FDA Scientific Workshop
Advancing the Development of Interchangeable Products: Identifying Future Needs

Darlese Solorzano, MS, MBA, Program Manager of the BsUFA III Regulatory Science Pilot Program, OPQAIII|OPQ|CDER|FDA

Agenda

Time	Event (and Proposed Speakers / Panelists)
9:00 – 9:10am	**Opening Remarks** (Sarah Yim)
9:10 – 9:30am	**Keynote Address** (George Tidmarsh)
9:30 – 10:30am	**Landscape of Stakeholder Perspectives: Future Needs for the Development of Interchangeable Products** *(15 min presentation each)* AAM (Jessica Greenbaum) Biosimilar Forum (Juliana Reed) PhRMA (Kristy Lupejkis)
	10:30 – 11:00am Break
11:00 – 11:20am	**Specific scientific topic: Analytical considerations around interchangeability of a biologic** (CDER/OPQ – Maria-Teresa Gutierrez Lugo)
11:20 – 11:40am	**Specific scientific topic: User interface and human factor considerations around interchangeability** (CDER/OSE/DMEPA – Ariane O. Conrad and Matt Barlow)
11:40am – 12:00pm	**Specific scientific topic: Other considerations around interchangeability of biological products** (CDER OND – Stacey Ricci)
12:00 – 12:45pm	**Panel Discussion** (Moderated by Sarah Yim) Moderated dialogue/panel discussion between presenters Panelists include speakers from earlier presentations (Representatives from AAM, Biosimilar Forum, PhRMA, OPQ, and DMEPA) Audience Q&A
12:45 – 1:00pm	**Summary and Close Out** (Sarah Yim)

Todays Presenters & Panelist

George Francis Tidmarsh, MD, PhD
Director
Center for Drug Evaluation and Research (CDER)
FDA

Sarah Yim, MD
Director
Office of Therapeutics Biologics and Biosimilars (OTBB)
Office of New Drugs (OND) |CDER|FDA

Jessica Greenbaum
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AAM Representative

Juliana M. Reed
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Biosimilars Forum

Kristy Lupejkis
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Office of New Drugs (OND) | CDER | FDA

Ground Rules & Housekeeping

No policy or guidance will be made today.

Step out and take breaks as needed (Kiosk open) but refrain from calls etc. that could be distracting.

The public meeting is being recorded and will be made available post meeting on the Biosimilars | Science and Research | FDA website.

For Questions and Answers (Q&A):

Virtual and In-Person Attendees: please use the QR Code provided for questions.

All questions should include the name of the panelist the question is being addressed to.

Thank you!

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Center for Drug Evaluation and Research

fda.gov/biosimilars

FDA SCIENTIFIC WORKSHOP

Advancing the Development of Interchangeable Products: *Identifying Future Needs*

September 19, 2025

Sarah Yim, M.D.
Director
Office of Therapeutic Biologics and Biosimilars (OTBB)
Office of New Drugs/CDER/FDA

Biological Product Regulation

- **351(a) "stand alone" Biologics License Application (BLA):** contains all information and data necessary to demonstrate that the proposed biological product is safe, pure and potent
- **The Biologics Price Competition and Innovation Act** of 2009 (BPCI Act)
  - Created an **abbreviated licensure pathway (351(k))** for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product (originator biological product)

General Requirements

A 351(k) application must include information demonstrating that the biological product:

- Is **biosimilar** to a reference product
  - **Highly similar to and has no clinically meaningful differences from the** FDA-approved reference product
- Utilizes the **same mechanism(s) of action** for the proposed condition(s) of use -- but only to the extent the mechanism(s) are known for the reference product;
- **Condition(s) of use** proposed in labeling **have been previously approved** for the reference product;
- Has the **same route of administration, dosage form,** and **strength** as the reference product; and
- Is manufactured, processed, packed, or held in a facility that **meets standards** designed to assure that the biological product continues to be **safe, pure, and potent.**

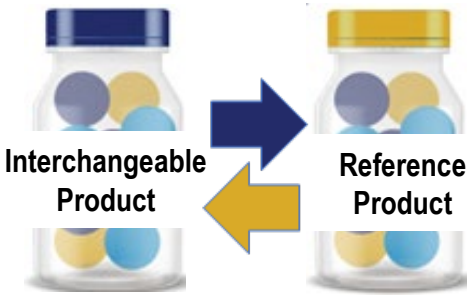
Key Definitions from the BPCI Act

Reference Product

A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared

Biosimilar Product

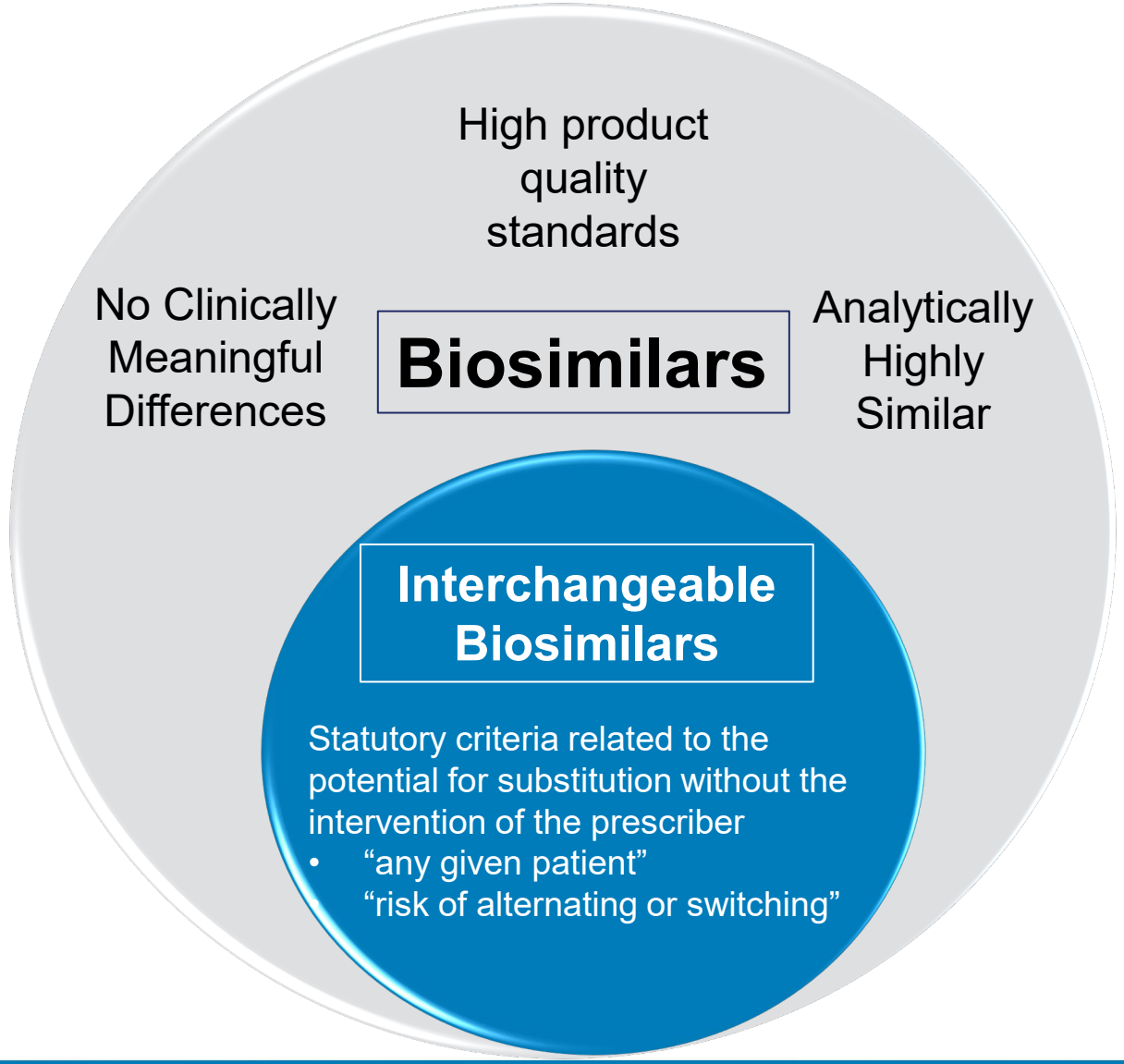
A biosimilar is a biological product that is **highly similar to and has no clinically meaningful differences from** an existing FDA-approved reference product



Interchangeable Product

- Is a biosimilar
- Expected to produce the same clinical result as the reference product (RP) in any given patient
- Switching between the proposed product and the RP does not ↑safety risks or ↓effectiveness compared to using the RP without switching

Biosimilars and Interchangeable Biosimilars



- Applicants can request licensure as a biosimilar or interchangeable biosimilar
- The analytical similarity and product quality standards are **the same** for biosimilars and interchangeable biosimilars
- Statutory criteria related to the potential for substitution without the intervention of the prescriber
- HCPs prescribe reference products or biosimilars **by name**
- A pharmacist can substitute an interchangeable product for the reference product without consulting the prescribing HCP (subject to state laws)

Why does the US have an "interchangeable" category?

