

Biosimilar Biological Products

2018 Clinical Investigator Training Course

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Overview of Presentation

- Biological products
- Biosimilar biological products
 - Regulatory background, definitions
 - Development concepts
- Study design considerations in biosimilar development
 - Comparative clinical study (“Phase 3” trial)
- Safety
 - Biological products, biosimilars



Biological Products

What is a biological product?

- Biological products can be made of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues
- Produced in/obtained from a living system such as a microorganism, plant or animal cells, or produced by recombinant DNA technology
- Many types
 - Proteins, blood products, vaccines, tissues, gene and cellular therapies
- Biological products make up a growing portion of new drugs approved each year¹

Drugs vs. Biological Products - Generally

Small Molecule Drugs	Biological Products
Generally low molecular weight	Generally high molecular weight
Usually made by organic or chemical synthesis	Made with/from live cells/organisms → <i>inherent & contamination risk</i>
Fewer critical process steps	Many critical process steps
Well-characterized	Less easily characterized
Known structure	Structure may or may not be completely defined or known
Homogeneous drug substance	Heterogeneous mixtures → <i>May include variants</i>
Usually not immunogenic	Often immunogenic

Biosimilar Biological Products

TITLE VII—IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES

Subtitle A—Biologics Price Competition and Innovation

SEC. 7001. SHORT TITLE.

(a) **IN GENERAL.**—This subtitle may be cited as the “Biologics Price Competition and Innovation Act of 2009”.

(b) **SENSE OF THE SENATE.**—It is the sense of the Senate that a biosimilars pathway balancing innovation and consumer interests should be established.

SEC. 7002. APPROVAL PATHWAY FOR BIOSIMILAR BIOLOGICAL PRODUCTS.

(a) **LICENSURE OF BIOLOGICAL PRODUCTS AS BIOSIMILAR OR INTERCHANGEABLE.**—Section 351 of the Public Health Service Act (42 U.S.C. 262) is amended—

- (1) in subsection (a)(1)(A), by inserting “under this subsection or subsection (k)” after “biologics license”; and
- (2) by adding at the end the following:

Background



- The **Biologics Price Competition and Innovation Act of 2009 (BPCI Act)** was signed into law on March 23, 2010.
- BPCI Act creates an ***abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with*** an FDA-licensed reference product.
- The abbreviated licensure pathway **does not mean that a lower approval standard is applied** to biosimilar or interchangeable products than to originator biological products.
- The ability to rely on FDA's previous finding regarding the reference product to support approval of the biosimilar product allows for a potentially shorter and less costly drug development program. This is what is meant by an **abbreviated** licensure pathway.
- The **data package** required for approval of a biosimilar or interchangeable product is quite **extensive**.

Are biosimilars the same as generic drugs?

NO



Biosimilars and generic drugs are versions of brand name drugs and may offer more affordable treatment options to patients

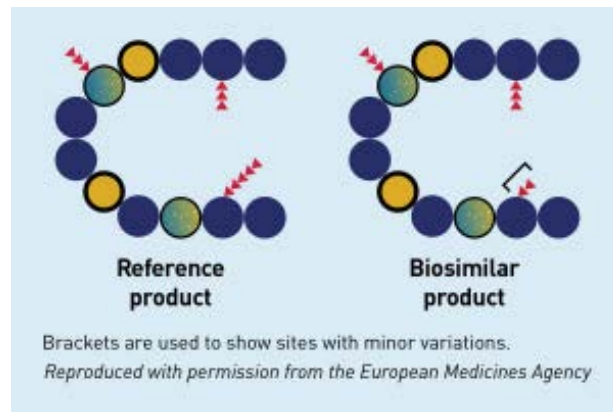
Biosimilars and generics are each approved through different abbreviated pathways that avoid duplicating costly clinical trials

- The active ingredients of generic drugs are the same as those of brand name drugs.
- By contrast, biosimilar manufacturers must demonstrate that the biosimilar is highly similar to the reference product, except for minor differences in clinically inactive components
- Manufacturer of a generic drug must demonstrate that the generic is bioequivalent to the brand name drug
- Biosimilar manufacturers must demonstrate that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety and effectiveness

Biosimilarity

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.



