Biosimilar Program Updates and What's New Under BsUFA III

Regulatory Education for Industry (REdI) Annual Conference 2023

Office of Therapeutic Biologics and Biosimilars

OND/CDER/FDA

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Presentation Overview*

Biosimilars by the Numbers

BsUFA III Overview – selected topics

- BsUFA III Supplement Categories A-F
- Regulatory Science Pilot Program
- BsUFA III Guidance Commitments and Other Milestones

Legislative Updates

Education and Outreach

Biosimilar and OTBB Resources

*Presentation Recorded May 19, 2023

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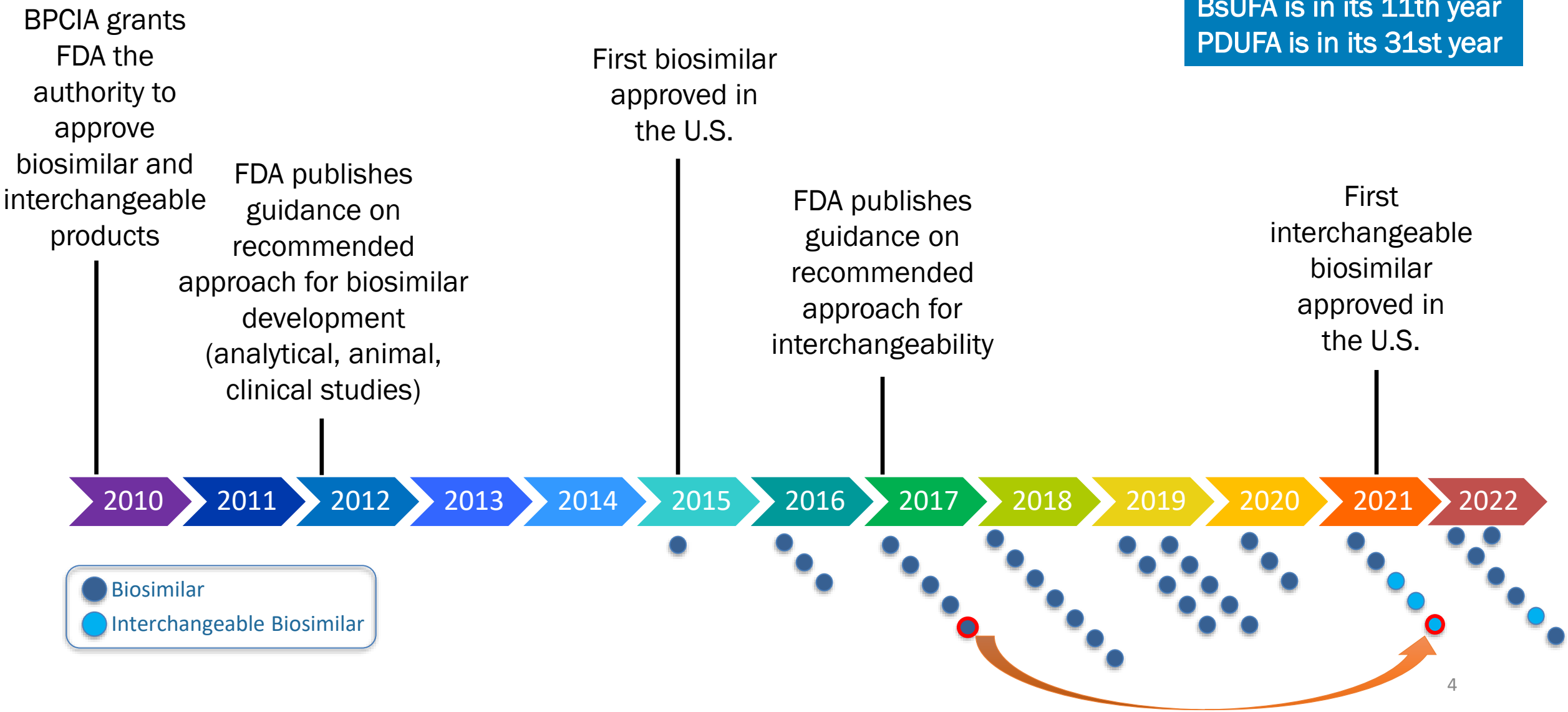
Biosimilars By the Numbers