- An interchangeable biosimilar product can be **substituted for the reference product at pharmacies** without the intervention of the prescribing health care provider (like small molecule generics), subject to state pharmacy laws.
- At the time the law was being drafted, there was a concern that certain biologics might be susceptible to altered risks or efficacy when switching back and forth; for example those with significant immunogenicity-related concerns
  - This theoretical concern has not been observed thus far and is likely to be a much more limited concern scientifically than first thought
  - Additionally, it has become clearer that any real concerns related to the "interchangeability" criteria would also be a potential safety concern for biosimilarity as well

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KEYNOTE

George F. Tidmarsh, M.D., Ph.D.
Director
Center for Drug Evaluation and Research

Perspective on the Future Needs for the Development of Interchangeable Products: PhRMA

PhRMA
RESEARCH • PROGRESS • HOPE

Future Needs for the Development of Interchangeable Products

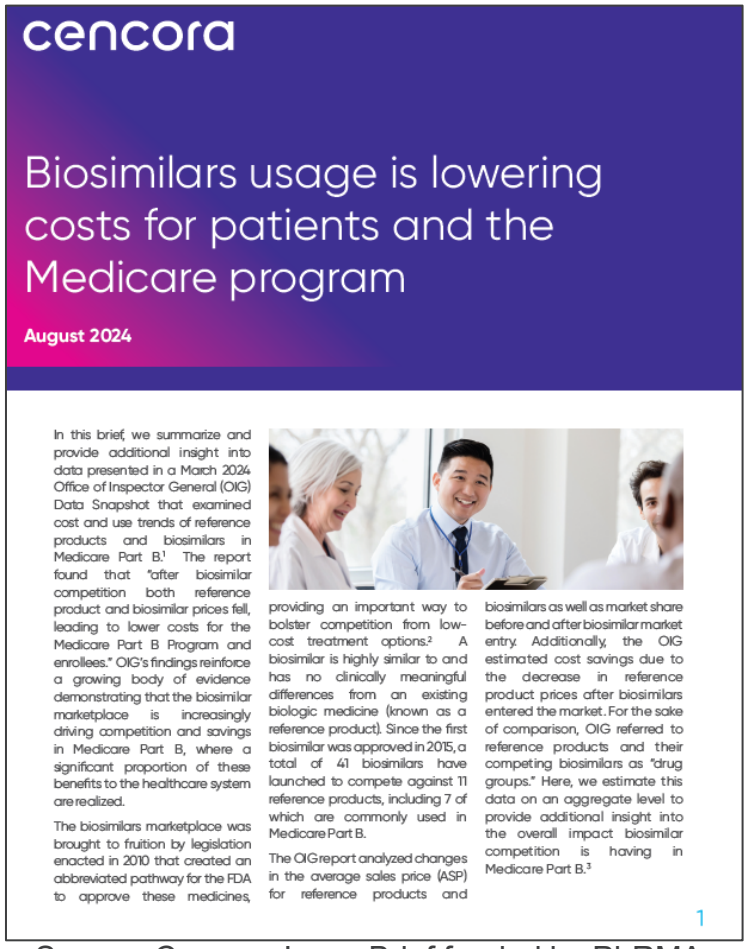
September 19, 2025

PhRMA Support for Biosimilars and Interchangeable Biosimilars

Market Continues to Yield Increased Competition and Substantial Savings

PhRMA:

- Supported the creation of the approval pathway for biosimilar and interchangeable biosimilar products under the Biologics Price Competition and Innovation Act ("BPCIA")
- Supports and participated in implementation, including negotiations for Biosimilar User Fee Act ("BsUFA") III
- Shares FDA's commitment to continuing implementation of BPCIA and BsUFA III and to ensuring the safe use of biosimilar and interchangeable products



cencora

Biosimilars usage is lowering costs for patients and the Medicare program

August 2024

In this brief, we summarize and provide additional insight into data presented in a March 2024 Office of Inspector General (OIG) Data Snapshot that examined cost and use trends of reference products and biosimilars in Medicare Part B.[1] The report found that "after biosimilar competition both reference product and biosimilar prices fell, leading to lower costs for the Medicare Part B Program and enrollees." OIG's findings reinforce a growing body of evidence demonstrating that the biosimilar marketplace is increasingly driving competition and savings in Medicare Part B, where a significant proportion of these benefits to the healthcare system are realized.

The biosimilars marketplace was brought to fruition by legislation enacted in 2010 that created an abbreviated pathway for the FDA to approve these medicines, providing an important way to bolster competition from low-cost treatment options.[2] A biosimilar is highly similar to and has no clinically meaningful differences from an existing biologic medicine (known as a reference product). Since the first biosimilar was approved in 2015, a total of 41 biosimilars have launched to compete against 11 reference products, including 7 of which are commonly used in Medicare Part B.

The OIG report analyzed changes in the average sales price (ASP) for reference products and biosimilars as well as market share before and after biosimilar market entry. Additionally, the OIG estimated cost savings due to the decrease in reference product prices after biosimilars entered the market. For the sake of comparison, OIG referred to reference products and their competing biosimilars as "drug groups." Here, we estimate this data on an aggregate level to provide additional insight into the overall impact biosimilar competition is having in Medicare Part B.[3]

1

Source: Cencora Issue Brief funded by PhRMA (2024)

Advancing Development of Interchangeable Biosimilar Products

Foundational Guidance

BsUFA III Draft Guidance Status

- ✓ *Labeling for Biosimilar and Interchangeable Biosimilar Products* (Sept. 2023)
- ✓ *Postapproval Manufacturing Changes to Biosimilar and Interchangeable Biosimilar Products Questions and Answers* (July 2024)
- ✓ *Promotional Labeling and Advertising Considerations for Prescription Biological Reference Products, Biosimilar Products, and Interchangeable Biosimilar Products: Questions and Answers* (April 2024)
- ❑ *Biosimilar and Interchangeable Biosimilar Products: Considerations for Container Closure Systems and Device Constituent Parts* (due Sept. 30, 2025)

Advancing Development of Interchangeable Biosimilar Products

Draft Strategy Document Will Outline Specific Actions FDA Will Undertake

Stakeholder Engagement: FDA will hold a scientific workshop on the development of interchangeable products to help identify future needs (e.g., guidance, research) on or before October 31, 2025. Within 12 months following the public workshop, FDA will issue a draft strategy document for public comment that outlines the specific actions the agency will take to facilitate the development of interchangeable biosimilar biological products. The strategy document may identify activities and deliverables including updating or creating new procedures, MAPPs, SOPPs, guidances, and other changes to FDA's scientific and other programs related to the topics discussed in the workshop. The strategy document will also include proposed timeframes for the specific actions outlined in the document. FDA will consider public input and will publish a final strategy document within 9 months after the close of the public comment period on the draft strategy document.

Current Statutory Framework Appropriately Enables Fact-Specific Determinations

- **Statute:** Application must have "information" that is "sufficient to show" that:
  - the biosimilar "can be expected to produce the same clinical result as the reference product in any given patient"

    and
  - for multiple use products, "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."

- Provides FDA with ample statutory authority to address data requirements for interchangeability on a case-by-case basis

Need for Clarity on Interchangeability Standard

There Has Been Confusion Stemming from Range of Statements

Considerations in Demonstrating Interchangeability With a Reference Product: Update

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Communications, Division of Drug Information at (855) 543-3784 or (301) 796-3400, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2024
Biosimilars

FDA Summary of FY 2026 Legislative Proposals

The FY 2026 budget includes several legislative proposals that support agency efforts to protect American consumers and patients. The proposals include enhanced authorities to address the import of problematic medical devices and ensure data quality in medical product applications. The proposals would change labeling requirements for active pharmaceutical ingredients to include original manufacturer and supply origin and enhance the utility of drug manufacturing amount information to be reported to the Agency. The Agency also seeks authority to ensure that data supporting application and non-application medical products are reliable and verifiable for as long as the product may be legally marketed and has sufficient tools to act on findings of fraudulent or unreliable data. The budget would also expand the type of information required to prevent drug shortages and resolve a statutory distinction between biosimilar products and interchangeable biosimilar products. The budget would also give FDA the authority to require an importer to destroy any FDA-regulated product(s) refused entry into the United States that presents a significant public health concern, thus removing their option to export such product(s).

Eliminate the Statutory Distinction Between the Approval Standard for Biosimilar and Interchangeable Biosimilar Products and Deem that Approved Biosimilars are Interchangeable

The statutory distinction between biosimilar products and interchangeable biosimilar products has led to confusion and misunderstanding, including among patients and healthcare providers, about the safety and effectiveness of biosimilars and about whether interchangeable biosimilars are safer or more effective than other biosimilars. Interchangeability pertains to pharmacy substitution of an interchangeable biosimilar for its reference product. However, both biosimilars and interchangeable biosimilars are just as safe and effective as their respective reference products and can be used in place of their respective reference products. Accordingly, FDA seeks to amend section 351 of the Public Health Service Act to no longer include a separate statutory standard for a determination of interchangeability and to deem all approved biosimilars to be interchangeable with their respective reference products. This proposal would make the U.S. biosimilar program more consistent with current scientific understanding, as well as with the approach adopted by other major regulatory jurisdictions such as the European Union that permit interchangeability of biosimilars with their respective reference products upon approval. This proposal is expected to increase uptake of biosimilars, with potential downstream effects of increasing competition, access, and affordability.

