Biosimilars and Interchangeables
Regulatory Highlights

SBIA 2019

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Leila Hann
Office of Therapeutic Biologics and Biosimilars
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Regulatory Background

- An application submitted under section 351(a) of the PHS Act is a "stand-alone" application that must contain all information and data necessary to demonstrate that the proposed product is safe, pure and potent (safe and effective).

  - The Biologics Price Competition and Innovation Act of 2009 (**BPCI Act**) created an ***abbreviated licensure pathway*** for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product.

    - The abbreviated licensure pathway means manufacturer may rely, in part, on FDA's ***previous determination*** for the reference product.

      - Generally, biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products. However, the biosimilar or interchangeable product is still subject to ***FDA's rigorous approval standards***.

FDA's Role: Balancing Innovation and Competition

- FDA recognizes our important role in helping to ensure the U.S. remains a driving force in medical innovation, as well as the importance of robust and timely competition to enhance patient access and reduce cost burdens on patients and our health care system.

- The FDA has and will continue to play a critical role in facilitating increased access to biosimilars.

FDA's Biosimilars Action Plan (2018)

Biosimilars Action Plan (BAP) provides information about key actions the Agency is taking to encourage innovation and competition among biologics and the development of biosimilars.

1. Improving the efficiency of the biosimilar and interchangeable product development and approval process
2. Maximizing scientific and regulatory clarity for the biosimilar product development community
3. Developing effective communications to improve understanding of biosimilars among patients, clinicians and payors
4. Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition

Completed BAP Deliverables	
December 2018	Questions and Answers on Biosimilar Development and the BPCI Act; Final Guidance
December 2018	New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2); Draft Guidance
December 2018	Interpretation of the Deemed to be a License Provision of the Biologics Price Competition and Innovation Act; Final Guidance
December 2018	The Deemed to be a License Provision of the BPCI Act: Questions and Answers; Draft Guidance
December 2018	Definition of the Term Biological Product; Proposed Rule
December 2018	Preliminary List of Approved NDAs for Biological Products That Will Be Deemed to be BLAs on March 23, 2020
March 2019	Nonproprietary Naming of Biological Products – Update; Draft Guidance
May 2019	Biosimilar and Interchangeable Insulins; Part 15 Public Hearing
May 2019	Considerations in Demonstrating Interchangeability with a Reference Product; Final Guidance
May 2019	Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations
September 2019	Posting of first biosimilar approval using biosimilar review template
September 2019	New educational materials for patients about biosimilar medications
Fall/Winter 2019	Enhanced purple book

Biosimilars- State of the Program

As of October 1, 2019: **23** 351(k) BLAs for biosimilar products have been approved for 9 reference products.

- **9** biosimilar products are believed to have been commercially launched

Development-Stage Advice to Sponsors

- **73** programs (for **38** different **reference products**) were enrolled in the Biosimilar Product Development (BPD) Program to discuss development of proposed biosimilar products or interchangeable products

Since Program Inception

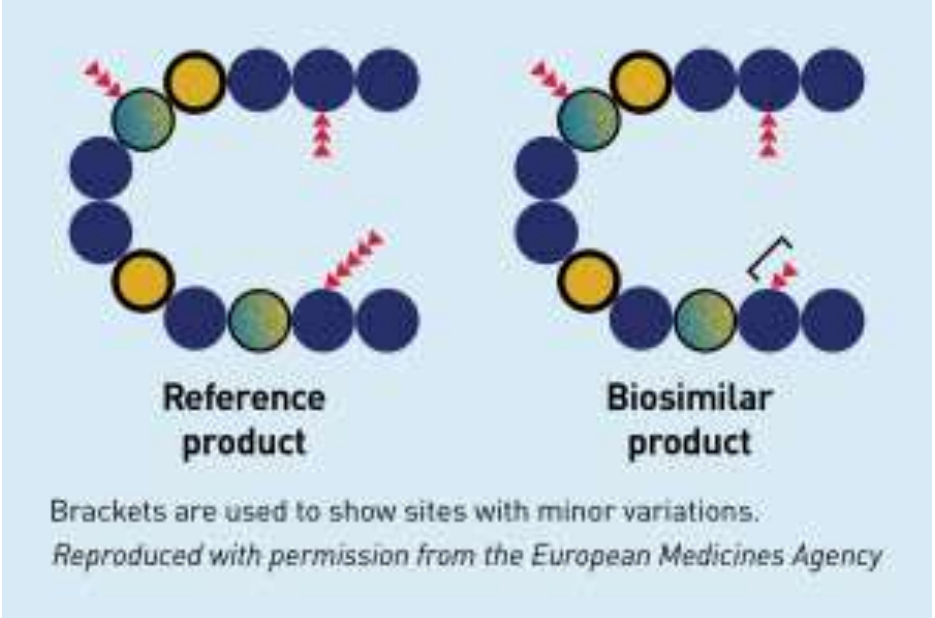
- **30** planned 351(k) submissions (from **12** companies) have been publicly announced for 9 different reference products

“Biosimilar” or “Biosimilarity”

Goal: To establish biosimilarity between proposed product and reference product, not to re-establish safety and effectiveness.

