U.S. FOOD & DRUG ADMINISTRATION

BsUFA III Regulatory Research Pilot Program:

RESEARCH ROADMAP

CONTENTS

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 an 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 biosimilars 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, animal studies, and/or comparative clinical studies.[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, an existing FDA-licensed reference product.[4] 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).

After or contemporaneously 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 prescriber, subject to state law. To meet the standards for interchangeability, an applicant must provide data to demonstrate that the biosimilar 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 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] Often, the safety data used to support an interchangeability determination is a switching study, which is a clinical study that evaluates the impact of alternating or switching between the proposed interchangeable product and the reference product.[6]

To date, FDA has licensed 40 biosimilar products and 3 interchangeable products; 24 of which are actively marketed. As of October 2021, actively marketed biosimilar products have been reported to account for a range of their market share from 3 to 89 percent.[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]

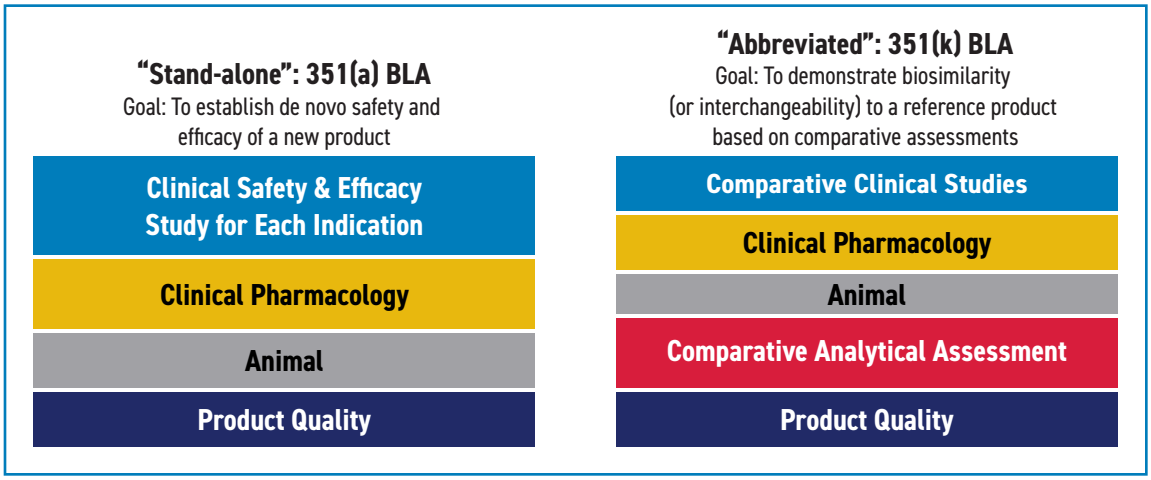


Figure 1. Typical data composition of a "Standalone" 351(a) Biologics License Application (BLA) and an "Abbreviated" 351(k) BLA

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), the Agency focused on effective scientific coordination and review consistency through review, procedural, and meeting performance enhancements.[10]

Starting Oct 1, 2022, 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. Additionally, 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 regulatory research pilot program has two aims, called demonstration projects: **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 generation of information and methodologies to meet the safety standards for determining interchangeability and specifically highlights development of 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 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) 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 BsUFA III REGULATORY RESEARCH PILOT PROGRAM

To achieve the demonstration projects outlined for the BsUFA III regulatory research pilot program, FDA is publishing this research roadmap to highlight scientific areas where advancement is expected to impact science-based recommendations and regulatory decision making. Researchers, both external and internal to FDA, should use this roadmap to guide research proposals, collaborations, and other efforts as they seek BsUFA III research funding opportunities.

Of note, the BsUFA III regulatory research pilot program is structured around completion of deliverables by the end of BsUFA III, September 30, 2027. As such, research deliverables should achieve a clear regulatory impact or a key milestone toward a regulatory impact within this time frame. As specified in the BsUFA III commitment letter, the program is broadly applicable to facilitating biosimilar and interchangeable biological product development and project goals should not be specific to a product or product class.

