Update on BsUFA III Regulatory Science Research Priorities *in Draft Roadmap 2.0*

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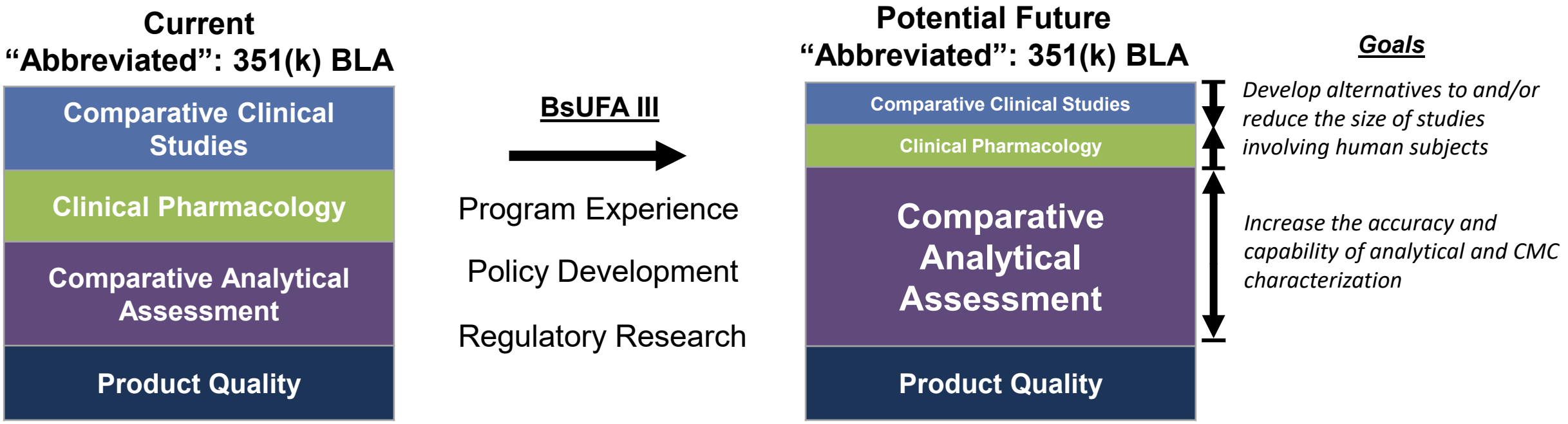
SBIA BsUFA III Regulatory Science Pilot Program October 16, 2023

Figure 1 from *Version 1* of Regulatory Research Roadmap



https://www.fda.gov/media/164751/download

External Engagement and Communication on Research Priorities since Release of the First Draft of the Roadmap

- ***Public Comment Period*** **on Draft Regulatory Roadmap** (January 25 – April 5, 2023)
- **Continuous Engagement Meetings as part of BsUFA III**
- **Invited non-FDA grant reviewers for RFA-FD-23-026**
- **Nine invited talks about the Reg Sci Pilot Program (Spring/ Summer 2023)**

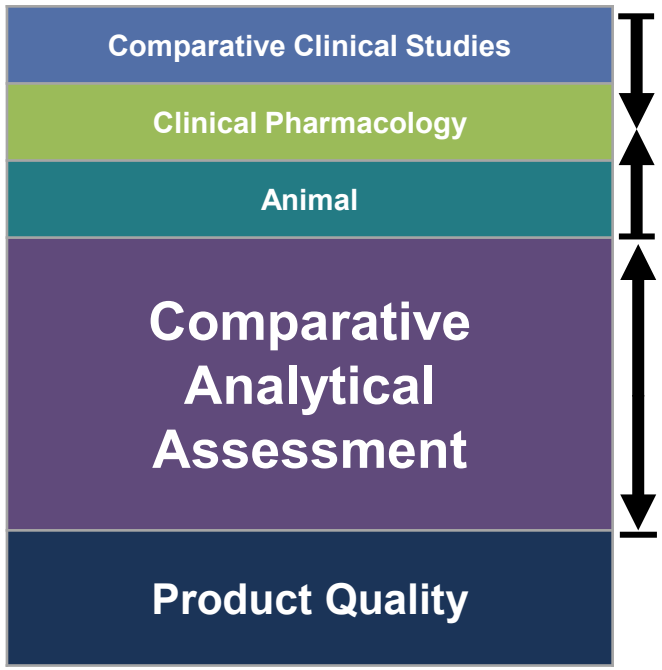
Public SBIA meeting and in-person discussion Oct 2023 (ongoing)

