U.S. FOOD & DRUG ADMINISTRATION

BsUFA III Regulatory Research Pilot Program:

Revised Research Priorities

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Biosimilar Introduction and Background

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) created an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with a Food and Drug Administration (FDA)-licensed biological product.[1] This pathway was established as a way to provide more treatment options, increase access to lifesaving medications, and potentially lower health care costs through competition.[2]

The development of biosimilar biological products (also referred to as biosimilars or biosimilar products) is grounded in the comparison of a proposed biosimilar product to an FDA-licensed biological product, referred to as the reference product. The comparative data for biosimilarity are generated from detailed analytical (structural and functional) characterization and clinical studies, as appropriate.[3]

For FDA licensure of a biosimilar product, the proposed biosimilar must be "*highly similar to*" and have "*no clinically meaningful differences… in… safety, purity, and potency*" from a reference product. As such, the goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar product and the reference product, not to independently establish the safety and effectiveness of the proposed biosimilar product (Figure 1).

Along with the demonstration of biosimilarity, a sponsor may request licensure of their biosimilar product as "interchangeable," which means that a biosimilar product may be substituted for the reference product without the involvement of the prescribing health care provider, subject to state pharmacy law. To meet the standards for interchangeability, an applicant must provide information to show that the proposed interchangeable biosimilar product is biosimilar to the reference product; "can be expected to produce the same clinical result as the reference product in any given patient"; and for a product administered more than once to an individual, switching between the proposed interchangeable biosimilar product and the reference product does not increase safety risks or decrease effectiveness compared to using the reference product without such switching between products.[5]

As of December 2023, FDA has licensed 45 biosimilar products, 7 of which are interchangeable; 38 are reported as being actively marketed. As of Fall 2022, actively marketed biosimilar products have been reported to account for a range of their market share from 3 to above 80 percent.[6,7] As the U.S. biosimilar market continues to evolve, clinical use of biosimilars is projected to save the U.S. health care system billions of dollars and is expected to increase access to patients.[8,9]

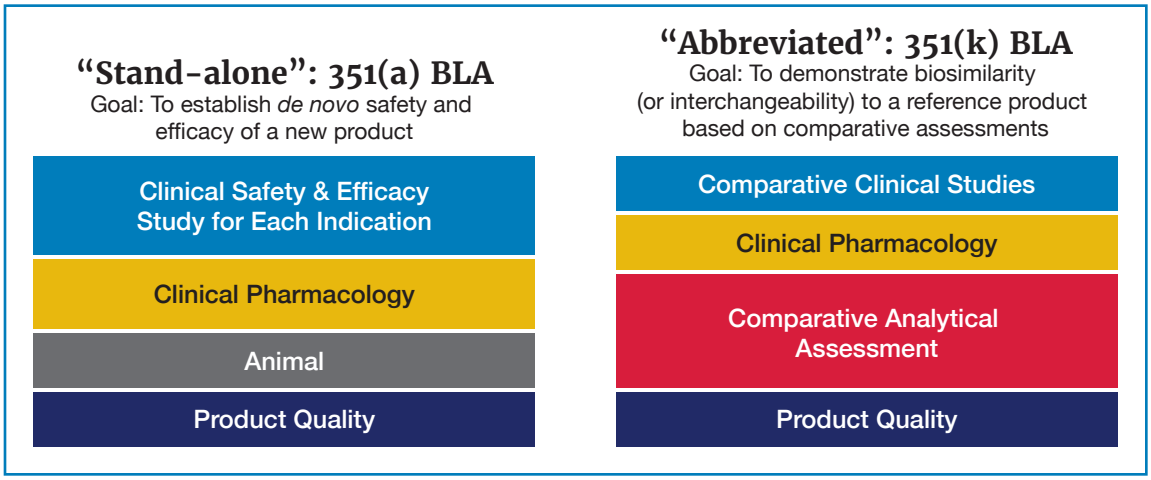

Figure 1: Typical Data Composition of a "Standalone" 351(a) Biologics License Application (BLA) and an "Abbreviated" 351(k) BLA