SCIENTIFIC AREAS FOR REGULATORY IMPACT

FDA has identified two scientific areas that are essential for achieving both demonstration projects: 1) Increasing the accuracy and capability of analytical (structural and functional), and chemistry, manufacturing, and controls (CMC) characterizations and 2) Developing alternatives to and/or reducing the size of studies involving human subjects (Figure 2).

1. Increasing the accuracy and capability of analytical (structural and functional), and chemistry, manufacturing, and controls (CMC) characterizations
(Research Priorities #1a-d)

Given that a reference product's manufacturing process is proprietary, biosimilar product developers cannot replicate the reference product manufacturing process exactly. Due to inherent variability associated with biological product manufacturing, proposed biosimilar products are shown to be "highly similar" to a reference product using current laboratory-based comparative structural analyses and functional assays.[13] Therefore, advancing the accuracy and capability of current analytical technologies and methodologies could reduce any uncertainty associated with previously undetected or small differences in product quality attributes between the reference product and proposed biosimilar product. More confidence from the analytical similarity assessment may decrease the need and, thus the time and resources required for, additional preclinical and/or clinical similarity data. As such, FDA has the following research priorities to increase the accuracy and capability of analytical and CMC characterizations (Box 2):

a. Define and standardize approaches for assessing and reporting product quality attributes:
Publicly available resources indicating parameters of commonly used methodologies for the structural and functional characterization of biosimilar candidates would be valuable (e.g., public repository cataloguing sensitivities and specificities

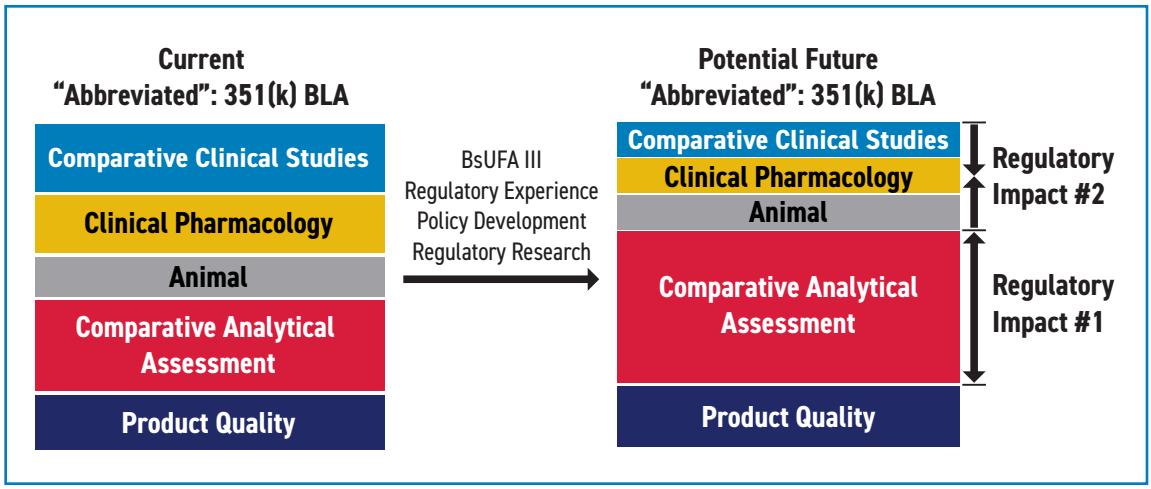


Figure 2. Potential Regulatory Impact of the BsUFA III Regulatory Science Pilot Program

for assays measuring aggregation). Such resources could build towards a broader public knowledge of method expectations and could contextualize when additional methods should be considered for inclusion in the analytical similarity assessment.

b. Characterize relationships between product quality attributes and clinical outcomes:
FDA's standard for approval allows for minor analytical differences between a biosimilar product and its reference product, but there must be no clinically meaningful differences in safety, purity, and potency.[14,15] As such, any analytical differences identified in the analytical similarity assessment must be justified as not clinically meaningful or further assessed, often through clinical studies, to show that they do not result in clinically meaningful differences in terms of safety, purity, and potency. A broader and more complete understanding of both 1) which product quality attributes (physiochemical and biological) have the potential to impact clinical safety, purity, and potency and 2) the magnitude of the difference that may result in a meaningful clinical impact would facilitate biosimilar development.[16] This knowledge, in turn, could reduce the need for additional clinical studies.