Biosimilar or **Biosimilarity** means:

- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and
- there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.



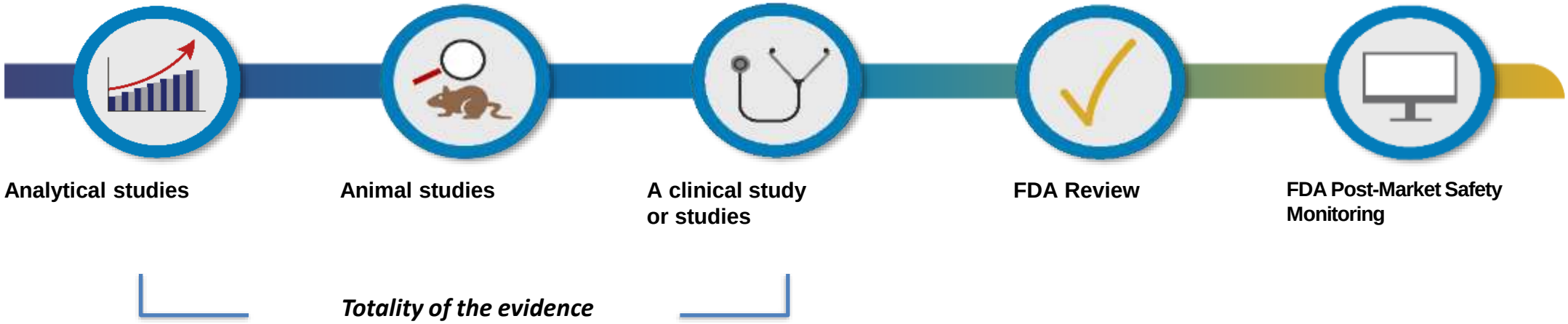
Demonstrating Biosimilarity

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

- Is biosimilar to a 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.

Demonstrating Biosimilarity

- **Approval of a biosimilar product** is based on the **totality of the evidence** submitted by the applicant to provide an overall assessment that the proposed product is biosimilar to the reference product.
- A demonstration supporting biosimilarity will be based upon data from: **analytical studies, animal studies**, if any; and **clinical study or studies.**
- Nature and scope of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products **after** conducting structural and functional characterization and relevant animal studies, if any.



Comparative Analytical Assessment

- FDA draft guidance for industry “Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality Considerations” describes recommendations for the design and evaluation of ***comparative analytical studies***

- This guidance includes considerations for the development of a comparative analytical assessment plan, using a ***stepwise approach***, to support a demonstration of biosimilarity

Comparative Analytical Assessment

Guidance lays out considerations for generating comprehensive comparative analytical data:

- Methods for detecting and characterizing differences between a proposed biosimilar and the reference product
- Assessment of differences to understand impact on clinical performance relative to reference product
- Comparative analytical data can inform decisions about the amount and type of animal and clinical data needed

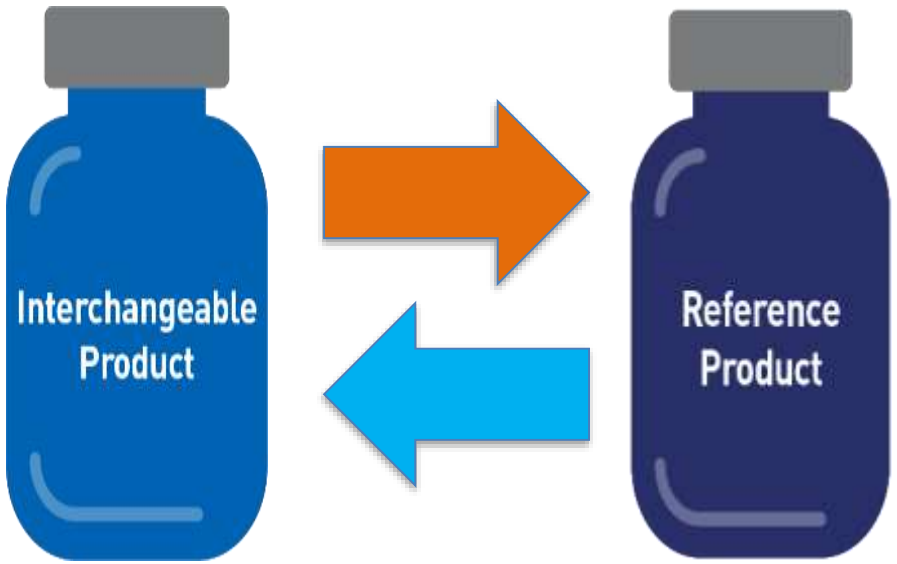
Comparative Analytical Assessment

New draft provides additional clarity and flexibility for developers on:

- Analytical approaches to evaluating **product structure and function**
- Updated recommendations for collection and analysis of **comparative analytical similarity data**
- Receptiveness to considering **alternative approaches** proposed by sponsors for the analysis of analytical similarity data.
- Aspects of the **chemistry, manufacturing, and controls** (CMC) portion (e.g., characterization, adventitious agent safety testing, process controls, specifications, and stability) of the marketing application

“Interchangeable” or “Interchangeability”

The term “**interchangeable**” or “**interchangeability**” means that biosimilar **may be substituted** for the reference product without the intervention of the health care provider who prescribed the reference product.



Interchangeability Final Guidance 2019

- FDA recently published final guidance, “Considerations in Demonstrating Interchangeability With a Reference Product,” which provides FDA’s current thinking on scientific considerations in demonstrating that a proposed biological product is interchangeable with a reference product.
- Outlines a **stepwise approach** to generate data
- **Totality-of-the-evidence** approach– no “one-size fits all” assessment
- Retained flexibility to provide space for the science in this area to evolve and for FDA to provide targeted advice on efficient study design in the context of product-specific meetings with prospective applicants.

Demonstrating Interchangeable Biosimilarity

1. The proposed interchangeable must be **biosimilar to the reference product**.
2. The application must demonstrate that the proposed interchangeable "can be expected to produce the **same clinical result** as the reference product **in any given patient**."
   - This will likely not involve additional clinical studies other than those necessary to support other elements of demonstrating interchangeability.

Demonstrating Interchangeable Biosimilarity, cont'd

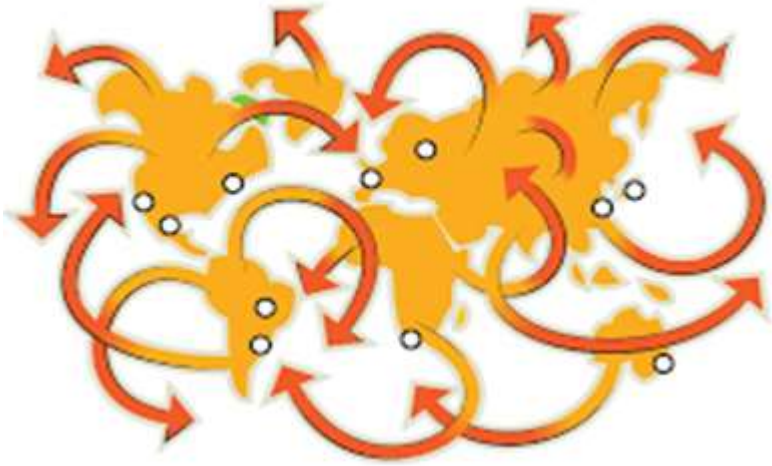
3. For products administered more than once to a patient, information sufficient to show that "the ***risk in terms of safety or diminished efficacy of alternating or switching*** between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."
   - To the risk, in terms of safety and diminished efficacy, of alternating or switching between the products, applications generally will include data from a switching study or studies in one or more appropriate conditions of use.

Interchangeability Final Guidance 2019

- **Switching studies**: outlines considerations for study design, including endpoints, design and analysis, study population, condition(s) of use, and routes of administration to be studied.
  - Integrated two-part study design may be appropriate
  - Option for sponsor to provide justification to FDA of why such data is not needed.
  - Switching studies generally not needed for biological products that are not intended to be administered to an individual more than once.

Interchangeability Final Guidance 2019: Non-U.S. Comparator

- The draft guidance "strongly recommend[ed]" the use of a US-licensed reference product in switching studies.
- The final guidance omits the "strongly recommends" statement and includes considerations for the type and extent of "**bridging" data needed to justify the use** of a non-U.S. licensed comparator in switching studies.



Interchangeability Final Guidance 2019: Post-Marketing Data

- Final guidance clarifies that a product may be first licensed as a biosimilar, and that data or information supporting that licensure may be submitted or referenced to support a demonstration of interchangeability.
- **Post-marketing data** from a licensed biosimilar product may help when considering what data is necessary.
- There may be situations where post-marketing data can **reduce uncertainty** about interchangeability and data needed to support demonstration of interchangeability.