Biosimilar User Fee Act (BsUFA)

The Biosimilar User Fee Act (BsUFA) provides FDA with user fee revenue for the review of biosimilar biological product submissions. The first authorization of BsUFA (Fiscal Year [FY] 2013–2017) enabled the development of the initial infrastructure needed to support the biosimilar review program. Under BsUFA II (FY 2018–2022), FDA focused on effective scientific coordination and review consistency through review, procedural, and meeting performance enhancements.[10]

BsUFA III (FY 2023–2027) builds on BsUFA I and II. Under BsUFA III, FDA is committed to ensuring effective scientific coordination and review consistency, as well as efficient governance and operations across the biosimilar biological product review program. In addition, the BsUFA III commitment letter includes a commitment for FDA to pilot a regulatory science research program to further enhance regulatory decision-making and facilitate science-based recommendations in areas foundational to biosimilar development.[11]

The Regulatory Science Research Pilot Program Under BsUFA III

The BsUFA III regulatory research pilot 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 BsUFA III commitment letter identified two aims, or demonstration projects, for the BsUFA III regulatory research pilot program: **(1) advancing the development of interchangeable products** and **(2) improving the efficiency of biosimilar product development.**

The "*advancing the development of interchangeable products*" demonstration project focuses on generating information and methodologies to meet the safety standards for determining interchangeability, including methodologies to predict immunogenicity and assess differences in product presentations and container closure systems. The "*improving the efficiency of biosimilar product development*" demonstration project aims to enhance efforts to streamline biosimilar product development and specifically highlights development of methodologies to predict immunogenicity and to conduct analytical and pharmacological assessments (Box 1).[12]

Box 1: Demonstration Projects from BsUFA III Commitment Letter

Advancing Development of Interchangeable Products

This demonstration project will be focused on progressing research to advance the development of interchangeable products. Specifically, this demonstration project will:

- Investigate and evaluate the data and information (including Real-World Evidence[RWE]) needed to meet the safety standards for determining interchangeability under Section 351(k)(4) of the PHS Act, including:
  - Investigate and evaluate informative, scientifically appropriate methodologies to assess the potential impact of differences between proposed interchangeable biosimilar and reference product presentations and container closure systems.
  - Investigate and evaluate informative, scientifically appropriate methodologies to predict immunogenicity by advancing the knowledge of analytical (including physical, chemical and biological function assays), pharmacological and clinical correlations as relates to interchangeability.

Improving the Efficiency of Biosimilar Product Development

This demonstration project will be focused on progressing research to advance the efficiency of biosimilar product development, enhance regulatory decision-making based on the latest scientific knowledge, and advance the use of innovative scientific methodologies and experience with biosimilars. Specifically, this demonstration project will:

- Review and evaluate opportunities for streamlining and targeting biosimilar product development in consideration of scientific advancements in analytical (including physical, chemical, and biological function assays), and pharmacological assessments and experience with prior biosimilar product development and marketed biosimilar products.
- Investigate and evaluate informative, scientifically appropriate methodologies to predict immunogenicity by advancing the knowledge of analytical (including physical, chemical, and biological function assays), pharmacological, and clinical correlations as it relates to biosimilarity.

Achieving Regulatory Impact from the Demonstration Projects of the Regulatory Science Research Pilot Program

DEFINING REGULATORY IMPACT

To achieve the demonstration projects in the BsUFA III commitment letter, all research outcomes and deliverables should have a clear regulatory impact. For the purposes of this document, **regulatory impact is defined as a research outcome(s) that is expected to inform science-based recommendations and regulatory decision-making at FDA**. Given that the end of BsUFA III is September 30, 2027, the BsUFA III regulatory research pilot program is broadly structured around completion of research outcomes, regulatory impact, and commitment letter deliverables by that date. However, given the goals of the BsUFA III regulatory research pilot program and the nature of research, research outcomes that are expected to achieve a critical milestone toward a regulatory impact are also relevant to completing the "demonstration projects" deliverables.[13] In general across all its research programs, FDA strives for balanced research portfolios with both shorter and longer-term goals. This approach allows FDA to be nimble enough to identify and address acute gaps or issues while laying the scientific groundwork for where regulatory practice is headed.