c. Improve on and/or develop new analytical technologies:
Ongoing advances in analytical sciences continue to improve the ability to characterize protein products in terms of their physicochemical and biological properties. Continuing to apply ongoing advancements to biosimilar development could expand the analytical similarity assessment to be more extensive, accurate and/or able to characterize more complex molecules (e.g., antibody drug conjugates). Such approaches could work synergistically with Research Priority #1b.

d. Assess the impact of differences of biosimilar or interchangeable, and reference product presentations (e.g., delivery device) and container closure systems on product protection, safety, compatibility, and performance:
Some design differences in the delivery device or container closure system between a proposed biosimilar product and its reference product may be acceptable, if the proposed product meets the standards for biosimilarity. For a proposed biosimilar product in a different delivery device or container closure system, as a scientific matter, the delivery device or container closure system must be shown to be compatible for use with the final formulation of the biological product through appropriate studies, including, for example, extractable/leachable studies and stability studies. Also, for design differences in the delivery device or container closure system, performance testing and a human factors study may be needed. Additionally, data and information supporting the appropriate use and performance testing of the delivery device constituent part of a proposed interchangeable product should be submitted.[18] As such, methodology and data to identify which device-product interactions may impact overall product protection, safety (including immunogenicity), compatibility, and performance is needed.

Taken together, research focused on these four Priorities (#1a-d) should aim to advance the accuracy and capability of current analytical technologies and methodologies, which could reduce any uncertainty associated with previously undetected or small differences in product quality attributes between the reference product and a proposed biosimilar or interchangeable product.

2. Developing alternatives to and/or reduce the size of studies involving human subjects

(Research Priorities #2e-j)

Any remaining uncertainty about similarity between the proposed biosimilar product and reference product following the analytical similarity assessment is subsequently addressed with clinical studies, including pharmacokinetic, pharmacodynamic, and/or comparative clinical studies.[19] Additionally, appropriate use and performance testing (e.g., comparative use human factor [CUHF] study) may be needed for device design differences or container closure system.[20,21] In general, studies involving human subjects are substantially more resource-intensive in terms of time and money compared to laboratory-based assessments.

Recent efforts have resulted in alternatives to comparative clinical studies for certain biosimilars, such as use of a pharmacodynamic (PD) biomarker (absolute neutrophil count) for development of a pegfilgrastim product as a biosimilar.[22] Neither comparative efficacy nor switching studies was needed for making a determination that an insulin product was biosimilar and interchangeable.[23] Additionally, neither a dedicated pharmacokinetic and switching study were needed to make a determination that certain ranibizumab products met the standards for biosimilarity[24,25] and interchangeability, respectively.[26]

Despite these examples of alternatives to clinical studies, many biosimilar development programs continue to conduct comparative efficacy studies for biosimilarity and switching studies for interchangeability.[27]

Therefore, the Agency has the following research priorities to develop alternatives to and/or reduce the size of studies involving human subjects for a larger set of biosimilar biological products (Box 2):

Comparative Clinical Study (biosimilarity)

e. Develop alternatives to the comparative immunogenicity assessment currently conducted as part of the comparative clinical study:

Specifically, this priority includes the prediction of differences in the immunogenicity, if any, between a proposed biosimilar and its reference product using in silico and/or in vitro methods. Data generated could include 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.[28,29,30]

BOX 2: RESEARCH PRIORITIES THAT RESULT IN REGULATORY IMPACT

REGULATORY IMPACT #1: INCREASE THE ACCURACY AND CAPABILITY OF ANALYTICAL (STRUCTURAL AND FUNCTIONAL) AND CMC CHARACTERIZATION

a. Define and standardize approaches for assessing and reporting product quality attributes
b. Characterize relationships between product quality attributes and clinical outcomes
c. Improve on and/or develop new analytical technologies
d. Assess the impact of differences of biosimilar and reference product presentations (e.g., delivery device) and container closure systems on product protection, safety, compatibility, and performance