BsUFA is still a relatively new program

BsUFA is in its 11th year
PDUFA is in its 31st year



FDA Approved Biosimilar and Interchangeable Biosimilar Products*

Product Class		Approvals
Supportive Care	Filgrastim	B B B
	Epoetin	B
	Pegfilgrastim	B B B B B B
Oncology	Rituximab	B B B
	Bevacizumab	B B B B
	Trastuzumab	B B B B B
Autoimmune	Infliximab	B B B B
	Etanercept	B B
	Adalimumab	B I B B B B B B
	Insulin Glargine	I I
Ophthalmology	Ranibizumab	B I

B Biosimilar

I Interchangeable Biosimilar

- 40 biosimilars approved to 11 different reference products
- 29 marketed to 9 different RPs
- 102 proposed biosimilars in active Biosimilar Development Programs (BPD)
- FDA met with companies to discuss biosimilars to 53 different RPs

*as of April 30, 2023

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Biosimilar User Fee Amendments of 2023 (BsUFA III)

BsUFA III Enhancement Areas

- **Supplements** | Introducing new supplement types and expedited review timelines
- **Meeting Management** | Enhancing communication and feedback during the biosimilar biological development process
- **Best Practices** | Implementing best practices in communication during application review
- **Inspections** | Enhancing pre-licensure inspection communication and clarifying use of alternative tools
- **Use-Related Risk Analysis (URRA) and Human Factors Timelines** | Introducing timelines for review of URRA and Human Factors studies
- **Interchangeable Products** | Introducing focused effort to advance the development of interchangeable products
- **Regulatory Science** | Introducing new pilot program to enhance regulatory decision-making and facilitate science-based recommendations
- **Finance** | Enhancing financial management and transparency
- **Hiring and Retention** | Focusing on the strategic hiring and retention of world-class technical and scientific staff
- **Information Technology** | Investing in modern technology to support enhanced and streamlined biosimilar product development and review

BsUFA III Commitment Letter: https://www.fda.gov/media/152279/download

BsUFA III Supplement Categories Overview

- Introduces six new supplement categories (A-F)

- Includes **expedited** timelines (3-6 months) for safety labeling updates and labeling updates to add/remove an indication where FDA does not need to review efficacy data
  - Where review of efficacy data is necessary, the timeline is 10 months from receipt date

- New categories allow for a more structured review process, which helps FDA meet review timeline goals

- **OTBB is managing the review for all Categories A, B and C sBLAs**

Category A, B, and C Descriptions:

OTBB will Manage and Review Supplement Categories A, B and C

Safety Updates (A)

Category A	Review Timeline	Acknowledgement Letter
• Update the labeling for safety information that has been updated in the reference product labeling	≤ 3 months of receipt	Within 60 calendar days of receipt

Add (B) or Remove (C) Indication(s)

Category B	Review Timeline	Acknowledgement Letter
• Seeks additional indication(s) and does not include new data sets (other than analytical in vitro data if needed to support the scientific justification for extrapolation) provided that: ○ It does not seek a new route of administration, dosage form, dosage strength, formulation, or presentation ○ If subject to section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), contains an up-to-date agreed initial pediatric study plan (iPSP), and that iPSP addresses PREA requirements for the additional indication(s) proposed for licensure	≤ 4 months of receipt	Within 60 calendar days of receipt
Category C		
• Seeks removal of approved indication(s)		

Category D, E, and F Descriptions:

OND Review Division will Manage and Review Supplement Categories D, E, and F

Add Indication(s) (D and E)

Category D	Review Timeline	Acknowledgement Letter
• Seeks an additional indication • Contains new data sets (other than efficacy data or data for initial determination of interchangeability, or only analytical in vitro data) **OR** • Does not contain new data sets (other than analytical in vitro data) but is subject to section 505(b) of the FD&C Act, and does not contain an up-to-date agreed iPSP that addresses PREA requirements for the additional indication(s) proposed for licensure	≤ 6 months of receipt	Acknowledgement within 60 calendar days of receipt
Category E	**Review Timeline**	**Filing Letter**
• Seeks an additional indication and contains efficacy data sets	≤ 10 months of receipt; 6 months for resubmissions	Filing letter within 74 calendar days of receipt

Interchangeability (F)

Category F	Review Timeline	Filing Letter
• Seeks an initial determination of interchangeability	≤ 10 months of receipt; 6 months for resubmissions	Filing letter within 74 calendar days of receipt

BsUFA III Establishes Use-Related Risk Analysis (URRA) and Human Factors (HF) Review Timelines

- Establishes **60-day timeline** for providing feedback on URRA and HF Validation Study Protocols (Consistent PDUFA VII)