A Fact-Specific, Case-By-Case Approach to Data Requirements

Appropriate Supportive Data for a Proposed Interchangeable Product May Vary

PhRMA believes that FDA should determine the data and information needed to establish interchangeability on a fact-specific, case-by-case basis that considers all relevant factors and an applicant's justification for its approach

Examples of Relevant Factors for Assessing Appropriate Supportive Data
Product type, complexity, and novelty
Mechanism of action
Indications and patient populations
Chronic versus acute treatment
Presence or absence of known safety concerns with the product class

Key Open Scientific Issues Concerning Interchangeability

Additional Guidance Needed

Topics for Guidance
Switching Studies
Analytical Considerations for interchangeability
Presentation/Delivery Device Issues
Interchangeability of Products Other Than Therapeutic Proteins/Proteins With Approved Biosimilars

Other Open Scientific Issues

PhRMA Looks Forward to Future Guidance on the Following Topics

Switching Studies

- Articulate scientific standards describing when switching studies will and will not be necessary
- If presuming interchangeability from biosimilarity showing, explain rationale and examples of when the presumption would and would not apply
- Procedures

Analytics

- Recommend that FDA explain how new analytical technologies, and FDA's experience using them, have changed its thinking on interchangeability
- Guidance updates on this issue

Other Open Scientific Issues

PhRMA Looks Forward to Future Guidance on the Following Topics

Presentation/Delivery Device Issues for Proposed Interchangeable Products

- Expected by September 30, 2025
- Important topic for interchangeable development
- FDA should consider whether presentation is adequate to ensure automatic substitution for the reference product

Demonstrating Interchangeability for Non-Therapeutic Proteins

- To date, most of the evidence generated has involved certain monoclonal antibodies and fusion proteins, and Update guidance is limited to therapeutic proteins.
- Pipelines include complex and less well-understood potential interchangeable products
- Need to clarify how interchangeability expectations apply to such products

Policy Considerations for Future Guidance

Focus on Class-Wide Guidance and Incorporate Learnings from BsUFA III Research

- PhRMA supports the issuance of guidance documents that are ***cross-cutting for a class of biosimilar products*.**
  - Can be applied to multiple biosimilar products with shared features, such as mechanism of action.
  - Product-specific guidance is insufficiently flexible.
- PhRMA encourages FDA to commit to revising and refining any interchangeability guidance issued to reflect learnings from the ***BsUFA III Regulatory Science Research Pilot Program*** (final summary to be published Sept. 30, 2027).

Perspective on the Future Needs for the Development of Interchangeable Products: AAM

Perspective on the Future Needs for the Development of Interchangeable Products: Biosimilars Forum

Thank you!

Break Period

Break is from 10:30-11:00am

At 11:00am we will resume for the Specific Scientific Topics Presentations

All questions please submit using the QR code.

Or submit to:
BsUFARegSciProgram@fda.hhs.gov

Welcome Back to the Specific Scientific Topic Presentations

Analytical Considerations Around Interchangeability of a Biologic

Maria Teresa Gutierrez Lugo
CDER/OPQ/OPQAIII

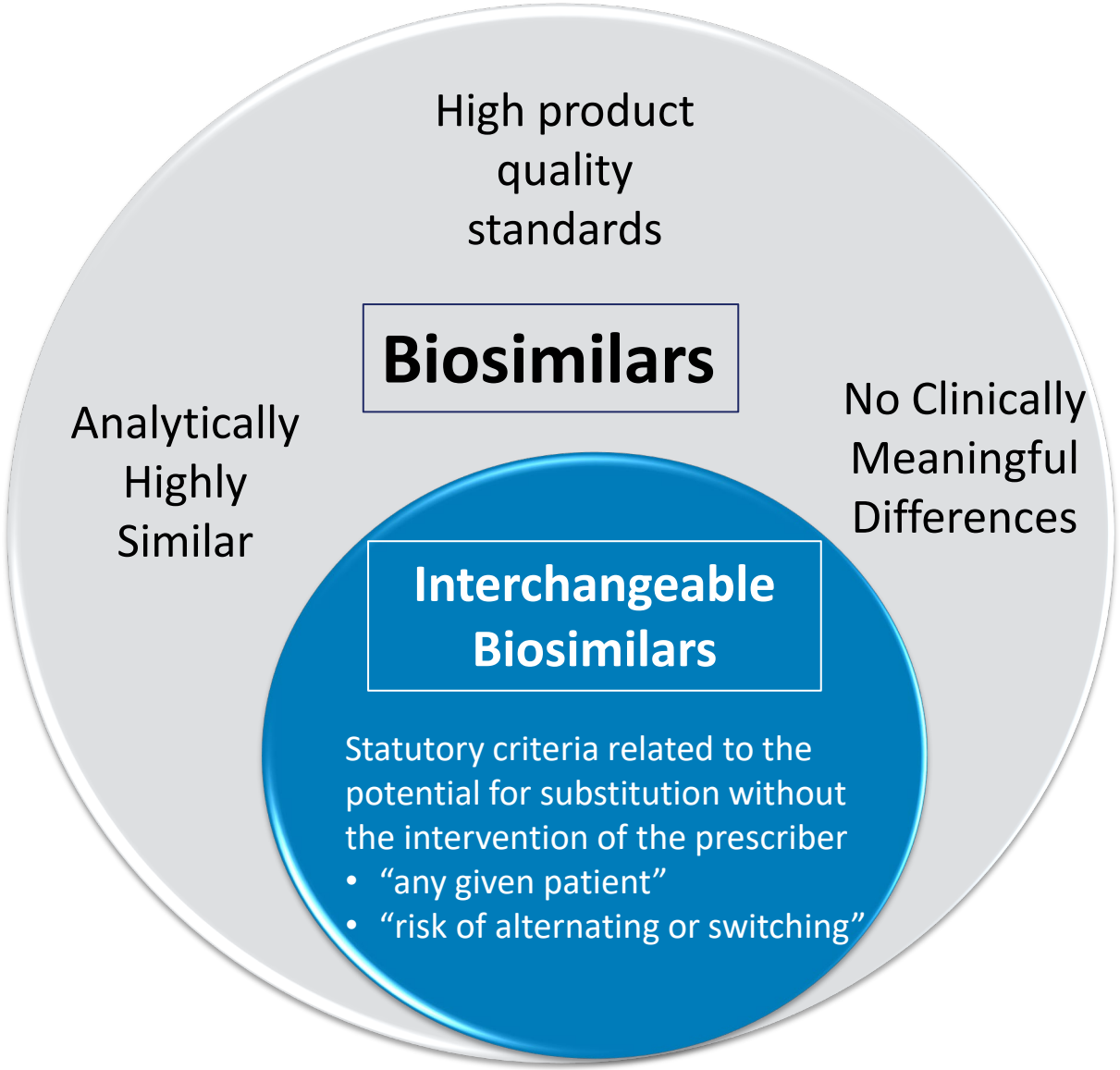
FDA Public Workshop: Future Needs for the Development of Interchangeable Products

September 19, 2025

Key Messages

- Analytical and product quality expectations for interchangeable biosimilars are the same as for non-interchangeable biosimilars
- A highly similar determination is the foundational evidence that the biosimilar should perform clinically as the reference product
- Analytical studies provide the most sensitive measure for assessing similarity compared to clinical studies
- Most well-characterized protein biological products should be amenable to comprehensive analytical characterization using state-of-the-art analytical technologies
  - This includes new classes of product types – ADCs, conjugates, bispecifics
  - Challenges for a highly similar demonstration remain for a small group of biological products

Analytical and Product Quality Expectations



- An interchangeable biosimilar
  - Is a biosimilar that meets statutory criteria for interchangeability
- The analytical similarity standard is **the same** for biosimilars and interchangeable biosimilars
- Product quality standards for biosimilars and interchangeable biosimilars [351 (k)] are **the same** as stand alone biological products [351(a)]

Highly Similar Demonstration

- Comprehensive analytical characterization of quality attributes (QA) of the reference and biosimilar product.

- QAs evaluated are ranked and assessed based on their known or potential impact on product quality and **clinical performance** (e.g., impact on safety, efficacy, PK, and immunogenicity).

Strength

Primary Structure

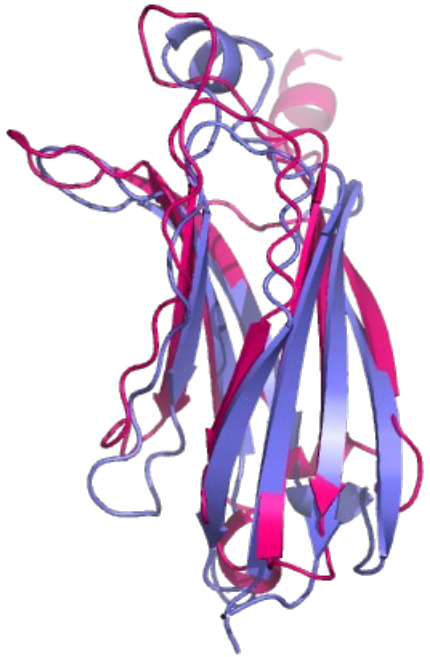
Higher Order Structure

Biological/Functional *

Post-translational modifications

Product-related variants

Comparative Degradation profiles



*Potential mechanism(s) of action, to the extent they are reasonably known

Highly Similar Demonstration

- Sufficiently sensitive, state-of-the-art, reliable analytical techniques capable to discriminate qualitative or quantitative differences in QAs are used

- Most QAs are evaluated using multiple orthogonal quantitative methods to compare the reference product and biosimilar. Results from these methods strengthen the conclusion of similarity
  - Testing includes targeted evaluation to confirm absence of a specific mechanism of action that is not expected, as applicable.

- The goal of the CAA is to be as comprehensive as possible to **maximize the potential for detection of differences in quality attributes** between the proposed biosimilar and the reference product.