REGULATORY IMPACT #2: DEVELOP ALTERNATIVES TO AND/OR REDUCE THE SIZE OF STUDIES INVOLVING HUMAN SUBJECTS

a. Develop alternatives to the comparative immunogenicity assessment currently conducted as part of the comparative clinical study
b. Develop alternatives to the comparative immunogenicity assessment currently conducted as part of the switching study
c. Develop alternatives to clinical bridging data from a non-U.S. approved comparator
d. Increase use of pharmacodynamic (PD) biomarkers instead of or in conjunction with clinical endpoints
e. Clarify which user interface differences that are likely to affect the safe and effective use of interchangeable products
f. Define methodologies to assess differences in user interfaces that may lead to differences in safe and effective use of interchangeable products

Switching Study (interchangeability)

f. **Develop alternatives to the comparative immunogenicity assessment currently conducted as part of the switching study:** Specifically, this priority includes the prediction of changes in immunogenicity, if any, due to switching between a proposed interchangeable and its reference product using in silico and/or in vitro methods. Additionally, real-world evidence may be useful to predict adverse events when patients are switched between reference and interchangeable products in the clinic. Further information on key knowledge gaps can be found at these citations.[31,32,33,34]

Clinical Pharmacology Studies (PK and/or PD and bridging studies)

g. **Develop alternatives to clinical bridging data for use of a non-U.S.-approved comparator:** Specifically, this priority includes defining the analytical data needed and the magnitude of the differences permitted between a U.S.-licensed reference product and a non-U.S.-approved comparator to reduce the need for clinical bridging data.[35,36] Also, see research priority #1b.

h. **Increase use of pharmacodynamic (PD) biomarkers instead of or in conjunction with clinical endpoints:** Use of PD biomarkers can reduce the need for larger comparative efficacy studies. BsUFA III sponsored research will focus on methods to identify, develop, and validate PD biomarkers such that these methods may be applied across multiple products and/or product classes (e.g., PD biomarkers related to a specific therapeutic area). Of note, in this context, antibody isotype subclass (e.g., IgG1) is not considered a product class. Some key knowledge gaps in this area were discussed at an FDA public workshop and these citations.[37,38,39,40]

Comparative Use Human Factor Studies (user interface)

i. **Clarify which user interface differences that are likely to affect the safe and effective use of an interchangeable product:** This priority includes clarifying which user interface differences between a proposed interchangeable product and a reference product could contribute to differences in use error rates when one product is switched with another; 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 via other methodologies. See research priority #2j.

j. **Define methodologies to assess differences in user interfaces that may lead to differences in safe and effective use of interchangeable products:** Specifically, this priority could include evaluating the use and acceptability of using the study methodology described in the draft guidance "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA" for interchangeable development programs.[41]

Research focused on these six priorities (#2e-j) should ultimately aim to develop validated alternatives to and/or reduce the size of studies involving human subjects while maintaining the rigorous standards for biosimilarity and interchangeability.