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BsUFA III Guidance Commitments and Other Milestones

BsUFA III Guidance Issuance goal dates

Year 1 10/2022 – 9/2023	Year 2 10/2023 – 9/2024	Year 3 10/2024 – 9/2025
Revised draft guidance: Formal Meetings Between FDA & Sponsors or Applicants of BsUFA Products and any related/relevant MAPPs/SOPPs 9/30/2023 **Guidance or MAPP on classifying supplements to a licensed 351(k) BLA for purposes of determining review timelines by 9/30/2023** **Guidance on labeling for interchangeable biosimilar products by 9/30/2023** **Guidance on use of alternative tools for inspections by 9/30/2023** **Update relevant guidances, MAPPs and SOPPs regarding best practices in communication between FDA & Applicants during application review by 10/31/2023**	**Guidance on URRA and HF validation studies for biosimilar-device combinations by 9/30/2024** **Guidance on promotional labeling and advertising considerations for interchangeable products by 9/30/2024** **Draft guidance on reporting category for post-approval manufacturing changes by 9/30/2024**	**Guidance on considerations for presentations, container closure systems and device constituent parts for interchangeable products by 9/30/2025**

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BsUFA III Regulatory Science Program

Biosimilar User Fee Act (BsUFA) III Regulatory Science Commitment

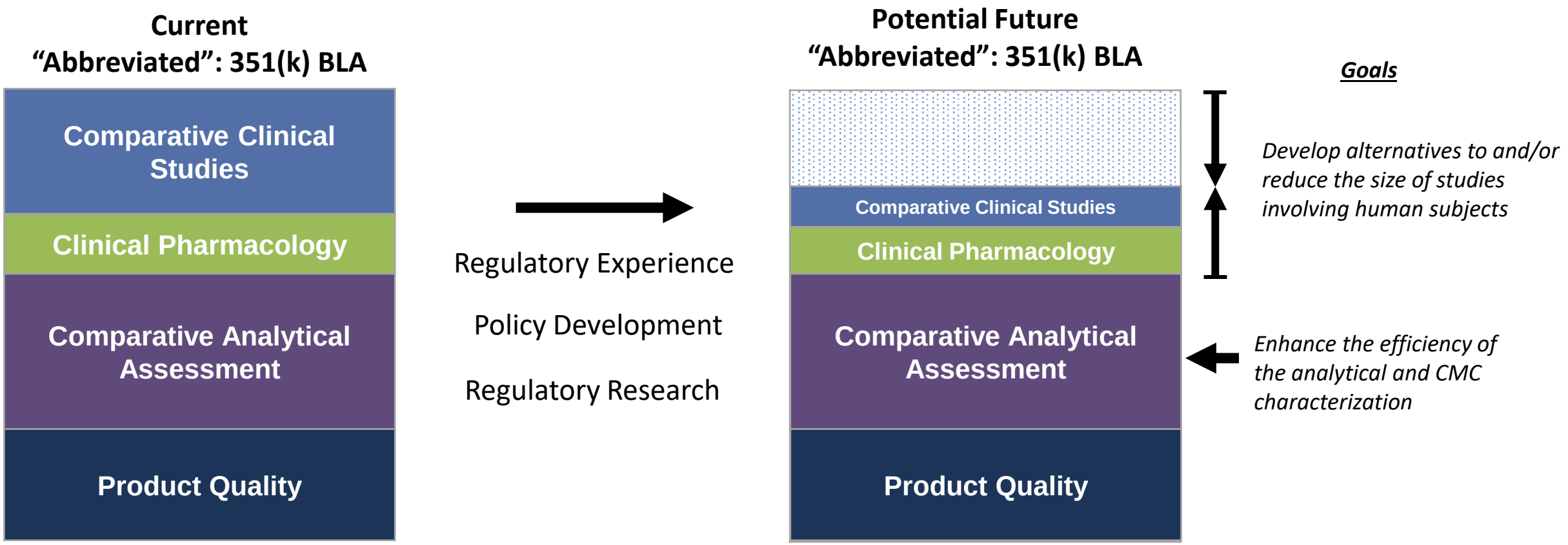
FDA is committed to enhancing regulatory decision-making and facilitating science-based recommendations in areas foundational to biosimilar development.

FDA will pilot a regulatory science program to facilitate ways to

(1) improve the efficiency of biosimilar product development and

(2) advance the development of interchangeable products.