SPECIFYING THE REGULATORY IMPACT THAT WOULD BE ACHIEVED BY THE DEMONSTRATION PROJECTS

To advance the development of interchangeable products and improve the efficiency of biosimilar product development, FDA is focused on the composition of the data package to support approval of a biosimilar or interchangeable biosimilar product and ways to streamline it while still ensuring that the submission can support the requirements for approval of such products. FDA identified two areas where the data package to support approval of a biosimilar or interchangeable biosimilar product under Section 351(k) of the Federal Food, Drug, and Cosmetic (FD&C) Act could be streamlined. The first is **increasing the reliance on analytical data in a demonstration of biosimilarity**. The second is **developing alternatives to and/or reducing the size of studies involving human participants** (Figure 2).

Demonstration projects undertaken in these two areas are expected to inform FDA science-based recommendations and regulatory decision-making about leveraging comparative analytical data and minimizing the clinical data needed to support approval of a biosimilar or interchangeable biosimilar product.[14]

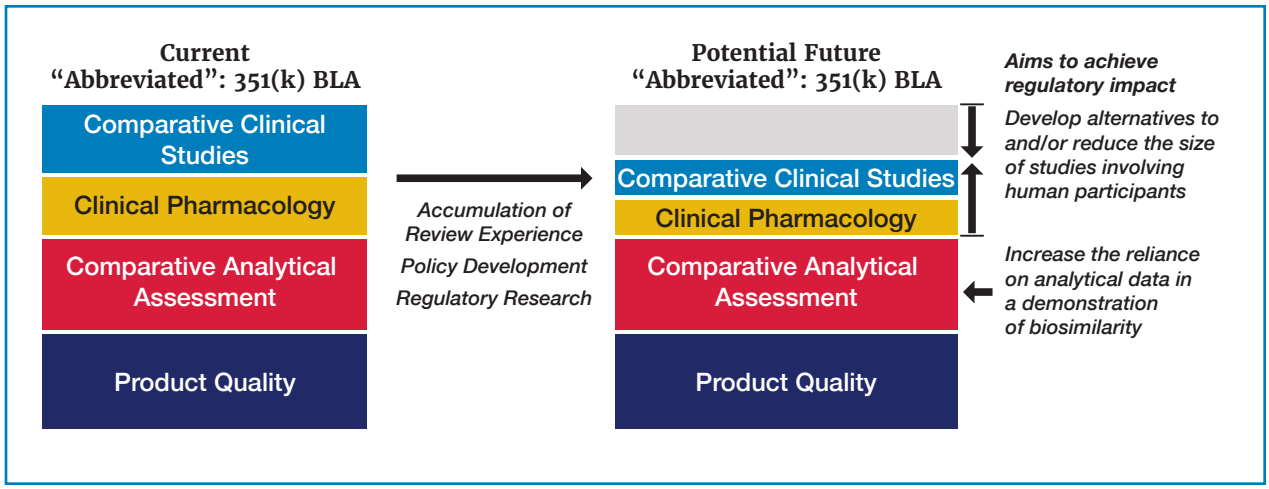

Figure 2: The Focus of the Regulatory Science Pilot Program Is on the Composition of the Data Package to Support Approval of Biosimilar or Interchangeable Products