- *Program updates via SBIA Webinar on Oct 16, 2023*
- *In-person feedback on revised roadmap on Oct 26, 2023*

Proposed Revision to BsUFA II Regulatory Science Pilot Program Goals

January 2023

Potential Future "Abbreviated": 351(k) BLA

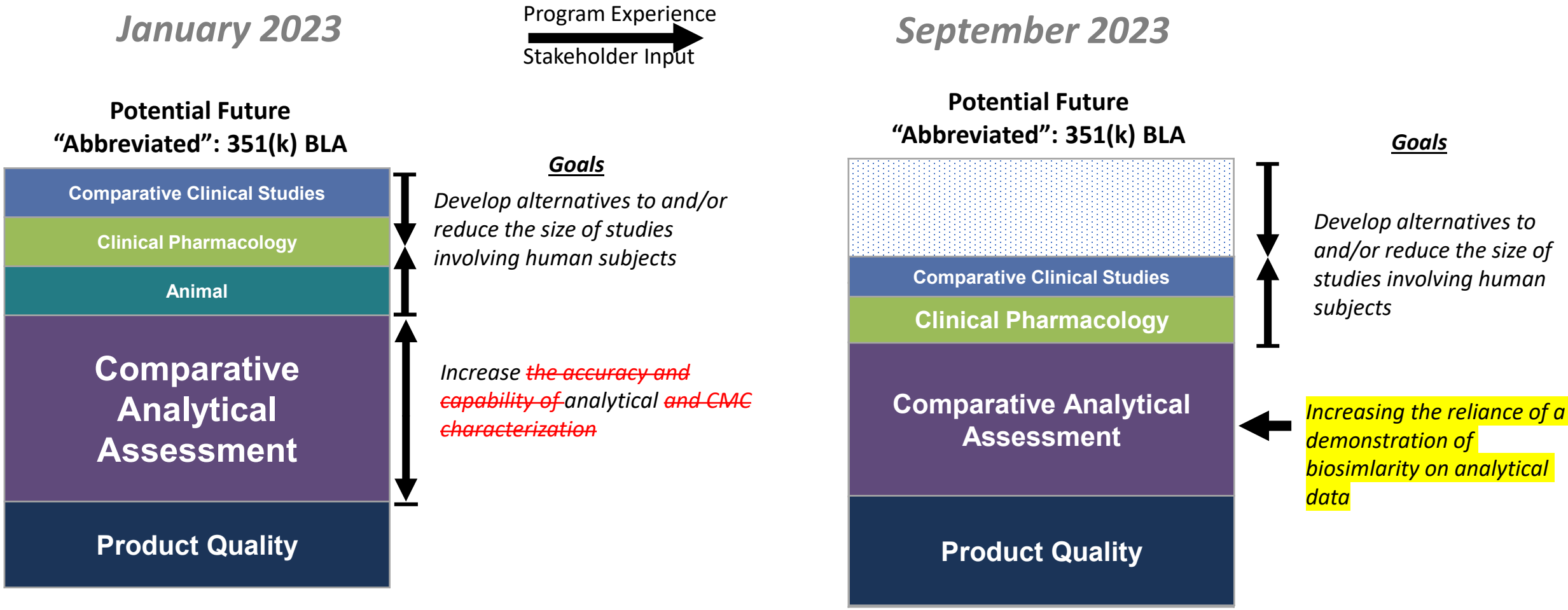


Goals

Develop alternatives to and/or reduce the size of studies involving human subjects

