unclear. Any research in this area should clarify when PD biomarkers would be needed/appropriate.
f. Identify user interface differences that will likely lead to difference in use error rates or use success rates in the context of pharmacy substitution	• Needed information or research about meaningful differences in devices or delivery systems includes (1) the shape of the injector, (2) the number of steps required for injection, (3) the number of doses delivered, and (4) which physical characteristics or aspects of clinical performance, if any, could be affected.

APPENDIX

This section includes all acronyms used in this document along with a corresponding definition.

Acronyms	Definition
BLA	Biologics License Application
BsUFA	Biosimilar User Fee Act
CAA	Comparative Analytical Assessment
FDA	U.S. Food and Drug Administration
GMP	Good Manufacturing Practices
PD	Pharmacodynamic
PK	Pharmacokinetic
PQA	Product quality attribute
U.S.	United States