RESEARCH PRIORITIES TO ACHIEVE REGULATORY IMPACT

To achieve the regulatory impact outlined above, FDA is publishing this research roadmap to highlight research areas of interest, herein called priorities. These priorities were initially compiled by a multidisciplinary team within FDA, with expertise in the disciplines relevant to biosimilar regulatory review (e.g., Product Quality, Clinical Pharmacology, Clinical, RWE, and Human Factors) and then updated based on comments from stakeholders.[15,16] An outline of the considerations used to identify and revise the research priorities are found in Box 2. Researchers, both external and internal to FDA, should use this roadmap to guide research proposals, collaborations, and other efforts to seek BsUFA III research funding opportunities. All proposed research should clearly identify the regulatory gap that the research is trying to address and how the research outcomes will have regulatory impact.

Box 2: Considerations for the Selection of Research Priorities

Knowledge/information/methodology that:

- Would help FDA apply the current scientific thinking and product-specific regulatory experience more broadly across all biosimilar development and regulation
- Is in alignment with the BsUFA III Commitment Letter and demonstration projects
- Would need FDA-specific expertise (e.g., principal investigator, project officer)
- Could be reasonably obtained through a (set of) research projects outcomes and deliverables
- Is not duplicated elsewhere internally or externally of FDA
- Is not product or product-class specific*

Other considerations include:

- Scientific or regulatory challenges identified by stakeholders and/or FDA
- Topics that have repeatedly required extensive internal debate across disciplines
- Knowledge or methodology gaps that, when filled, would expand the feasibility of certain biological products entering biosimilar development as reference products (e.g., biologics that are difficult to develop and/or part of a combination product)
- Areas where there is a lack of global regulatory convergence

** This consideration is a condition of the BsUFA III regulatory science commitment and is outlined in the commitment letter document. For the purposes of this document, a product class is defined as protein products that are homologous to the same gene-coded sequence. This definition includes additional novel flanking sequences (including sequences from other genes) and/or discrete changes in gene-coded sequence and/or discrete changes in post-translational modifications even if the result may be a change in product pharmacokinetics (PK).*

Research Priorities to Increase the Reliance on Analytical Data in a Demonstration of Biosimilarity

Approval of a biosimilar product requires, among other things, a demonstration that the biosimilar product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences in terms of safety, purity, and potency between a biosimilar product and its reference product.[17] In general, conducting laboratory-based comparative structural analyses and functional assays is relatively less resource-intensive than conducting clinical studies. Therefore, defining and standardizing analytical approaches that have known relevance to clinical performance could help support demonstrations of no clinically meaningful differences using less resources than clinical studies. As such, FDA has defined the following research priorities (Box 3).

a. **Characterize relationships between product quality attributes (physiochemical or biological) with clinical performance**
Additional data or studies are often requested in 351(k) development programs when the clinical relevance of a difference in a product quality attribute(s) is unknown. For these instances, understanding these two factors will inform the need for additional studies: (1) which product quality attributes have the potential to impact safety, purity, and potency, and (2) the magnitude of the difference that may result in a meaningful clinical impact. Specifically for biological assays, assays that mimic the physiological environment may be informative on mechanism(s) of action (MOA), pharmacokinetics/pharmacodynamics (PD), and immunogenicity.

b. **Explore how modernization of analytical technologies could better and/or more efficiently detect relevant quality attributes**
Ongoing advances in analytical sciences continue to improve on or accelerate the ability to characterize protein products in terms of their physicochemical and biological properties. Although current analytical methods are generally sufficiently sensitive and precise for the

comparative analytical assessment (CAA), applying ongoing scientific advancements to biosimilar development could allow modernization and/or the ability to streamline the CAA. Of note, the proposals aimed at addressing this priority should not be solely focused on technology/method development, but on how technology/method advancement may contribute to biosimilar development, and as such, proposals should work synergistically with research priority a.

c. **Define best practices for assessing and reporting quality attributes**
Efforts that produce publicly available resources identifying parameters of commonly used methodologies for the structural and functional characterization of biosimilar candidates could build toward a broader public knowledge of method expectations. This type of research could facilitate reliance of certain methodologies and identify best practices for CAAs. In addition, standardized reporting could also streamline regulatory review of certain methodologies.