Increase the accuracy and capability of analytical and CMC characterization

Proposed Revision to BsUFA II Regulatory Science Pilot Program Goals



Research Priorities for the BsUFA III Reg Sci Pilot Program

Research Priorities *from Version 1* of the Roadmap:

Revised

Regulatory Impact to Achieve Demonstration Projects:

1. Increasing the reliance of a demonstration of biosimlarity on analytical data
2. Develop alternatives to and/or reduce the size of studies involving human subjects

Demonstration Projects from BsUFA III

- Advancing the development of interchangeable products
- Improve the efficiency of biosimilar product development

Methods to consider for research conducted as part of the pilot program

Analytical methods
Biological assays
Efficient clinical design (e.g., statistical methods)
In silico/in-vitro modeling
Model-informed drug development (MIDD) applications
Machine Learning/ Artificial Intelligence
Real World Evidence/ Data
Pharmacological studies

Research Priorities for the BsUFA III Reg Sci Pilot Program

Research Priorities *from Version 1* of the Roadmap:

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

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

Revised

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Summary of Critiques of *Version 1* of the Research Roadmap

- Research outcomes must have direct regulatory impact
- Current analytical methods are sensitive, precise and discriminating
- The timeline for regulatory impact of non-clinical comparative immunogenicity assessments is unclear and maybe unnecessary when considering the potential of real-world data or evidence (RWD/E)
- Research on alternatives to clinical bridging data for use of a non-US-approved comparator is not needed
- Research related to PD biomarkers should only focus on existing biomarkers
- FDA should consider conducting analysis of anonymized biosimilar monoclonal antibody dossiers

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

Proposed Revision to Research Priorities

January 2023

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

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

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Program Experience

Stakeholder Input

September 2023

1. Increasing the reliance of a demonstration of biosimlarity on analytical data

a. Characterize relationships between product quality attributes with clinical outcomes

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

c. Define best-practices approaches for assessing and reporting quality attributes

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 success (e.g., modeling and simulation)

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

What is Regulatory Impact?

Regulatory impact is defined as a research outcome(s) that *is expected to inform* science-based recommendations and regulatory decision-making *at the FDA*.

- Includes achieving a critical milestone toward a research outcome that is expected to inform science-based recommendations…etc.
- A null or negative research result/ outcome can be informative from a regulatory perspective.

What will inform ‘science-based recommendations and regulatory decision-making’ at the FDA?

***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 to obtain
- Could be reasonably obtained through a (set of) research project(s) outcomes and deliverables
- Is not duplicated elsewhere internally or externally of FDA
- Is not product or product-class specific*

* See Guidance for Industry: Questions and Answers on Biosimilar Development and the BPCI Act, September 2021 Biosimilars, Revision 2, Q&A II.2.

What will inform ‘science-based recommendations and regulatory decision-making’ at the FDA?

Other Important Considerations Included:

- Concerns identified by stakeholders
- 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., complex biologics)
- Areas where there is a lack of global regulatory harmonization

Regulatory Impact #1: Increasing the reliance of a demonstration of biosimlarity on analytical data*

*Research Roadmap under revision!

Regulatory Impact #1: Increasing the reliance of a demonstration of biosimlarity on analytical data*

January 2023

1. Increase the accuracy and capability of analytical (structural and functional) and CMC characterization

b. Characterize relationships between product quality attributes and clinical outcomes

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

September 2023

1. Increasing the reliance of a demonstration of biosimlarity on analytical data

a. Characterize relationships between product quality attributes with clinical outcomes

- **Which product quality attributes have the potential to impact product safety, purity, and potency?**
- **What is the magnitude of the difference that may result in a meaningful impact?**

**Research Roadmap under revision!*

Regulatory Impact #1: Increasing the reliance of a demonstration of biosimlarity on analytical data*