Reference Product



Reference Product:

- the **single biological product, licensed under section 351(a) of the PHS Act**, against which a biological product is evaluated in an application submitted under section 351(k) of the PHS Act.
- 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.
- In contrast, an application submitted under section 351(k) needs to demonstrate that the proposed product is biosimilar to the reference product. For licensure, a proposed biosimilar relies on (among other things) comparative data with the reference product, as well as publicly-available information regarding FDA’s previous determination that the reference product is safe, pure and potent.

Interchangeability

Interchangeable or Interchangeability:

- the biological product is **biosimilar** to the reference product;
- it **can be expected** to produce the **same clinical result** as the reference product **in any given patient**; and
- for a product that is administered more than once to an individual, the risk in terms of **safety or diminished efficacy of alternating or switching** between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

An interchangeable product **may be substituted** for the reference product without the intervention of the health care provider who prescribed the reference product.

General Requirements

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.

FDA's Approach to the Development of Biosimilars

Key Development Concepts

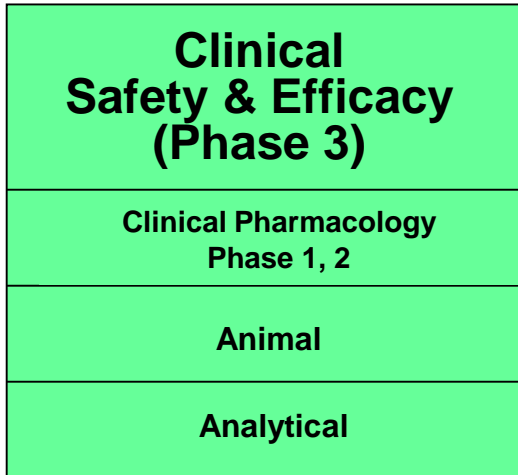


Goals of “Stand-alone” and Biosimilar Development are different



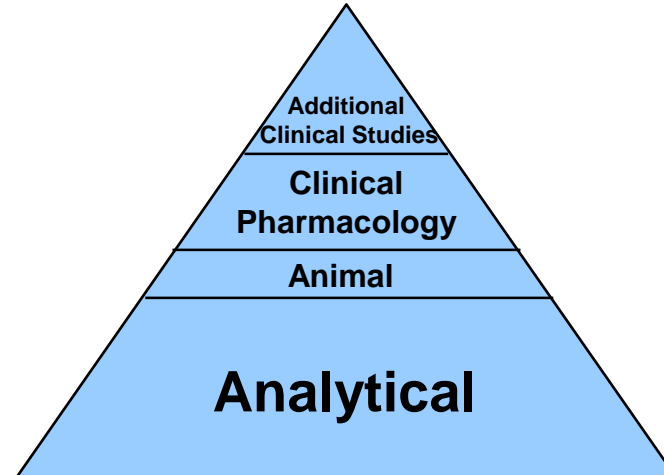
“Stand-alone” Development Program, 351(a)

Goal: To establish safety and efficacy of a new product



“Abbreviated” Development Program, 351(k)

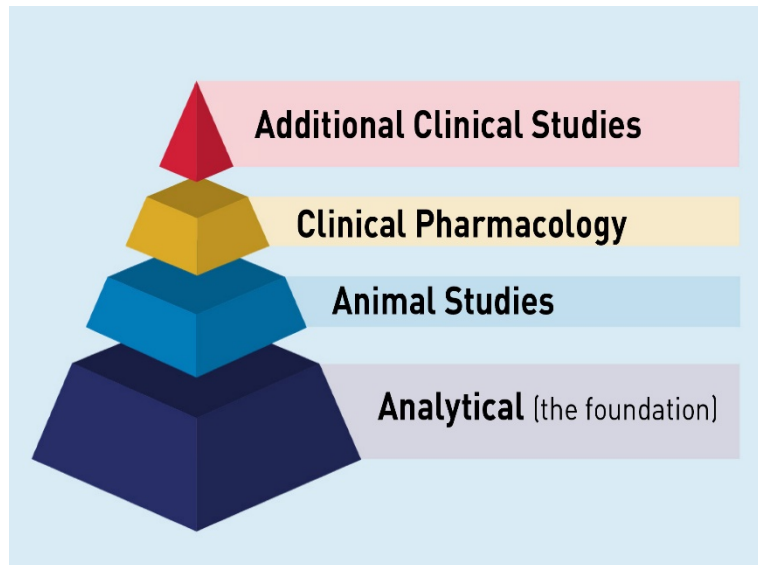
Goal: To demonstrate biosimilarity (or interchangeability)