Taken together, research focused on these three priorities (a–c) should aim to increase the ability of comparative analytical assessments to reduce any uncertainty associated with previously undetected or small differences in product quality attributes between the reference product and a proposed biosimilar.

Research Priorities to Develop Alternatives to and/or Reduce the Size of Studies Involving Human Participants

Applicants have historically shown "no clinically meaningful differences" in terms of safety, purity, and potency between a biosimilar product and its reference product through clinical studies, including comparative human pharmacokinetic and PD studies (if there is a relevant PD biomarker available) and a descriptive comparison of immunogenicity in an appropriately sensitive study population. When there weren't relevant or suitable PD biomarkers available, a comparative efficacy study in patients was generally recommended to establish statistical evidence that the biosimilar was neither inferior nor superior to the reference product. To meet the standards of interchangeability, switching studies and/or comparative use human factor (CUHF) studies have been recommended.

Because studies involving human participants are generally substantially more resource-intensive in terms of time and money compared to laboratory-based comparative assessments, FDA is interested in alternative methods, approaches and/or leveraging accumulation of regulatory experience[18,19,20] to establish that there are "no clinically meaningful differences" in terms of safety, purity, and potency between a biosimilar product and its reference product and/or to establish that the biological product can be expected to produce the same clinical result as the reference product "in any given patient." Examples of biosimilar approvals that are consistent with these ideas can be found in Table 1. To advance these ideas, FDA has the following research priorities (Box 3).

Box 3: Research Priorities That Aim to Result in Regulatory Impact

Regulatory Impact #1: Increase the reliance on analytical data in a demonstration of biosimilarity

- Characterize relationships between product quality attributes (physiochemical or biological) with clinical performance
- Explore how modernization of analytical technologies could better and/or more efficiently detect relevant quality attributes
- Define best practices for assessing and reporting quality attributes

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

- Develop alternatives to the comparative clinical immunogenicity assessment(s)
- Define approaches that will increase feasibility of biosimilar development (e.g., PD biomarkers, model informed drug development [MIDD] including artificial intelligence and/or machine learning)
- Identify user interface differences that will likely lead to differences in use error rates or use success rates

Table 1: Examples of Biosimilar Approvals That Used Alternative Methods, Approaches, and/or Accumulation of Regulatory Experience

Biosimilar BLA Number	Reference Product	Year of Licensure	Reference	Result from Use of an Alternative Approach and/or Accumulation of Regulatory Experience
BLA761173	Pegfilgrastim	2022	Drug Approval Package: STIMUFEND (fda.gov)	PK/PD studies, without clinical efficacy data, supported a demonstration of biosimilarity
BLA761084	Pegfilgrastim	2022	Drug Approval Package: FYLNETRA (fda.gov)	
BLA761111	Pegfilgrastim	2020	Drug Approval Package: NYVEPRIA (fda.gov)	
BLA761039	Pegfilgrastim	2018	Drug Approval Package: UDENYCA (fda.gov)	
BLA761201	Insulin glargine	2021	Drug Approval Package: SEMGLEE (fda.gov)	PK/PD studies, without clinical efficacy or switching data, supported a demonstration of biosimilarity and interchangeability
BLA761215	Insulin glargine	2022	Drug Approval Package: REZVOGLAR (fda.gov)	
BLA761165	Ranibizumab	2022	Drug Approval Package: CIMERLI (fda.gov)	No clinical switching data was needed to support a demonstration of interchangeability
BLA761322	Natalizumab	2023	Drug Approval Package: TYRUKO (fda.gov)	PK/PD studies, without clinical efficacy data, supported a demonstration of biosimilarity

d. Develop alternatives to comparative clinical immunogenicity assessment(s)