January 2023

1. Increase the accuracy and capability of analytical (structural and functional) and CMC characterization

c. Improve on and/ or develop new analytical technologies

September 2023

1. Increasing the reliance of a demonstration of biosimlarity on analytical data

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

- **Can scientific and technology advancements further simplify the CAA?**
- **General technology and method development is out of scope**

**Research Roadmap under revision!*

Regulatory Impact #1: Increasing the reliance of a demonstration of biosimlarity on analytical data*

January 2023

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

September 2023

1. Increasing the reliance of a demonstration of biosimlarity on analytical data

c. Define best-practices for assessing and reporting quality attributes

- **Publicly available resources identifying parameters of commonly used methodologies for the structural and functional characterization of biosimilar candidates**
- **Facilitate regulatory acceptance of certain methodologies**

**Research Roadmap under revision!*

Regulatory Impact #1: Increasing the reliance of a demonstration of biosimlarity 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

**Research Roadmap under revision!*

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

**Research Roadmap under revision!*

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

January 2023

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

September 2023

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

- **Analytically de-risk any immunogenicity concerns following the comparative analytical assessment (CAA)**
- **Leverage real world data/ evidence for clinical experience with reference product and/ or biosimilar in non-US markets**

**Research Roadmap under revision!*

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

January 2023	*September 2023*
g. Develop alternatives to clinical bridging data for use of a non-US approved comparator	Removed

- **Not a research question**

**Research Roadmap under revision!*

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

January 2023

h. Increase use of pharmacodynamic (PD) biomarkers instead of or in conjunction with clinical endpoints

September 2023

e. Define development approaches that will increase feasibility and/ or likelihood of success

- **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 subjects with healthy volunteers**
- **Use of modeling and simulation to reduce the size and/or duration of clinical pharmacology studies study**

**Research Roadmap under revision!*

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

January 2023

h. Clarify which user interface differences that are likely to affect the safe and effective use of an interchangeable product
i. Define methodologies to assess differences in user interfaces that may lead to differences in safe and effective use of interchangeable products

September 2023

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

- **Which user interface differences between a proposed interchangeable product and a reference product could contribute to differences in use error rates?**
- **When these differences should be further evaluated to determine if they affect safe and effective use?**

**Research Roadmap under revision!*

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

**Research Roadmap under revision!*

Summary of Critiques of Version 1 of the Research Roadmap

Critique	Revision/ Change
Research outcomes must have direct regulatory impact	• Defined regulatory impact and clarified the vision for the research portfolio
Current analytical methods are sensitive, precise and discriminating	• Refocused research priority on leveraging technology/ method advances to specific address the efficiency of the CAA
The timeline for regulatory impact of non-clinical comparative immunogenicity assessments is unclear and maybe unnecessary when considering use of RWD/E	• Highlighted analytical de-risking immunogenicity concerns identified in the CAA • Use of RWD/E to inform immunogenicity risk of biosimilar product
Research on alternatives to clinical bridging data for use of a non-US-approved comparator is not needed	• Removed research priority
Research related to PD biomarkers should only focus on existing biomarkers	• Clarified and expanded research priority to be about feasibility of success
FDA should consider conducting analysis of anonymized biosimilar monoclonal antibody dossiers	• Ongoing effort

Research Priorities Addressed by Awarded Funds

Funding Year	A: Clin outcome of PQA	B. Modernize methods for CAA	C. Best practices for analytics	D. Alter to compare Immuno	E. Increased feasibility (e.g., PD biomarkers)	F. Impact of user interface on likelihood of error rate
FY24 Internal						
FY23 External						
FY23 Internal						
FY22 External						

Increasing the reliance of a demonstration of biosimlarity on analytical data

Develop alternatives to and/or reduce the size of studies involving human subjects

Take home/ TLDR:

The BsUFA III Regulatory Science Pilot Program aims to support projects that are expected to inform FDA science-based recommendation(s) and regulatory decision-making about leveraging analytical data and minimizing the clinical data needed to meet 351(k) statutory requirements.

Thank you!