Regulatory Science Pilot Program Goals



Research Priorities for the BsUFA III Reg Sci Pilot Program

Research Priorities That Result in Regulatory Impact:

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

Regulatory Impact to Achieve Demonstration Projects:

1. Enhance the efficiency of the analytical (structural and functional) and CMC characterization

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
Real world data/ evidence (RWD/E)

Pharmacological studies

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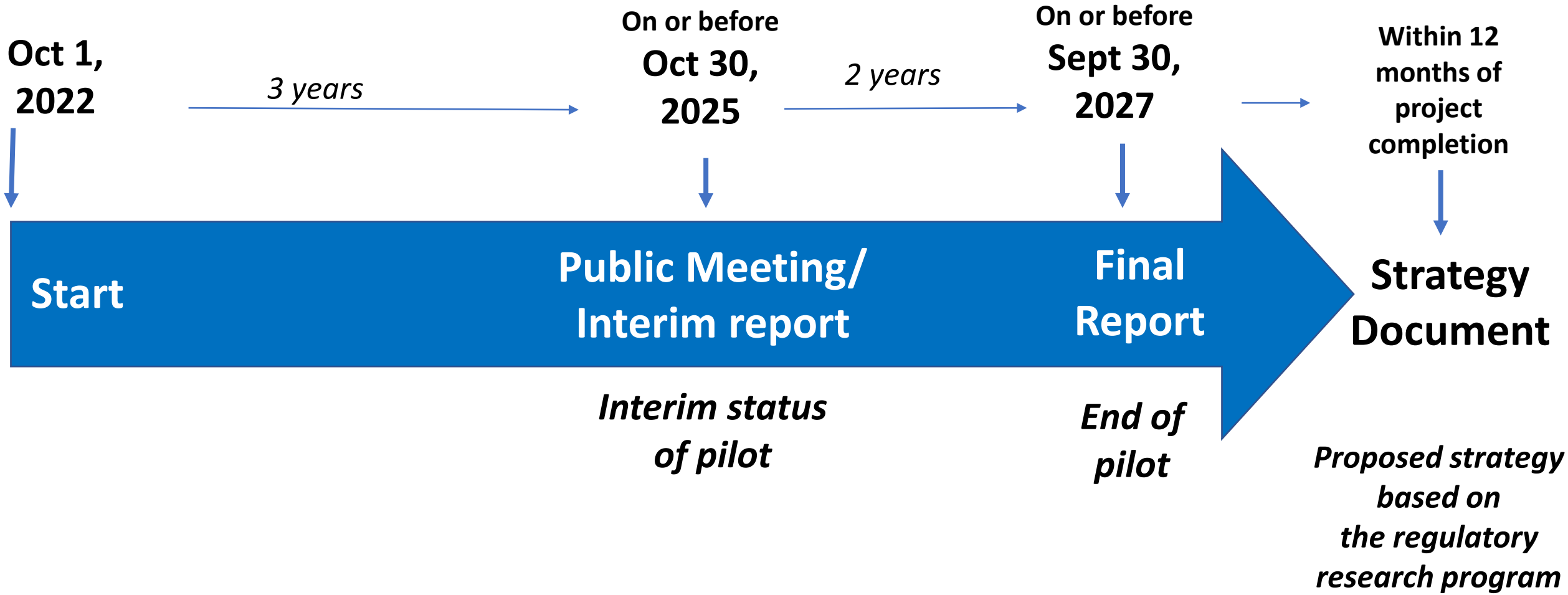
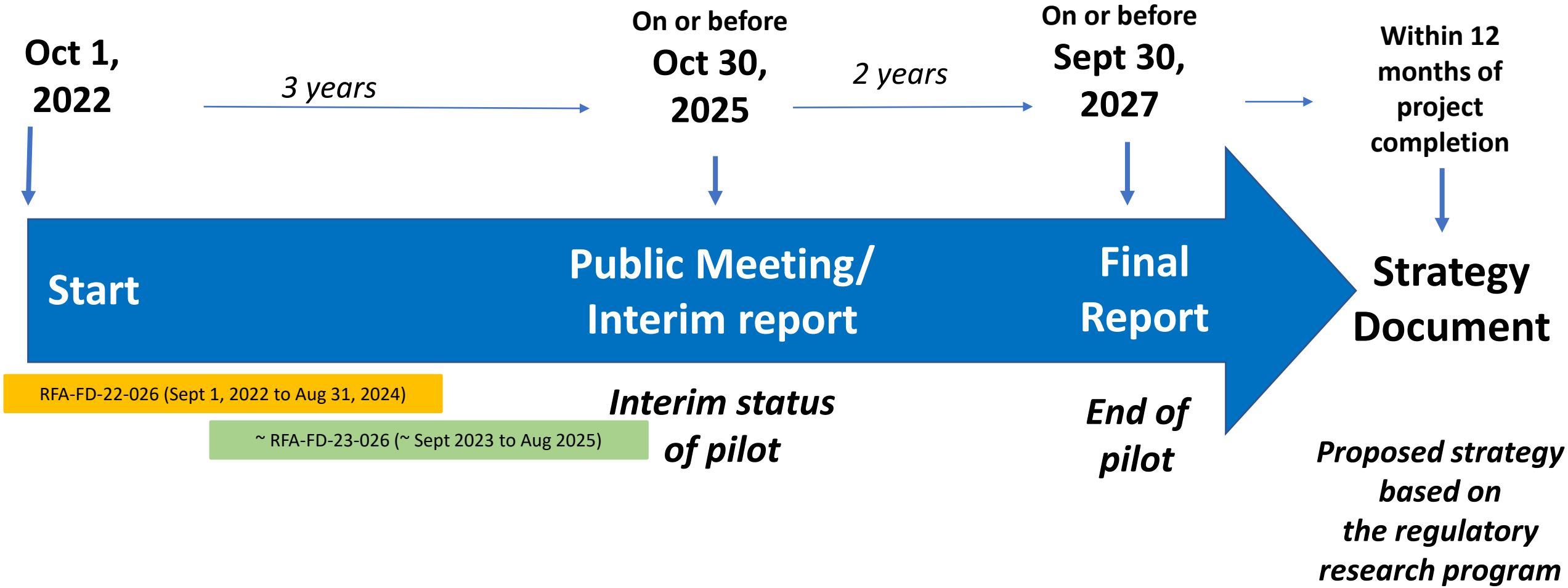
Deliverables for Pilot Program