Comparative Analytical Assessment: Breadth of Analytics

Hypothetical Release (~12 tests)

- Appearance
- pH
- Strength
- Identity
- Potency
- Glycans
- Size Variants
- Charge Variants
- Bioburden/Endotoxin

Additional Attributes

Orthogonal Techniques

Hypothetical CAA (> 40 tests)

- Strength (n=1)
- Primary Structure (n=4)
- Higher Order Structure (n=5)
- Biological/Functional (n=24)
- Post-translational modifications (n=15)
- Product-related variants (n=6)
- Degradation profiles (n=7)

Slide prepared by Patrick Lynch

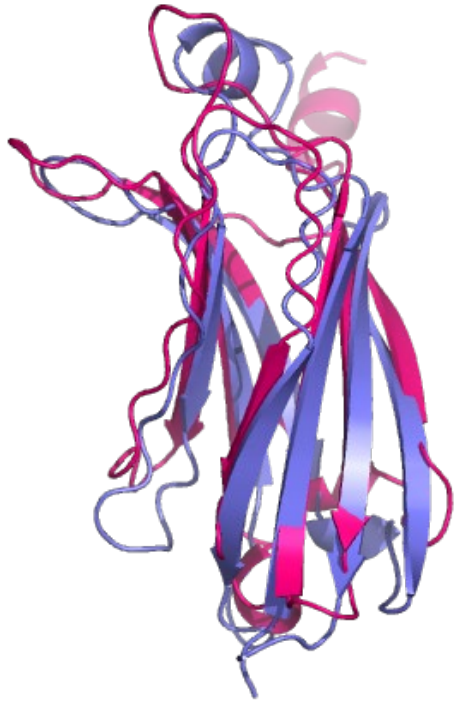
Highly Similar Demonstration

- To meet the **highly similar** standard, the biosimilar QAs should be within an appropriately defined and scientifically justified limit, range, or distribution (similarity acceptance criteria) compared to the reference product.
  - Similarity acceptance criteria are determined by a comprehensive analysis of the reference product
    - Biological products are heterogenous, analyses of multiple RP lots are needed to determine RP quality attribute ranges and batch-to-batch variability.
  - If present, differences should be justified based on their potential impact to product quality and clinical performance (e.g., impact on safety, efficacy, PK, and immunogenicity).
    - If differences cannot be explained by additional analytical studies or justified, there may be a need to modify the biosimilar manufacturing process to better match the quality attributes profile of the RP
- Assessment of highly similar considers **the totality of the analytical data and information,** including justification for analytical differences (if present)

Implications of a Highly Similar Determination

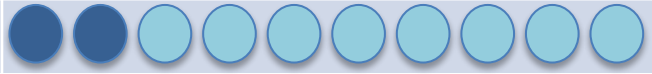
- A **highly similar** determination provides **evidence that the biosimilar should behave clinically like the reference product**

- When there is sufficient evidence of high similarity to the RP, the BS is not expected to behave different from the **RP when alternating or switching**



Align - PyMOLWiki

Approved Biosimilars 2015-2025 (n=73)

Immunology/Rheumatology	
Humira (adalimumab)	
Stelara (ustekinumab)	
Remicade (infliximab)	
Actemra (tocilizumab)	
Enbrel (etanercept)	
Soliris (eculizumab)	
Tysabri (natalizumab)	

Oncology	
Herceptin (trastuzumab)	
Avastin (bevacizumab)	
Xgeva/Prolia (denosumab)	
Rituxan (rituximab)	

Supportive Care	
Neulasta (pegfilgrastim)	
Neupogen (filgrastim)	
Epogen (epoetin-alfa)	

Ophthalmology	
Eylea (aflibercept)	
Lucentis (ranibizumab)	

Glycemic Control	
Lantus (insulin glargine)	
Novolog (insulin aspart)	

Pulmonary	
Xolair (omalizumab)	

Biosimilar

Interchangeable biosimilar (n=27)

Slide prepared by Patrick Lynch

Current Biosimilar Experience

- For well-characterized therapeutic proteins, when there is comprehensive coverage of quality attributes and they match between the biosimilar and reference product (strong evidence of high similarity), the BS and RP are not expected to clinically perform differently.

- Most therapeutic proteins are well-characterized (e.g., monoclonal antibodies, enzymes, cytokines, fusion proteins, ADCs) and suitable for comprehensive analytical characterization

Current Challenges for Highly Similar Demonstration

- A small number of products are more difficult to comprehensively characterize e.g.
  - Active ingredient is difficult to isolate for comprehensive characterization
  - Complex mixtures
  - Limited knowledge regarding structural/functional relationships of every component

➢**These products are likely to raise uncertainty around biosimilarity**

- Strongly encourage discussion on potential approaches to analytical similarity with the Agency

Concluding Remarks

- Today's analytical tools can accurately evaluate the structure, biological activity and other physicochemical properties of biotechnology products with more precision and sensitivity than clinical studies, including switching studies.

- We have gained valuable experience with biosimilar and interchangeable biosimilars over the last 10 years. Both biosimilars and interchangeable biosimilars meet the same high standard of biosimilarity for FDA approval and both are as safe and effective as the reference product.

FDA updates guidance on interchangeability | FDA

Acknowledgements

Joel Welch

Sarah Yim

Susan Kirshner

Stacey Ricci

Patrick Lynch

Kristen Nickens

Thank you for your attention

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User Interface and Human Factors Considerations to Support Biosimilarity and Interchangeability

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Associate Director for Human Factors

Matthew Barlow, BSN, RN
Human Factors Team Leader

Division of Medication Error Prevention and Analysis I (DMEPA I)
Office of Medication Error Prevention & Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)

FDA Public Workshop: Future Needs for the Development of Interchangeable Products
September 19, 2025

Agenda

- Key definitions
- Use-Related Risk Analysis (URRA) and Comparative Analyses (CA) principles
- Design differences and sample product walkthrough
- Data requirements when other design differences are identified
- General advice

U.S. FOOD & DRUG ADMINISTRATION

Key Definitions

Definition of Human Factors/Ergonomics (HF/E)

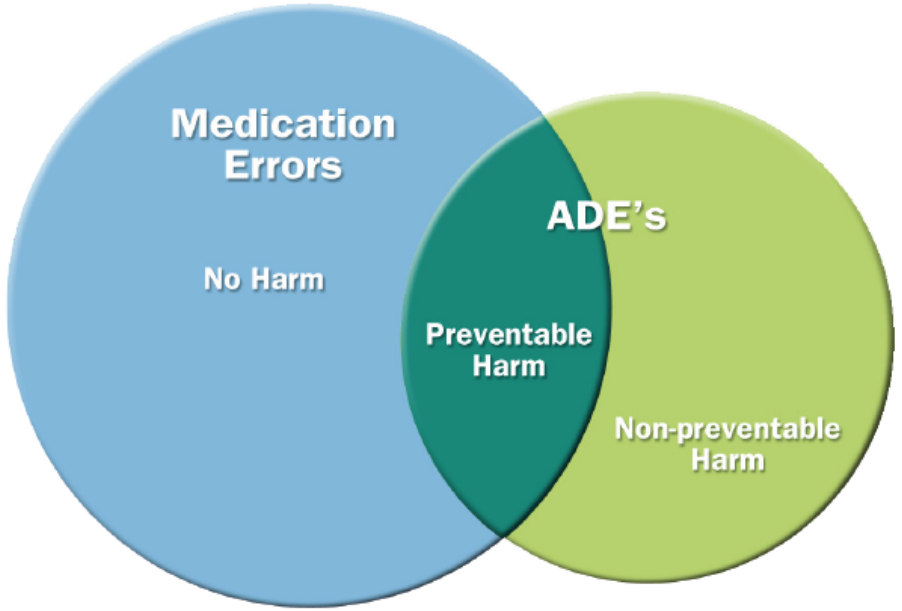
Ergonomics (or human factors) is the scientific discipline concerned with the understanding of interactions among humans and other elements of a system, and the profession that applies theory, principles, data and methods to design in order to optimize human well-being and overall system performance.

International Ergonomics Association (IEA)

What is a Medication Error?

A medication error is any **preventable** event that may cause or lead to **inappropriate medication use** or **patient harm** while the medication is in the control of the health care professional, patient, or consumer

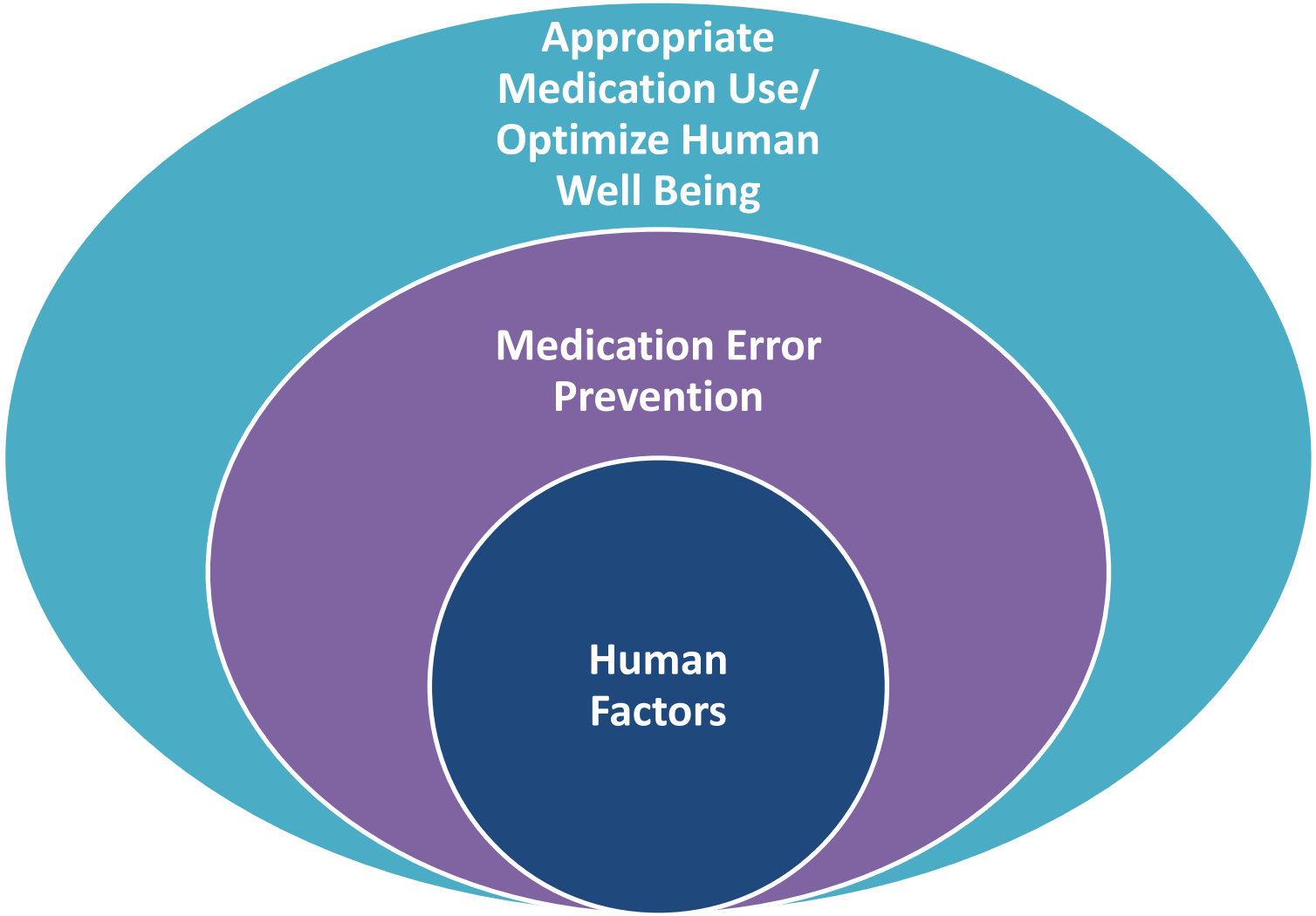
Figure 1: Relationship between medication errors and ADEs