In general, clinical studies are inefficient at detecting rare adverse immune events. FDA aims to explore additional methods and/or other approaches to generate the evidence needed to compare potential adverse immunogenic responses between a proposed biosimilar and a reference product. These approaches could include, but are not limited to, in-silico and in-vitro assays to compare immunogenicity risk and RWE from clinical experience with the reference product and/or global experience with a biosimilar(s). For existing in-silico and in-vitro assays, a key knowledge gap is how changes in assay read-outs correlate to changes in immune-mediated adverse events in the clinic. Additional key knowledge gaps were discussed at three FDA public workshops.[21,22,23] For RWE, a key knowledge gap is availability of relevant clinical endpoints and data standardization. Further information on key knowledge gaps can be found at these citations.[24,25,26,27]

e. Define approaches that will increase feasibility of biosimilar development (e.g., PD biomarkers, MIDD including artificial intelligence and/or machine learning)

In addition to development of new or alternative approaches that not only reduce the need for comparative efficacy studies in patients, research could also aim to increase the feasibility of development of biosimilars to certain reference products. Examples could include: (1) use of PD biomarkers that are not surrogate clinical endpoints to reduce the size of clinical studies and/or replace patients, if appropriate, as study participants with healthy volunteers; (2) use of modeling and simulation to reduce the size and/or duration of clinical pharmacology studies. Some key knowledge gaps in these areas were discussed at these citations.[28,29,30]

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

There needs to be criteria for determining which user interface differences between a proposed interchangeable product and a reference product could contribute to differences in use error rates and when these differences should be further evaluated to determine if they affect safe and effective use.

Research approaches for this priority could include comparative use human factor (CUHF) studies and/or other methodologies.

Research focused on these three priorities (d–f) should ultimately aim to develop alternatives to and/or reduce the size of studies involving human participants while maintaining the rigorous standards for biosimilarity and interchangeability.

Methods to Consider for Research Conducted as Part of the Pilot Program

Development of a range of methodologies will be important for achieving the goals outlined for the BsUFA III regulatory research program. These can include, but are not limited to:

- Analytical methods
- Biological functional assays
- Efficient clinical study design (e.g., statistical methods)
- In-silico/in-vitro modeling
- MIDD applications including artificial intelligence and machine learning
- Pharmacological studies
- Real-world data/RWE

Award Management at the FDA

FDA's Office of Acquisition and Grant Services (OAGS)[31] manages all external FDA awards. This process is subject to the terms and conditions, cost principles, and other considerations described in the HHS Grants Policy Statement[32] and 45 *Code of Federal Regulations* (CFR) 75.

The BsUFA III regulatory science pilot program has been using the Notice of Funding Opportunity (NOFO) mechanism to solicit cooperative agreement proposals.[33,34] The program is also using or planning on using other award mechanisms, such as the Broad Agency Agreement (BAA)[35,36] and/or Center(s) of Excellence for Regulatory Science and Innovation (CERSI).[37] To ensure notification of funding opportunities, please email BsUFARegSciProgram@fda.hhs.gov to be included in the distribution and communication of funding opportunities.

For external awards, the BsUFA III regulatory science pilot program has been assigning two project officers who have the regulatory and technical expertise required to oversee the research. Interactions between the awardees and project officers occur at regular progress meetings, and upon evaluation of the submitted annual and final reports as stipulated in the Notice of Award (NOA).

Internal awards are overseen by a multidisciplinary team within FDA, with expertise in the relevant disciplines to biosimilar regulatory review (e.g., Product Quality, Clinical Pharmacology, Clinical Medicine, RWE, and Human Factors).