Funding Cycles for Regulatory Research



Ongoing External Projects (RFA-FD-22-026)

INSTITUTION	TITLE	Research Priority	Regulatory Impact
ACADEMY OF MANAGED CARE PHARMACY, INC.	Improving the Efficiency of Regulatory Decisions for Biosimilars and Interchangeable Biosimilars by Leveraging Real-World Data	F. Develop alternatives to the comparative immunogenicity assessment currently conducted as part of the switching study	**Develop alternatives to and/ or reduce the size of studies involving human subjects**
EPIVAX, INC.	ISPRI-HCP: CHO protein impurity immunogenicity risk prediction for improving biosimilar product development and assessing product interchangeability	E and F. Develop alternatives to the comparative immunogenicity assessment currently conducted as part of the switching study	
NATIONAL INSTITUTE FOR PHARM TECH/EDUC	Platform for reliable characterization and evaluation of comparability of biosimilar drug products in lyophilized and liquid formulations	D. Assess the impact of differences of biosimilar and reference product presentations and container closure systems on product protection, safety, compatibility, and performance	**Enhance the efficiency of analytical (structural and functional) and CMC characterization**
UNIVERSITY OF MICHIGAN AT ANN ARBOR	Systematic Analytical Characterization of Innovator and Biosimilar Products with the Focus on Post-translational Modifications	A. Define and standardize approaches for assessing and reporting product quality attributes	
U.S. PHARMACOPEIA	Assessment of the performance of MAM vs conventional QC methods for evaluation of Product Quality Attributes of adalimumab and etanercept	C. Improve on and/ or develop new analytical technologies	

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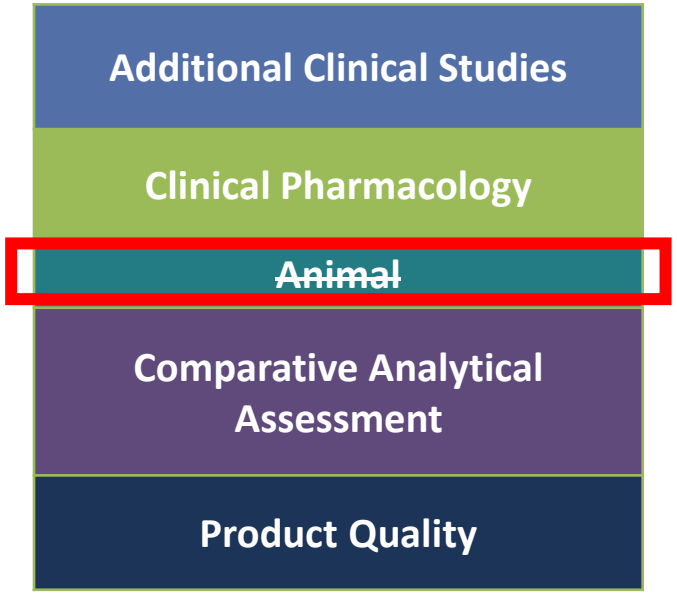
Regulatory Updates Under FDORA