[1]Adapted from Figure 1 in Qual Saf Health Care 2004;13:306–314. doi: 10.1136/qshc.2004.010611

National Coordinating Council for Medication Error Reporting and Prevention. Available at: www.nccmerp.org. Accessed 8/18/2025

Medication Error Prevention and HF – A Natural Fit!



Additional Definitions

User Interface (UI)

- All components of the product with which a user interacts
- Includes delivery device constituent part and any associated controls, displays, product labeling, and packaging

Critical Task

- A user task that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include compromised medical care

Use-Related Risk Analysis (URRA) and Comparative Analyses (CA) Principles

Use-Related Risk Analysis (URRA)

- Includes:
  - comprehensive evaluation of all the steps involved in using the product (based on a task analysis),
  - the errors that users might commit or the tasks they might fail to perform,
  - the potential clinical consequences of use errors and task failures,
  - the risk controls employed to reduce risks to acceptable levels, and
  - the method of validating the risk control strategies.
- Helpful tool for identifying critical tasks

Comparative Analyses (CA)

Side-by-side analyses conducted to identify differences in user interface design between two products (e.g., proposed biosimilar/interchangeable biosimilar compared to reference product)

Physical Comparison	Comparative Task Analysis	Labeling Comparison
• Visual, tactile, audible examination of the physical features (e.g., size, shape, visual or tactile feedback)	• Highlights when differences in tasks arise due to differences in user interface design • Interested in understanding whether differences represent new critical tasks or impact an existing critical task.	• Instructions for use • Container label • Carton labeling

Comparative Analyses Best Practices

- Identify ALL user interface differences
- Classify ALL differences based on definitions in the guidance
- Focus on potential differences in the critical tasks between the reference product and proposed biosimilar or interchangeable biosimilar combination products.
  - Remember that **not every task is a critical task**
- Consider the product and its context of use
  - Same difference could be classified and assessed differently
  - Focus on the individual reference product

Comparative Analyses Outcomes

- For each difference found in the physical, task, or labeling comparison performed during CA, provide one of the following outcomes:
  - **No Differences**
  - **Minor Design Difference**
    - The difference in the user interface of the proposed biosimilar or interchangeable biosimilar combination product, in comparison to the user interface of the reference product, does not affect how a user performs a critical task.
  - **Other Design Difference**
    - The comparative analyses suggests that the difference in the design of the user interface of a proposed biosimilar or interchangeable biosimilar combination product, as compared to the reference product, *may* impact how a user performs a critical task that involves administration of the product.
- Consider any identified differences in the context of the overall risk profile of the product

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Design Differences and Sample Product Walkthrough

Examples of Minor* Design Differences

- Reference product's single-dose prefilled syringe includes graduation lines while the proposed single-dose prefilled syringe does not
- Some color differences in the device design (e.g., prefilled syringe plunger rod and flange, autoinjector body) between the reference product and proposed product

*Note: depending on the user interface, specific drug product, intended use, intended users, and use environment, the examples above may be considered other design differences

Example of an Other Design Difference

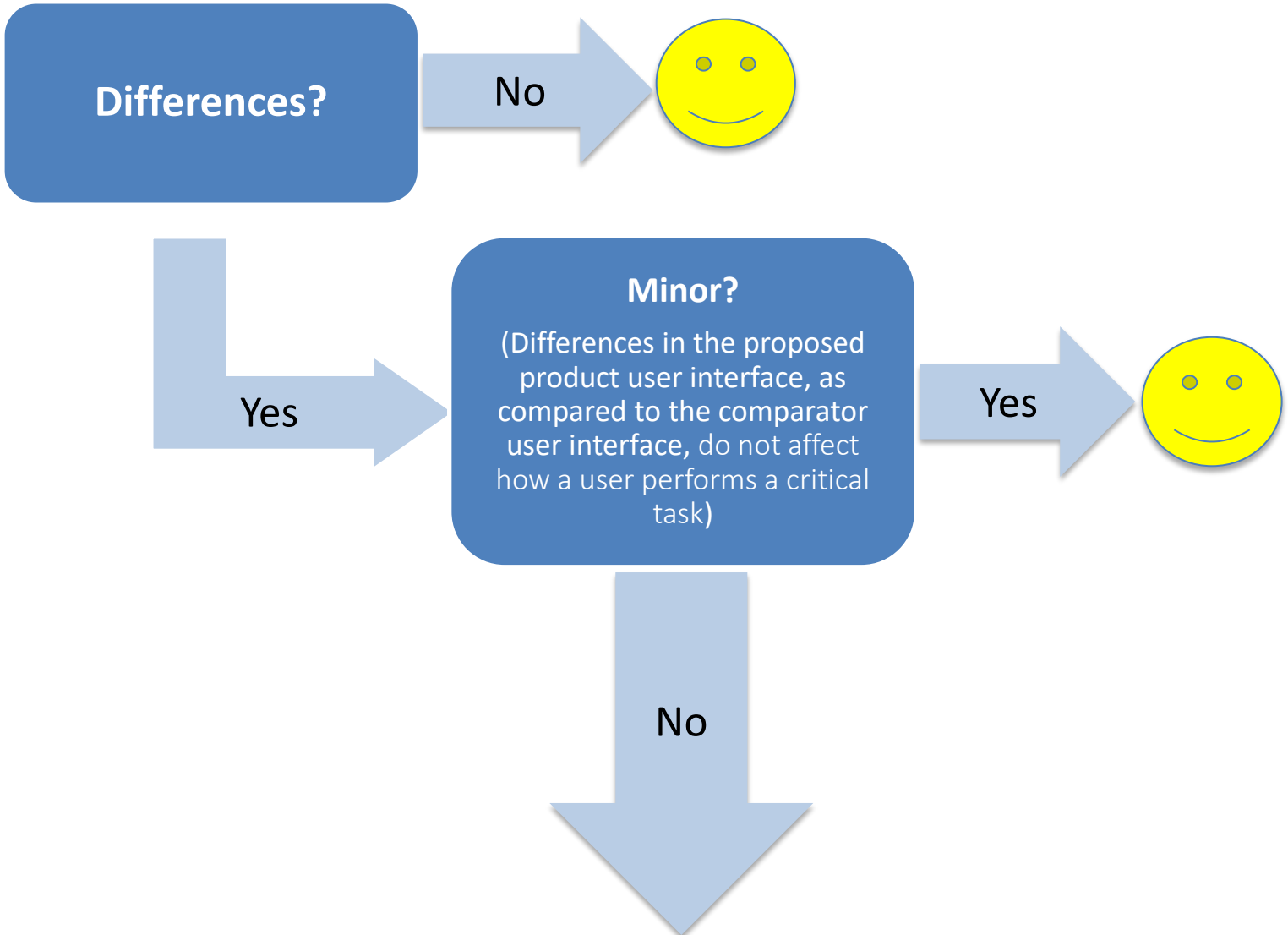
Reference product: task of holding button

Task No.	Task Description	Potential Use Error	Description of Harm/Severity	Task Criticality	Risk Control
4	Press green button and hold for 10 seconds	Button held for less than 10 seconds	Full dose not injected, leading to death	Critical	IFU states that the green button should be held for 10 seconds

Proposed product: task of holding button

Task No.	Task Description	Potential Use Error	Description of Harm/Severity	Task Criticality	Risk Control
4	Press green button and hold for 20 seconds	Button held for less than 20 seconds	Full dose not injected, leading to death	Critical	IFU states that the green button should be held for 20 seconds

Comparative Analyses Process Overview



What are my options?

- **Re-design** of the proposed user interface to minimize differences from the reference product
- **Potential need for additional information and/or data** to support the BLA submission
  - Additional human factors study data and/or information

    OR

  - You may already have the information or data that FDA needs!