METHODS TO CONSIDER FOR RESEARCH CONDUCTED AS PART OF THE PILOT PROGRAM

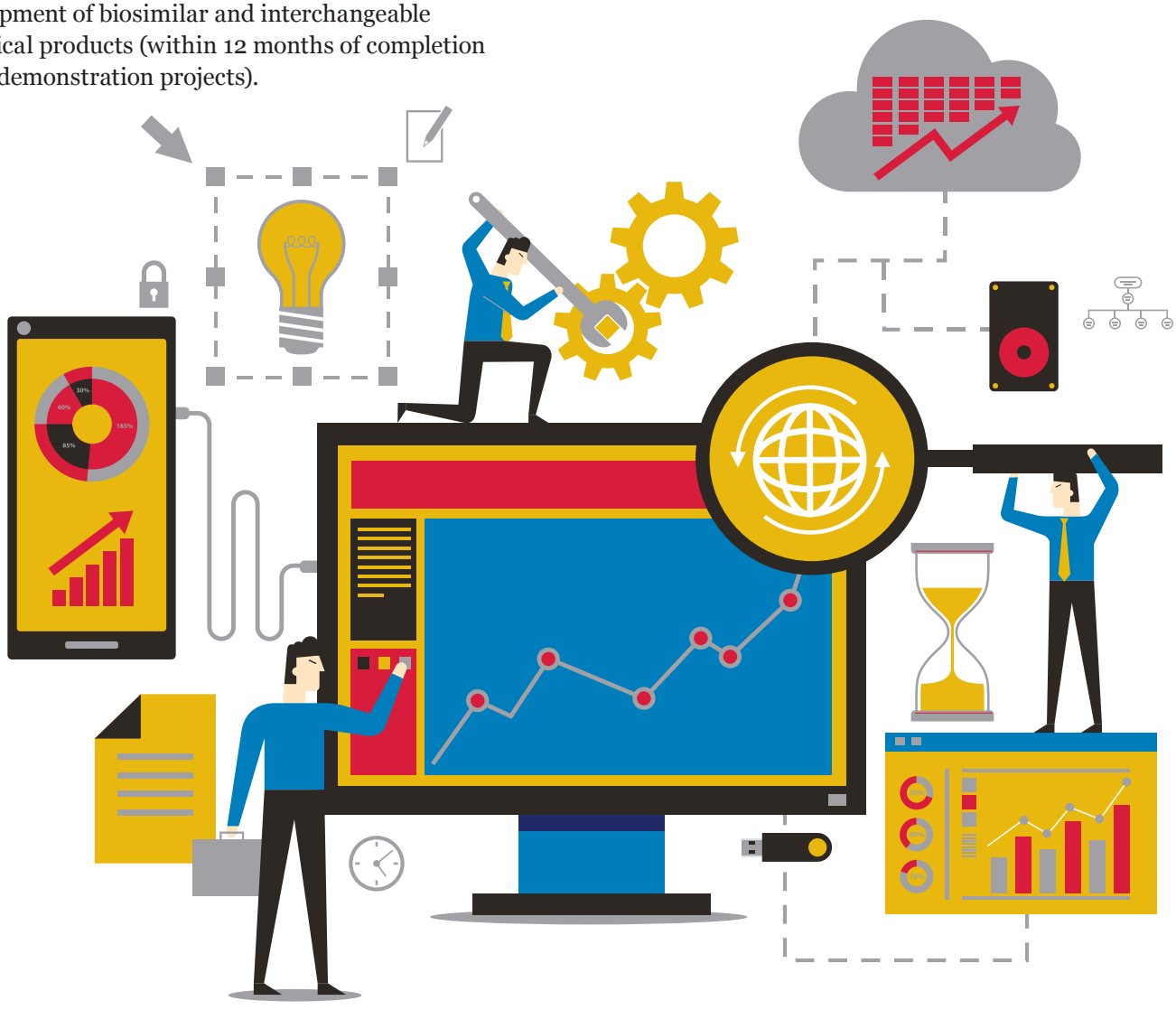
Development of a range of methodologies will be important for achieving the goals outlined for the BsUFA III regulatory research program. These can include, but are not limited to:

- Analytical methods
- Biological functional assays
- Efficient clinical study design (e.g., statistical methods)
- In silico/in-vitro modeling
- Model-informed drug development (MIDD) applications
- Pharmacological studies
- Real world data/evidence (RWD/RWE)

DELIVERABLES AND IMPACT 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).