Deliverables of the BsUFA III Regulatory Research Pilot Program

FDA is committed to a continuous and transparent conversation with both its internal and external stakeholders about designing research that will push biosimilar development forward. Outlined in the commitment letter, publicly available deliverables for the BsUFA III Regulatory Research Pilot Program include: (1) an **interim progress report and workshop** of research progress mid-way through BsUFA III (on or before October 31, 2025), (2) a **final summary report** of the outcomes from the pilot program at the end of BsUFA III (on or before September 30, 2027), and (3) a **comprehensive strategy document** using the learnings from the demonstration projects and outlining specific actions the agency will take to facilitate the development of biosimilar and interchangeable biological products (within 12 months of completion of the demonstration projects).

FDA anticipates that the biosimilar and interchangeable landscape will continue to evolve. As such, both regulatory experience and policy development may inform and change the knowledge gaps for the research pilot program as BsUFA III progresses. FDA welcomes all stakeholder input on the regulatory research pilot program and its ability to enhance regulatory decision-making and facilitate science-based recommendations in areas foundational to biosimilar development (Figure 3).

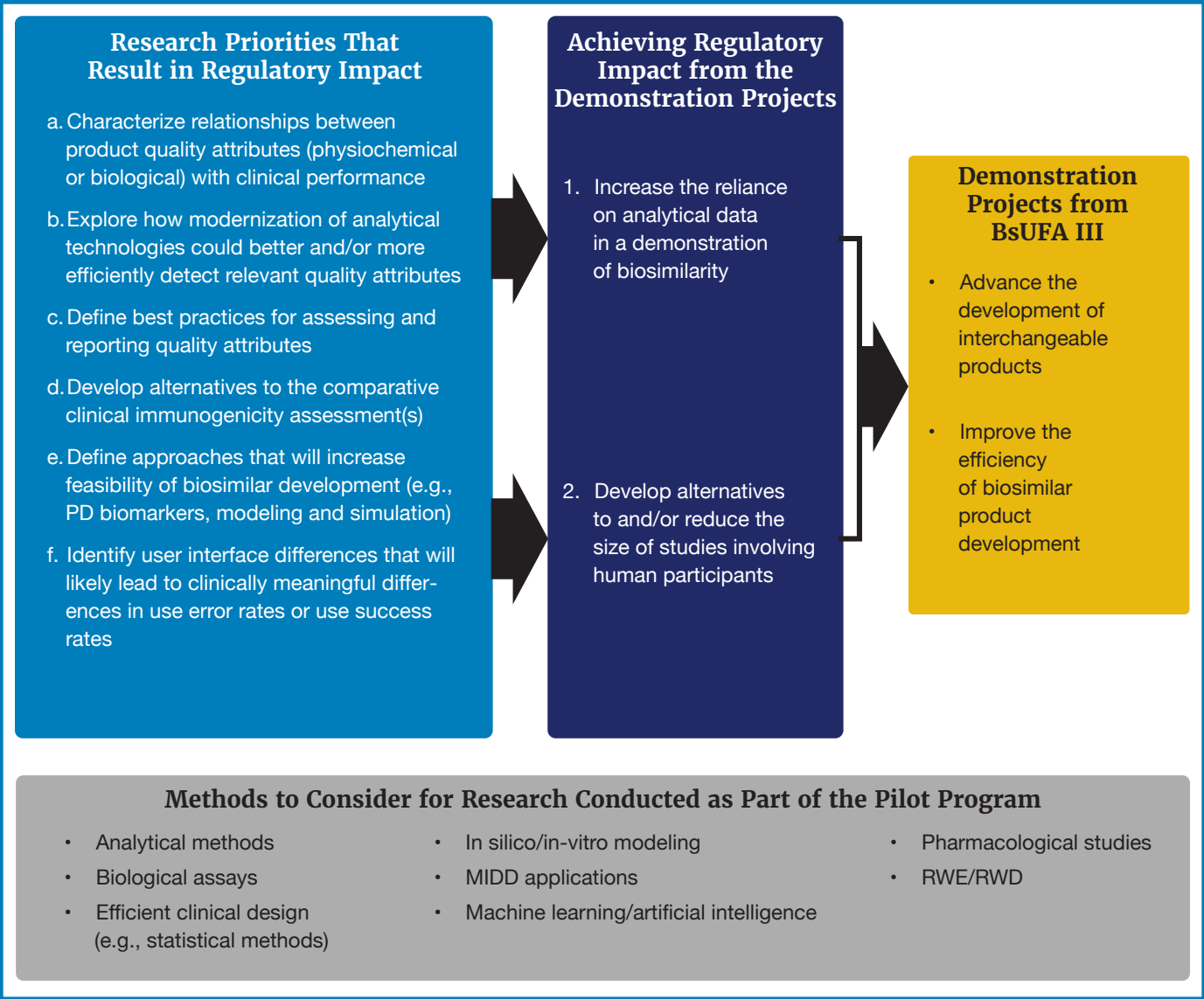

Figure 3: Structure of the BsUFA III Regulatory Research Pilot Program

Notes

1 https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars.

2 https://www.fda.gov/media/114574/download

3 https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval

4 Section 351(i)(2) of the Public Health Service (PHS) Act

5 https://www.fda.gov/drugs/biosimilars/review-and-approval

6 https://www.cardinalhealth.com/content/dam/corp/web/documents/Report/cardinal-health-biosimilars-report-2023.pdf

7 https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/biosimilars-in-the-united-states-2023-2027/iqvia-institute-biosimilars-in-the-united-states-2023-usl-orb3393.pdf

8 https://www.ajmc.com/view/projected-us-savings-from-biosimilars-2021-2025

9 https://accessiblemeds.org/sites/default/files/2023-09/AAM-2023-Generic-Biosimilar-Medicines-Savings-Report-web.pdf