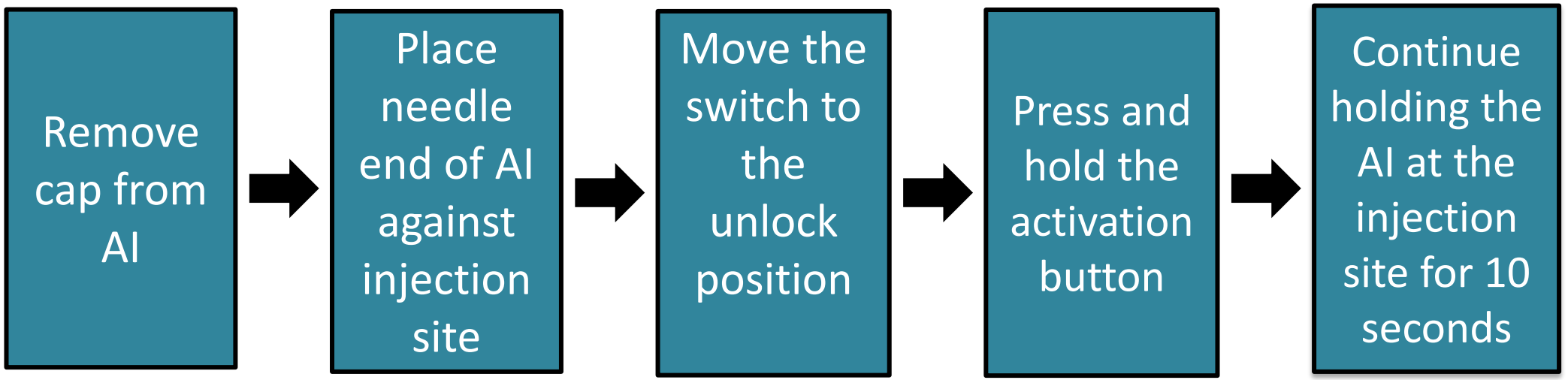
Walkthrough of a Proposed Biosimilar Product Example

	Product X (Reference Product)	Product Y (Proposed Biosimilar)
Indication	Treatment of rheumatoid arthritis in adult patients	
Dosing	200 mg once every 4 weeks	
Supplied as	One 200 mg/mL autoinjector (AI) per carton	
Intended Users	Patients; Caregivers; Healthcare Professionals (HCPs)	
Intended Use Environment	Home; Clinic/Healthcare facility	

Walkthrough of the Reference Product X

Product X Device Constituent Part:

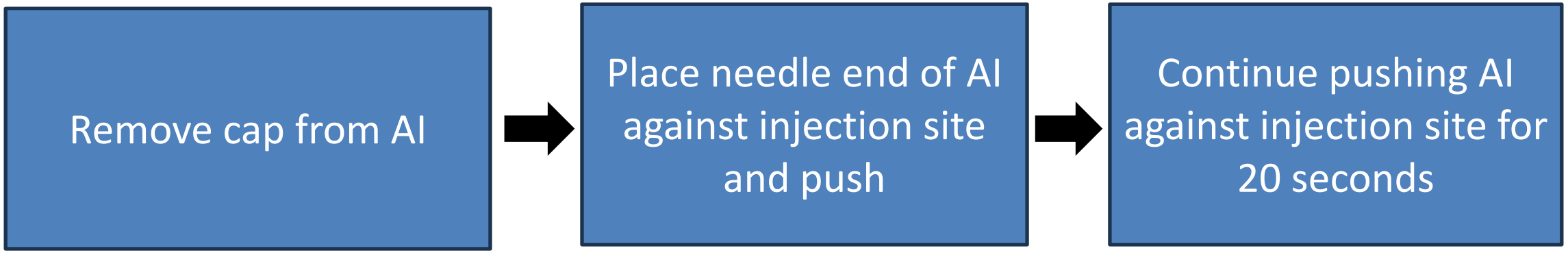
- The autoinjector has an unlocking mechanism and activation button.



Walkthrough of a Proposed Biosimilar Product Y

Proposed Product Y Device Constituent Part:

- The autoinjector is a 2-step device without an activation button.



Walkthrough of a Proposed Biosimilar Product Y

Agency Evaluation of Differences Identified in Sponsor's Physical Comparison		
Reference Product X	**Proposed Product Y**	**Agency's Categorization of Difference**
Has an **activation button**	**Does not** have a button	Other Design Difference
Locking mechanism requires the user to **manually** move to the unlock position before pressing against the injection site and pushing the activation button	Locking mechanism requires the user to apply force when pressing the needle guard against the injection site to unlock/activate the injection	Other Design Difference

Walkthrough of a Proposed Biosimilar Product Y

Agency Evaluation of Differences Identified in Sponsor's Comparative Task Analysis		
Reference Product X	**Product Y**	**Agency's Categorization of Differences**
User must **twist to manually unlock** the AI.	This product **does not** require manual unlocking.	Other Design Difference
User presses the AI against the injection site and **pushes the button to activate** the injection	User **presses the AI against the injection site to activate** the injection.	Other Design Difference
User holds the AI against the injection site for **10 seconds**	User holds the AI against the injection site for **20 seconds**	Other Design Difference

Data Requirements when Other Design Differences are Identified

Information/Data to Support Other Design Differences in the Context of Biosimilarity

Human factors validation study:

- Designed to demonstrate whether the proposed biosimilar combination product user interface has no clinically meaningful difference from the reference product

Information/Data to Support Other Design Differences in the Context of Interchangeability

- Verify if you already have the information or data that FDA needs
- Consider if other data may be supportive – e.g., comparative use human factors (CUHF) study
  - Study designed to demonstrate that the difference in design does not impact a critical task or, if the difference in design may impact a critical task, that potential use errors related to the difference do not preclude a showing that the proposed interchangeable product meets the standards in the PHS Act
  - Noninferiority (NI) study designs are generally appropriate
  - Includes current users of the reference product

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General Advice

General Advice

- Review relevant guidance documents from FDA
- Consult FDA early to discuss product development plans before your design is finalized
- Once you've completed your proposed intend-to-market user interface, submit your HF study protocol to the IND for FDA's review and feedback on the study design before conducting your study
- If you determine that a study is not needed for your intend-to-market user interface, submit your URRA and comparative analyses, and justification for FDA's review and concurrence before submitting your marketing application

Key FDA Guidance Documents Referenced

- Comparative Analyses for Drug-Device Combination Products in ANDAs (2017)
- Considerations in Demonstrating Interchangeability With a Reference Product (2019)
- Application of Human Factors Engineering Principles for Combination Products Q&A (2023)
- Purpose and Content of URRAs for Drugs, Biologics, and Combination Products (2024)

Thank you!

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

fda.gov/biosimilars

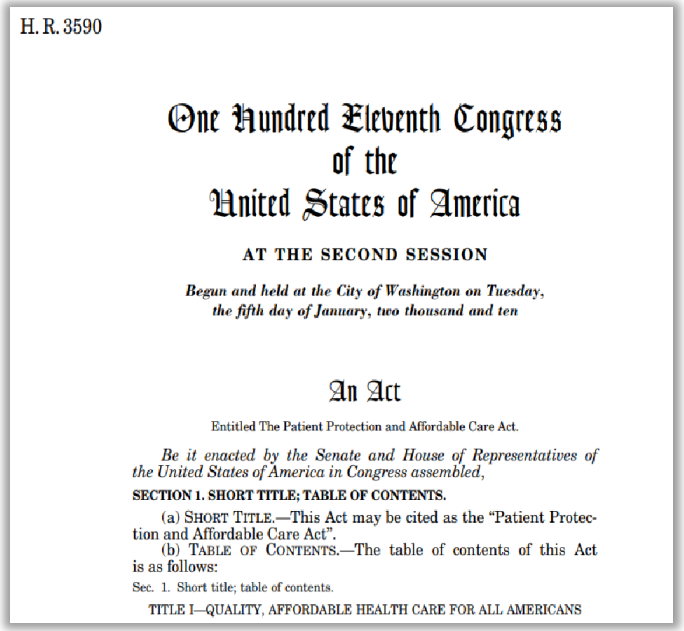
FDA PUBLIC WORKSHOP

Facilitating Development of Interchangeable Biosimilars

September 19, 2025

M. Stacey Ricci, M.Eng., Sc.D.
Director Scientific Review Staff
Office of Therapeutic Biologics and Biosimilars
Office of New Drugs | CDER | FDA

"Determining Interchangeability"



H. R. 3590

One Hundred Eleventh Congress
of the
United States of America

AT THE SECOND SESSION

Begun and held at the City of Washington on Tuesday, the fifth day of January, two thousand and ten

An Act

Entitled The Patient Protection and Affordable Care Act.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "Patient Protection and Affordable Care Act".

(b) TABLE OF CONTENTS.—The table of contents of this Act is as follows:

Sec. 1. Short title; table of contents.

TITLE I—QUALITY, AFFORDABLE HEALTH CARE FOR ALL AMERICANS

The BPCI Act requires three standards to be met for a biological product to be interchangeable:

- ✓ **Biosimilarity**

  It is **biosimilar** to the reference product.

- ✓ **"Any Given Patient"**

  It is expected to produce the **same clinical result** as the reference product in **any given patient**.