Safety and Monitoring

- All drugs have risks and benefits. Biosimilars can have side effects, which are expected to be the same as those of the reference product.
- As part of its review, FDA assesses the manufacturing process and the manufacturer's strategy to control within-product variations.
  - These control strategies are put in place to help ensure that manufacturers produce biological products with consistent clinical performance.
- **Robust post-marketing safety monitoring** is also an important component in ensuring the safety and effectiveness of all biological products, including biosimilar products.

Looking Ahead: Biosimilars Action Plan

- Biological Product Regulatory Modernization; Proposed Rule
- Finalize Reference Product Exclusivity Guidance
- Educate patients and consumers about biosimilars
- Awareness of Stakeholders Seeking Additional Guidance

Looking Ahead: Biologics Regulatory Modernization

- The BLA regulations were written before addition of the 351(k) pathway.
- We are working to update and modernize the Agency's biological product regulations with targeted revisions related to the submission and review of BLAs.
- Updated regulations will provide enhanced clarity and regulatory certainty to manufacturers of both originator and biosimilar/interchangeable products, and will help prevent "gaming" that could prevent or delay competition.

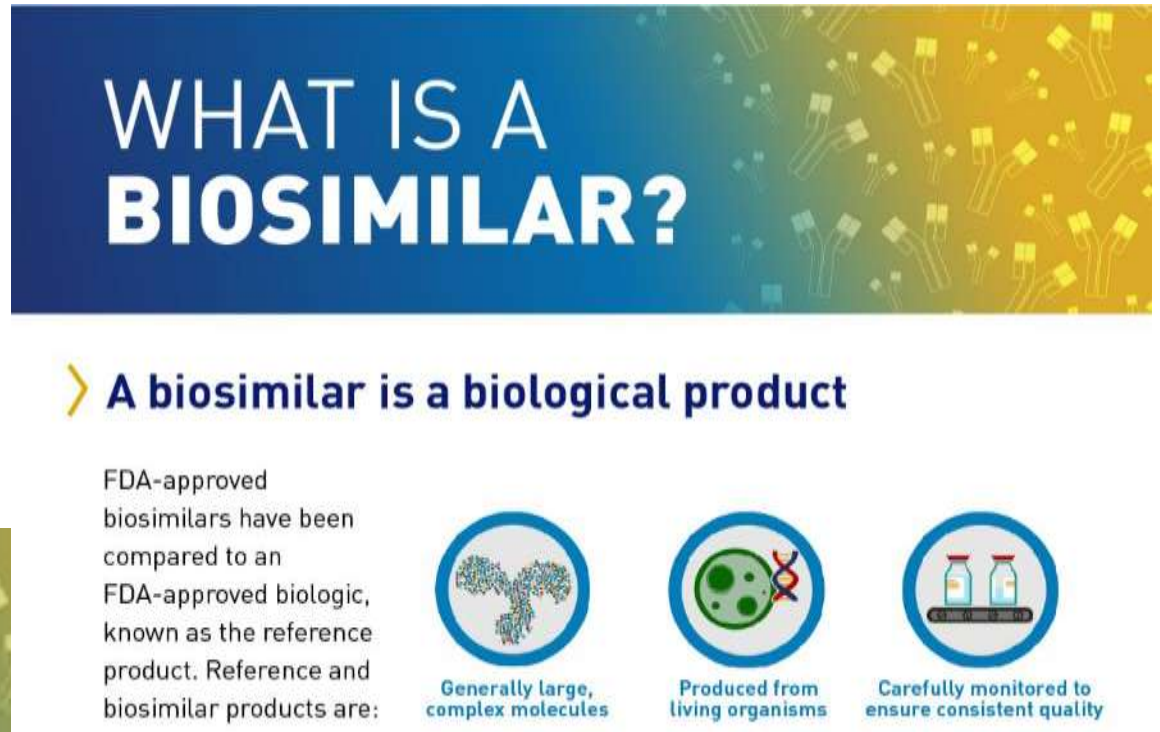
Looking Ahead: Enhanced Purple Book

- **FDA's Purple Book** provides a list of biological products licensed under the PHS Act, includes:
  - Information about biosimilarity, interchangeability
  - Information about exclusivity
- **An enhanced Purple Book is in development:**
  - Improved interface to provide user-friendly information to the public about approved biologics
  - Enhanced information for patients, prescribers, pharmacists, and other stakeholders

- **Key BAP Action 3:** *Enhancing the Purple Book to include more information about approved biological products, including information relating to reference product exclusivity determinations.*

Education

Key BAP Deliverable 6:
continue providing critical education



Any Questions?