10 https://www.fda.gov/about-fda/user-fee-performance-reports/bsufa-performance-reports

11 https://www.fda.gov/industry/biosimilar-user-fee-amendments/bsufa-iii-fiscal-years-2023-2027

12 https://www.fda.gov/media/152279/download

13 A null or negative research result/outcome can be informative from a regulatory perspective.

14 See Section 351(i)(2) & (k)(3) of the PHS Act.

15 https://www.regulations.gov/document/FDA-2023-N-0254-0001

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

17 Section 351(i)(2) and (k) of the PHS Act

18 https://pubmed.ncbi.nlm.nih.gov/33031559/

19 https://pubmed.ncbi.nlm.nih.gov/37831324/

20 https://pubmed.ncbi.nlm.nih.gov/37788264/

21 https://www.fda.gov/science-research/advancing-regulatory-science/predictive-immunogenicity-better-clinical-outcomes

22 https://www.fda.gov/drugs/news-events-human-drugs/non-clinical-immunogenicity-assessment-generic-peptide-products-development-validation-and-sampling

23 https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/model-informed-drug-development-approaches-immunogenicity-assessments-06092021-06092021

24 https://healthpolicy.duke.edu/publications/revisiting-interchangeability-realize-benefit-biosimilars

25 https://pubmed.ncbi.nlm.nih.gov/34143406/

26 https://pubmed.ncbi.nlm.nih.gov/31298463/

27 https://pubmed.ncbi.nlm.nih.gov/31692176/

28 https://pubmed.ncbi.nlm.nih.gov/36178447/

29 https://pubmed.ncbi.nlm.nih.gov/30395832/

30 https://www.fda.gov/science-research/about-science-research-fda/modeling-simulation-fda

31 https://www.fda.gov/about-fda/doing-business-fda

32 https://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf

33 https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-22-026.html

34 https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-23-026.html

35 https://sam.gov/opp/43715c8512d1425eb082486f6dc00ef7/view

36 https://www.fda.gov/science-research/advancing-regulatory-science/regulatory-science-extramural-research-and-development-projects

37 https://www.fda.gov/science-research/advancing-regulatory-science/centers-excellence-regulatory-science-and-innovation-cersis

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Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

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