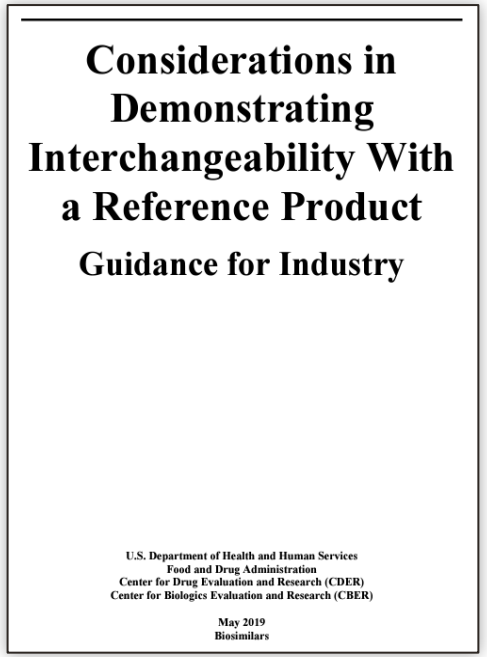
- ✓ **Switching**

  Switching between the proposed product and the reference product **does not ↑safety risks or ↓effectiveness** compared to using the RP without switching.

Meeting the Interchangeability Standards

FDA granted authority to approve biosimilar and interchangeable products

First biosimilar approved


Considerations in Demonstrating Interchangeability With a Reference Product

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Biosimilars

Draft

Final

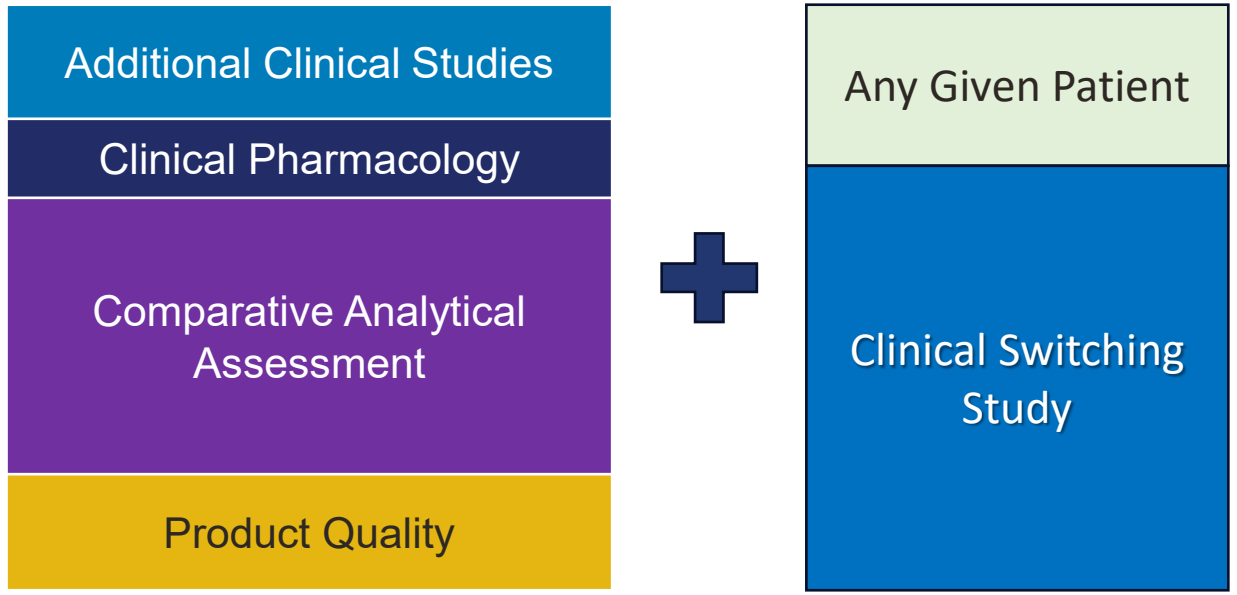
2010 2011 2012 2013 2014 2015 2016 2017 2018 2019

The Guidance focused on potential differences in the product to be administered ("what's inside the vial")

Meeting the Interchangeability Standards

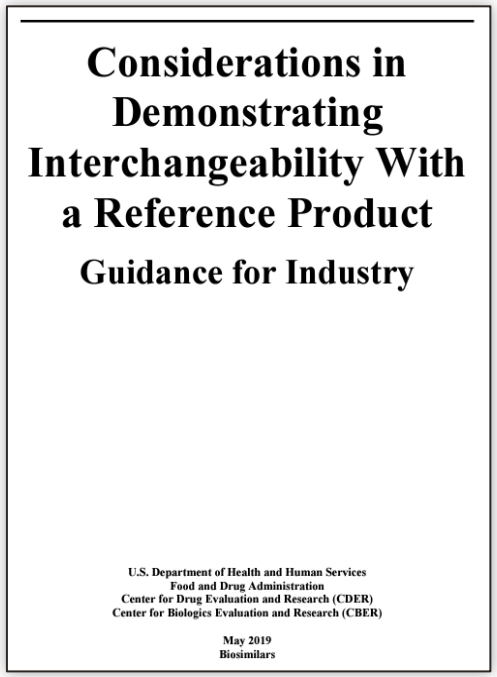
Biosimilarity

Interchangeability



More data and information will be needed

Meeting the Interchangeability Standards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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Biosimilars

Considerations focused on:

- Ability to analytically characterize products and evaluate differences
- Data needed to address product-specific immunogenicity risk
- Clinical study design to assess switching between products

Assumed most products would be approved as biosimilar first, marketed and approved as interchangeable afterwards

Addressing "Any Given Patient" Standard

- Focused on **potential differences in product quality aspects** of proposed product, and whether they were evaluated in terms of how they could impact clinical outcomes across patient populations
  - Mechanism(s) of action, PK, PD, immunogenicity, safety, efficacy

- **No additional data from clinical studies was expected** to meet the "any given patient" standard

Addressing "Switching" Standard

- A **switching study was expected** as part of the data package generally needed to demonstrate interchangeability
  - Purpose was to address **potential concerns about increased risk of immunogenicity for patients** who chronically use certain reference biologics and are at risk in terms of hypersensitivity, anaphylaxis, neutralizing antibody, or other reactions

Using the RP without switching

Switching between the proposed product and RP

FACILITATING DEVELOPMENT

Considerations for Demonstrating Interchangeability—Then and Now

Considerations for Interchangeability

Ability to analytically characterize products and evaluate differences

Then

- A product's "structural and functional complexity" will influence the extent of clinical data needed
- Structurally complex products will require more clinical data to support interchangeability

Now

- Analytical tools can accurately evaluate the structure, biological activity and other physicochemical properties with more precision and sensitivity than clinical studies

Considerations For Interchangeability

Addressing product-specific immunogenicity risk

Then

- The severity of the clinical immunogenicity experience with the reference product will dictate amount of additional clinical data needed
- Switching study expected for products with low or high structural complexity and with or without history of severe adverse immune events

Now

- If the product is demonstrated to be biosimilar, then it should have no clinically meaningful differences in safety or adverse immune reactions caused by immunogenicity

Considerations For Interchangeability

Clinical data needed to assess switching between products

Then

- A clinical “switching study” is generally expected

Now

- Switching studies are not generally expected

FACILITATING DEVELOPMENT

Evolution of Scientific Expectations Supporting Interchangeability

Biosimilarity vs. Interchangeability

- Health Care Providers (HCPs) **can prescribe a biosimilar for any patient** in place of the reference product, whether treatment naïve or a previous user of the reference product[1]
  - Any concerns about potential differences between "what's in the vial" of the proposed product and its reference product are addressed when demonstrating biosimilarity
- As experience with the development and approval of biosimilars has grown, there has been increasing recognition that **comparative clinical studies are not as sensitive for detecting differences** in physicochemical, structural and functional testing, as modern analytical technologies[2]

[1] Cavazzoni P, Yim S. The Science of Biosimilars—Updating Interchangeability. *JAMA.* Published online September 18, 2024
[2] IPRP BWG Workshop: Increasing the Efficiency of Biosimilar Development Programs—Reevaluating the Need for Comparative Efficacy Studies, September 2023 Workshop Recording and Presentations, Workshop Summary Report

Immunogenicity—What's the Risk?

Biosimilars are expected to have the same safety and effectiveness as the reference product, including incidence and severity of immunogenicity

Possible causes	Biosimilar Risk?	Risk Mitigation Strategy
Dose, frequency, route of administration	Same as reference product (RP)	n/a
Mechanism of Action	Same as RP	n/a
Patient population	Same as RP	n/a
Product-related impurities	Product specific	Comparative analytical assessment
Process-related impurities	Product specific	Appropriate manufacturing and process controls

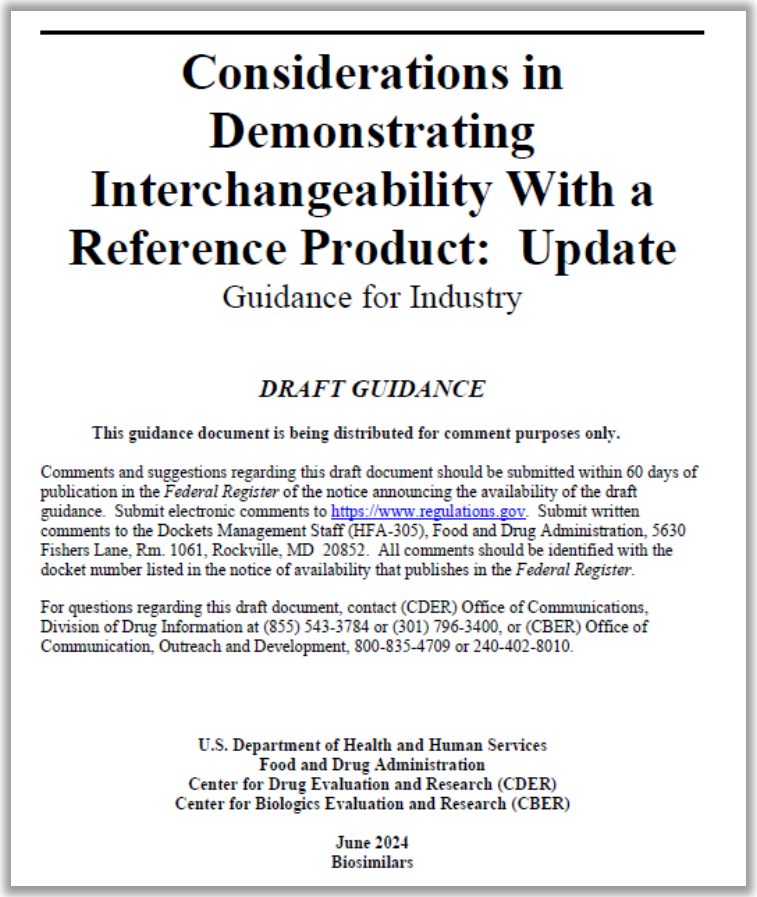
Does Switching Increase Immunogenicity Risk?