Food and Drug Omnibus Reform Act ("FDORA")

FDORA made changes to the Public Health Service Act's ("PHS Act")

- **Replaced** the language regarding **animal studies** with "an assessment of toxicity…" which may rely instead on an analytical or clinical study or studies

- **Clarified** aspects of **First Interchangeable Exclusivity (FIE)**
  1) if several first interchangeable products are approved on the same day, they each qualify for FIE
  2) when a subsequent application for an interchangeable product is blocked by FIE, FDA can approve that application as a biosimilar



Prompt Reports of Marketing Status to Purple Book

- The Purple Book contains information on FDA-licensed biological products regulated by CDER and CBER.
- Section 506I of the FD&C Act, as amended in FDORA, **imposes certain reporting requirements** on biologics license application (BLA) holders regarding the **marketing status of approved 351(a) and 351(k) products**, including a one-time marketing status report.
- Summary of reporting requirements:
  - **By June 27, 2023, BLA holders must submit a one-time report to the BLA file if their products are currently listed as marketed ("Rx") in the Purple Book.**
  - Notification must be submitted 180 days before (but no later than the date of discontinuation) a product is expected to be discontinued from sale.
  - Notification must be submitted within 180 days after initial approval if the product will not be available for sale within 180 calendar days of the approval.
- More information about Purple Book reporting requirements can be found in FAQs 8 and 9: https://purplebooksearch.fda.gov/faqs

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Biosimilar Education and Outreach

Education and Outreach

- FDA is committed to developing effective communications to improve understanding of biosimilars among patients, health care providers, and payers
  - **Engaging** with health care professional and patient stakeholders
  - **Developing** educational materials for health care prescribers, pharmacists, and patients
- Education is an undertaking that requires **multi-stakeholder engagement**

FDA is committed to fulfilling its important role as one of many stakeholders.

Health Care Provider Materials

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Biosimilar Regulatory Review and Approval

Biological products (biologics) are the fastest-growing class of medications in the United States and account for a substantial and growing portion of health care costs. The Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway to provide patients with greater access to safe and effective biological products. This pathway helps reduce the time and cost of development without compromising safety and effectiveness.

Overview of the Approval Process

- All FDA-approved biologics undergo a rigorous evaluation so that health care providers and patients can be confident of the safety, effectiveness, and quality of these products.
- A biosimilar is a biologic that is highly similar to and has no clinically meaningful differences from an existing FDA-approved biological medication, called a reference product.
- A reference product is approved in a standalone application that must contain all data and information necessary to demonstrate the product's safety and effectiveness.
- The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar and its reference product, not to independently establish the safety and effectiveness of the proposed biosimilar. This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials.
- The abbreviated pathway involves an extensive structural and functional comparison of the biosimilar and the reference product.
- Because biologics are usually made in cells, even with identical amino acid sequences, there will be inherent variations (for example, glycosylation) that result from the manufacturing process in any batch or dose.
- As part of the approval process for both reference products and biosimilars, FDA assesses a manufacturer's strategy to control for the pattern and degree of variations between different batches so that safety and effectiveness don't change.
- FDA monitors the safety and effectiveness of all medications after their approval. This involves inspecting manufacturing facilities and reviewing manufacturer, provider, and patient safety reports made to FDA.

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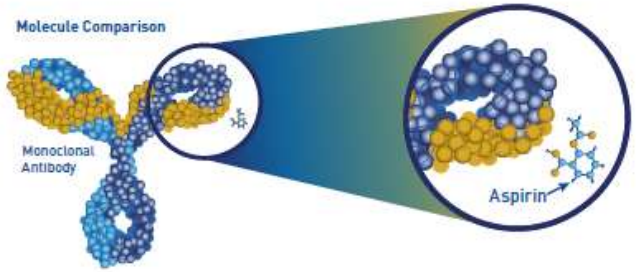
Overview of Biosimilar Products

Biosimilars are safe and effective biological medications for treating many illnesses, including chronic skin diseases, such as psoriasis; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; arthritis; kidney conditions; diabetes; and cancer. These medications can provide more treatment options and potentially reduce costs for patients.