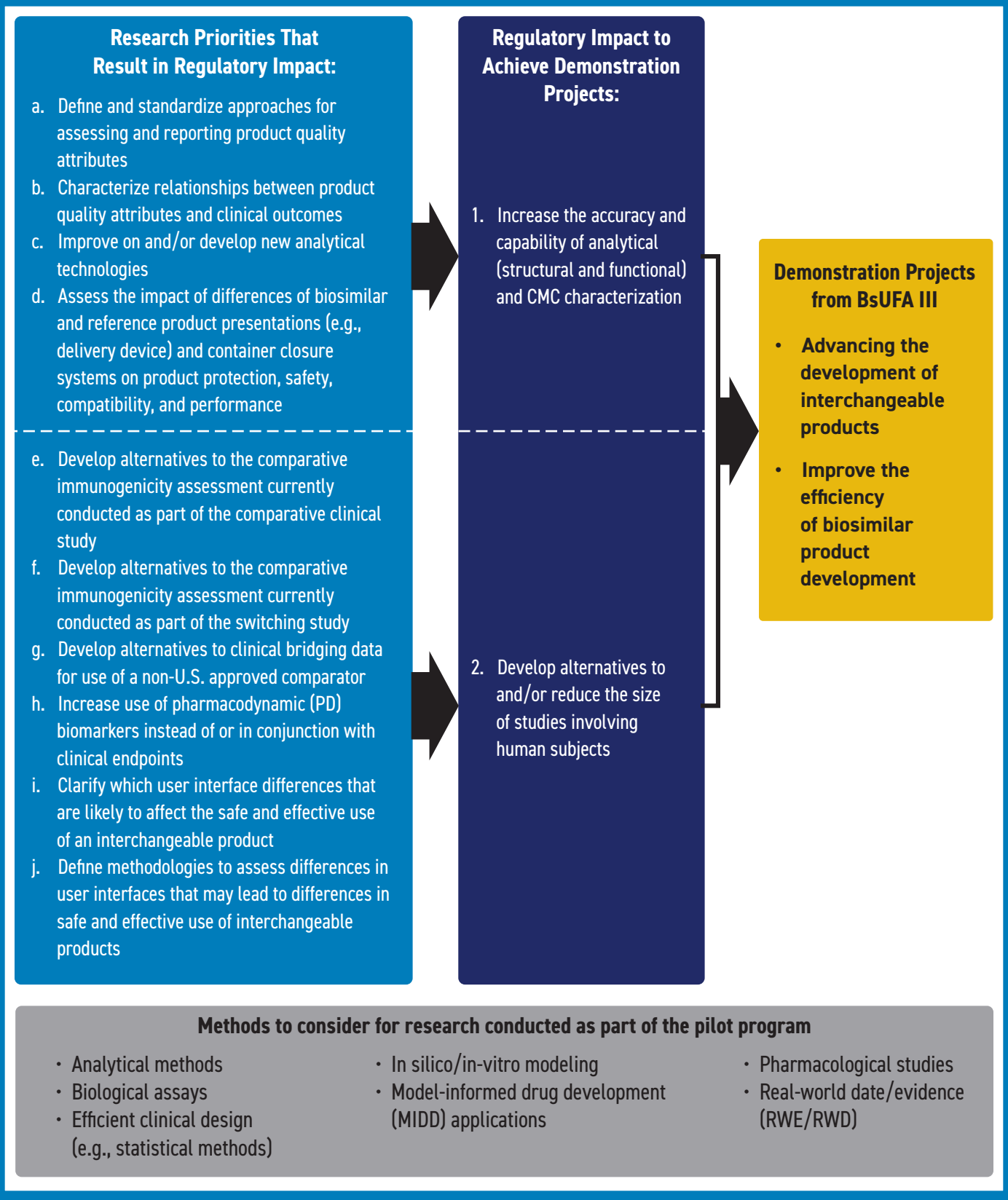


Figure 3. Overview of the BsUFA III Regulatory Research Pilot Program

NOTES

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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 Act (PHS Act)

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

6 https://www.fda.gov/media/124907/download

7 https://www.cardinalhealth.com/content/dam/corp/ web/documents/Report/cardinal health 2022 biosimilars-report.pdf

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

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37 https://pubmed.ncbi.nlm.nih.gov/31667825/

38 https://healthpolicy.duke.edu/events/biosimilar

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

40 https://pubmed.ncbi.nlm.nih.gov/31210051/

41 https://www.fda.gov/media/102349/download. This draft guidance, when finalized, will represent FDA s current thinking on this topic.

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