- **Our awareness and scientific understanding of immunogenicity concerns associated with biosimilars has increased** since the time when recommendations for the clinical data needed to demonstrate biosimilarity and interchangeability were developed
  - Safety and immunological concerns with switching between a biosimilar and its reference product, once or multiple times, have not been demonstrated in controlled clinical studies for FDA-approved biosimilars[1]
  - Post-marketing analyses in Europe led to the same conclusion[2]
- The **comparative analytical assessment** that is part of every biosimilar application is recognized as a **more sensitive evaluation than clinical** data for potential differences that can impact clinical performance of biosimilars

[1] Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: a systematic review and meta-analysis. PLoS One. 2023;18(10):e0292231.

[2] Kurki P, Barry S, Bourges I, Tsantili P, Wolff-Holz E. Safety, immunogenicity and interchangeability of biosimilar monoclonal antibodies and fusion proteins: a regulatory perspective. Drugs. 2021;81(16):1881-1896.

Maximizing Scientific and Regulatory Clarity



Considerations in Demonstrating Interchangeability With a Reference Product: Update

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Communications, Division of Drug Information at (855) 543-3784 or (301) 796-3400, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2024
Biosimilars

Updated Guidance

- Outlines a revised approach where switching studies will generally not be needed
- Provides clarity and transparency about the FDA's thinking
- Aligns the review and approval process with existing and emerging science

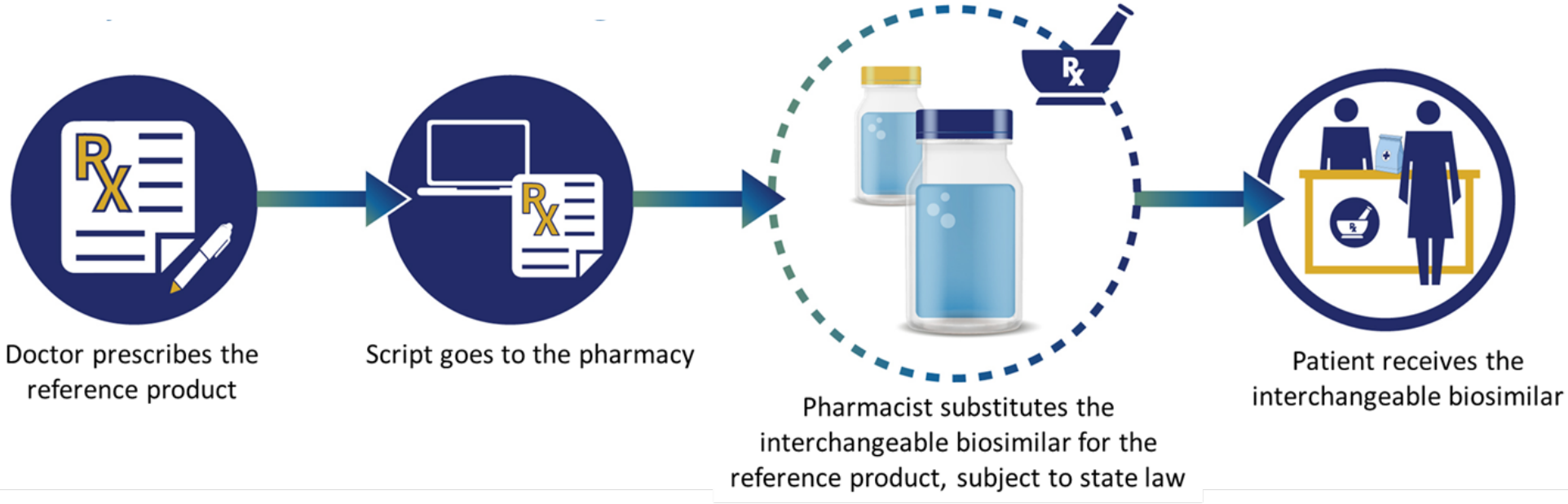
Spotlight on CDER Science: Safety Outcomes When "Switching" Between Biosimilars and Reference Products

FACILITATING DEVELOPMENT

Additional Considerations

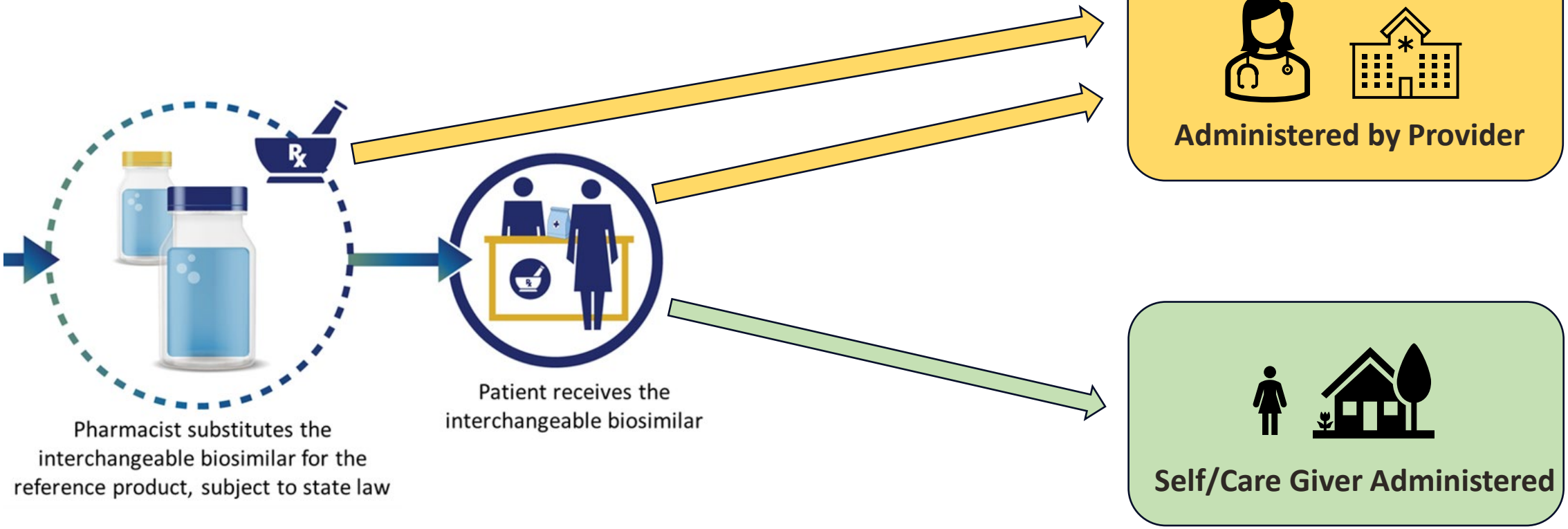
Pharmacy Substitution

An interchangeable biosimilar product can be **substituted for the reference product at pharmacies** without the intervention of the prescribing health care provider, subject to state pharmacy laws.



Will Patients and Providers…

…have what they need to be able to use the interchangeable product?



Special Considerations

- **Differences in the user interface with injectable products**
- **Pumps for subcutaneous injection**
  - Some insulins are self-administered using pumps
  - Confirmation needed that patients can safely administer their insulins in their insulin pumps (approved to be used with the reference product)
- **Dilutions**
  - Some insulins are diluted prior to administration
  - Confirmation needed that patients will have diluting medium available to them if needed

Summary

- In terms of “what’s in the vial,” **same data are used to support approval** of biosimilars and interchangeables

Patient receives the interchangeable biosimilar

- **Additional considerations** related to pharmacy substitution that may require more data are:
  - Differences in the user interface for combination products
  - Accessory products (e.g., pumps, diluents) the reference product is labeled for use with

Future Considerations

The past 15 years brought increased scientific understanding and confidence in biosimilars to a limited number of reference products regulated by CDER…

CDER	CBER
~300 currently approved 351(a) BLAs	**~300 currently approved 351(a) BLAs**
• Monoclonal antibodies • Cytokines • Growth factors • Enzymes • Immunomodulators } Therapeutic Proteins	• Allergenic extracts (e.g. for allergy shots and tests) • Blood and blood components • Gene therapy products • Devices and test kits • Human tissue and cellular products used in transplantation • Vaccines

… and many more are waiting to be developed

Thank You

Visit **www.FDA.gov/biosimilars**

Break Period

Break is from 11:30-11:40am

At 11:40am **we will resume for the** Panel Discussion

All questions please submit using the QR code.

Or submit to:
BsUFARegSciProgram@fda.hhs.gov

Industry Reaction and Panel Discussion Q&A

- **For all audience members:** please use the QR code to submit your questions. Please indicate who the question is being addressed to by following this format: *name of presenter: Jane Doe, question.*

Thank you!