Biosimilars Are Biological Products

- Biological products, or biologics, are generally large, complex molecules that are made from living sources such as bacteria, yeast, and animal cells. On the other hand, drugs made from chemicals are smaller molecules and easier to copy.
- Because they generally come from living organisms, biologics inherently contain many slight variations from batch to batch, and their structures are generally more complex than those of other medications. As a result, biologics are often more complicated to purify, process, and manufacture.
- There are many types of biologics approved for use in the United States, including therapeutic proteins; vaccines; blood, blood components, and their derivatives; allergenic products; and monoclonal antibodies.



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Interchangeable Biological Products

An interchangeable biological product is a biosimilar that meets additional requirements and may be substituted for the reference product at the pharmacy, depending on state pharmacy laws. Interchangeable biological products (also called interchangeable biosimilars or interchangeable products) may help increase patient access to biologics.

Interchangeable Biosimilars

- An interchangeable biosimilar may be substituted at the pharmacy for the reference product without the intervention of the prescribing health care provider — much like how generic drugs are routinely substituted for brand-name drugs.
- Not all biosimilars are interchangeable. Companies must submit an application with adequate information to support an interchangeability determination for their product to be approved as an interchangeable biosimilar.

Pharmacy-Level Substitution

Interchangeable Biosimilar Approval Process

- Unlike a reference product, which is approved in a standalone application, all biosimilar and interchangeable biosimilars are approved through an abbreviated pathway that compares the product to the reference product to show biosimilarity.
- For approval as an interchangeable biosimilar, manufacturers must provide additional data that reflect how the interchangeable biosimilar may be used in the marketplace with patients. Like generic drugs, patients receiving their medications through their pharmacies may switch between a brand-name biologic and an interchangeable biosimilar.
- To assess the safety of switching, manufacturers generally conduct studies in which patients alternate between the reference product and the interchangeable biosimilar and compare those patients to patients who are just being treated with the reference product. The results must show no decrease in effectiveness or increase in safety risk associated with switching.
- While this additional information helps FDA to determine the safety of pharmacy-level substitution, this does not mean that an interchangeable biosimilar is safer or more effective than other biosimilars.

All biological products are approved only after they meet FDA's rigorous approval standards, so health care professionals and patients can be confident in the safety and effectiveness of a biosimilar product, whether or not it has also been approved as an interchangeable biosimilar, just as they would be for a reference product.

Explore FDA's biosimilar resources for health care professionals at www.fda.gov/biosimilars.

FDA Biosimilar Materials for Patients

www.fda.gov/drugs/biosimilars/basics-patients

- English and Spanish fact sheets, infographics, articles, and more

FDA Biosimilar Materials in Spanish

English

La Administración de Alimentos y Medicamentos de los EE.UU. (FDA, por sus siglas en inglés) ha aprobado medicamentos biosimilares para tratar enfermedades como el cáncer, la enfermedad de Crohn, la colitis, la artritis reumatoide, la psoriasis y otras.

Pero, ¿qué son los medicamentos biosimilares y biológicos intercambiables? Para

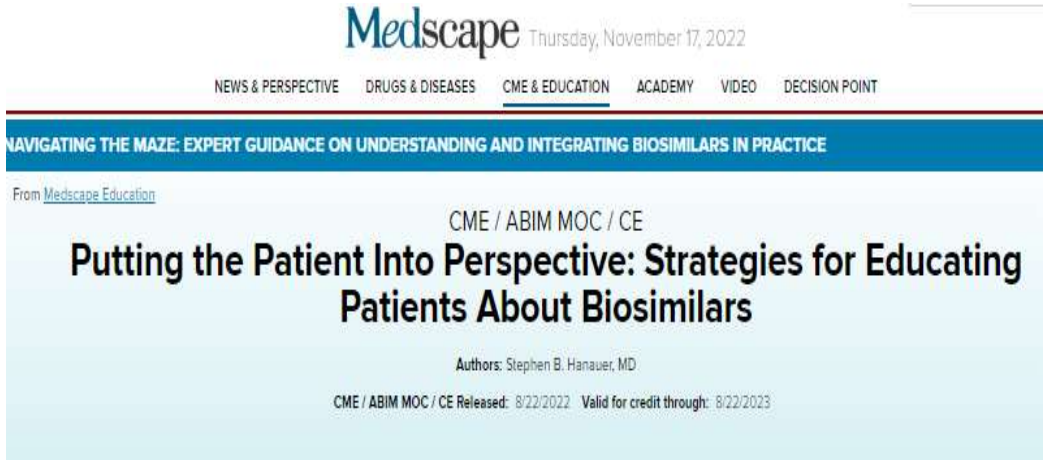
Curriculum for Healthcare Professional Programs

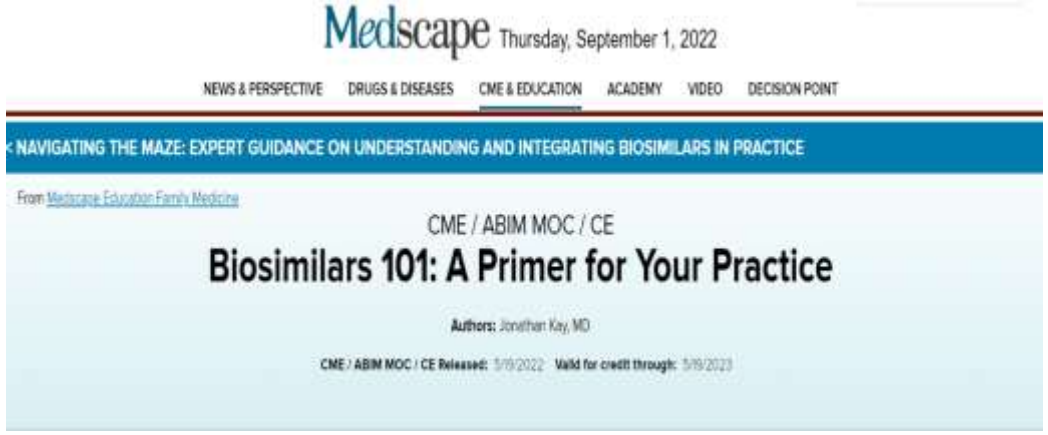
- The Biosimilar Curriculum Toolkit contains multiple types of materials to help faculty integrate biosimilars and interchangeable products into the education and professional training of healthcare students.
- Goal is to increase knowledge and real-world application of concepts among students in healthcare degree programs (Medicine, Nursing, Physician Associates, and Pharmacy).
- Materials are designed to meet a variety of needs and are divided into 2 levels of content.

https://www.fda.gov/drugs/biosimilars/curriculum-materials-health-care-degree-programs-biosimilars

Medscape Continuing Education

FDA is supporting the development of a series of continuing education (CE) courses through Medscape about biosimilar and interchangeable products. This includes 4 courses in 2022 and a dedicated website for the content.





Stakeholder Engagement

FDA works with government and non-government stakeholders to support uptake and utilization of biosimilars.

- USP/FDA Infographic on biosimilars and quality
- FDA/ FTC educational resource for patients about biosimilar treatment options

Conducting stakeholder outreach and offering education to stakeholders including patient advocacy organizations, medical and professional associations, payors, pharmacy organizations, and state and federal governments partners.

Future Education and Outreach Plans

- Materials and resources for **patients**:
  - Videos
  - Additional infographics and graphics

- Materials and resources for **health care providers**:
  - Videos
  - More continuing Education course options through Medscape
  - Updated educational curriculum/teaching resources for HCP schools

- Continue work with multiple stakeholders to increase educational opportunities and ensure unbiased, truthful information about biosimilars is available.

FDA Website Resources

FDA Biosimilars Webpage
- information for stakeholders, including industry and all educational materials

Guidance Webpage
- Guidance related to BsUFA, including details on BPCI (search on “biosimilar”)

The Purple Book: Database of Licensed Biological Products
- Info on all FDA-licensed (approved) biological products regulated by CDER, including licensed biosimilar and interchangeable products, and their reference products, and FDA-licensed allergenic, cellular and gene therapy, hematologic, and vaccine products regulated by CBER

Publicly Available Biosimilar Training – CE Credits
- Biosimilar and Interchangeable Biological Products: An Updated Review of Scientific Concepts and Practical Resources | FDA
- FDA Drug Topics: Biosimilar and Interchangeable Products in the U.S.: Scientific Concepts, Clinical Use, and Practical Considerations | FDA
- Curriculum Materials for Health Care Degree Programs | Biosimilars | FDA

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Thank You!

www.fda.gov/biosimilars

QUESTIONS?

Please contact us at DRUGINFO@fda.hhs.gov