What does this difference mean from a development perspective?

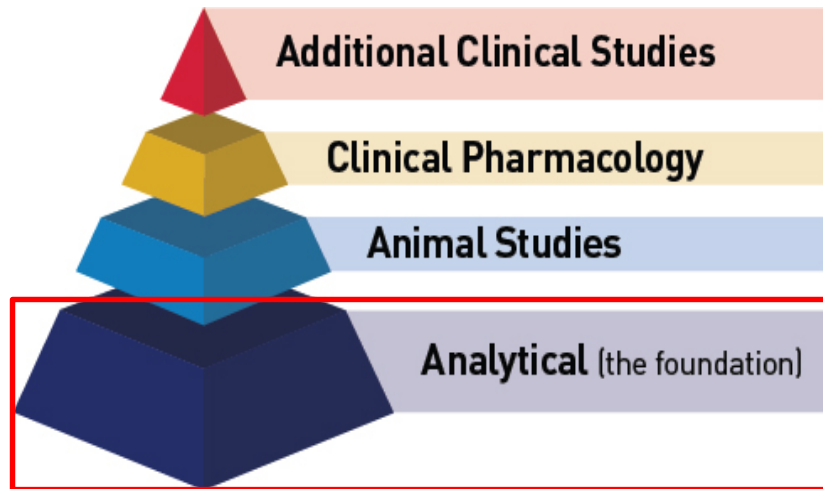
Stepwise Evidence Development

- FDA has outlined a **stepwise approach** to generate data in support of a demonstration of biosimilarity
- Evaluation of residual uncertainty at each step of data generation
- *Totality-of-the-evidence* approach in evaluating biosimilarity – no “one-size fits all” assessment
- **There is no one “pivotal” study that demonstrates biosimilarity**



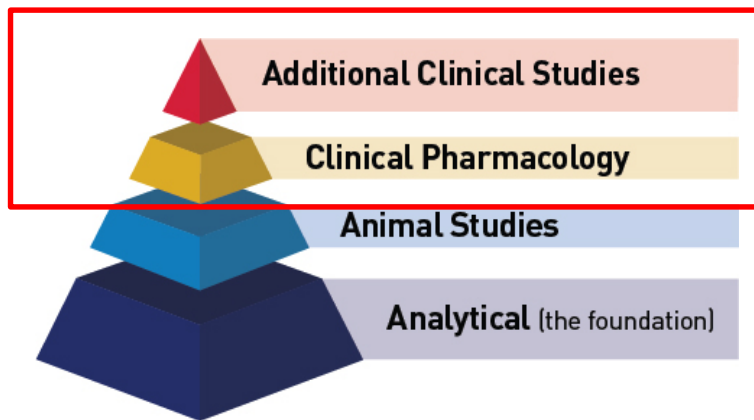
Analytical Similarity Data - The Foundation of a Biosimilar Development Program

- Extensive structural and functional characterization
 - Analytical study is more **sensitive** than clinical study in detecting differences between products, should differences exist
 - A biosimilar product with **highly similar structure and function** to the reference product should behave like the reference product (i.e., have **similar efficacy and safety** as the reference product)



Role of Clinical Studies

- The 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, where relevant, animal studies.
- No “pivotal” study in biosimilar development
- Additional clinical studies are not “pivotal” in the way Phase 3 clinical trials are for standalone development



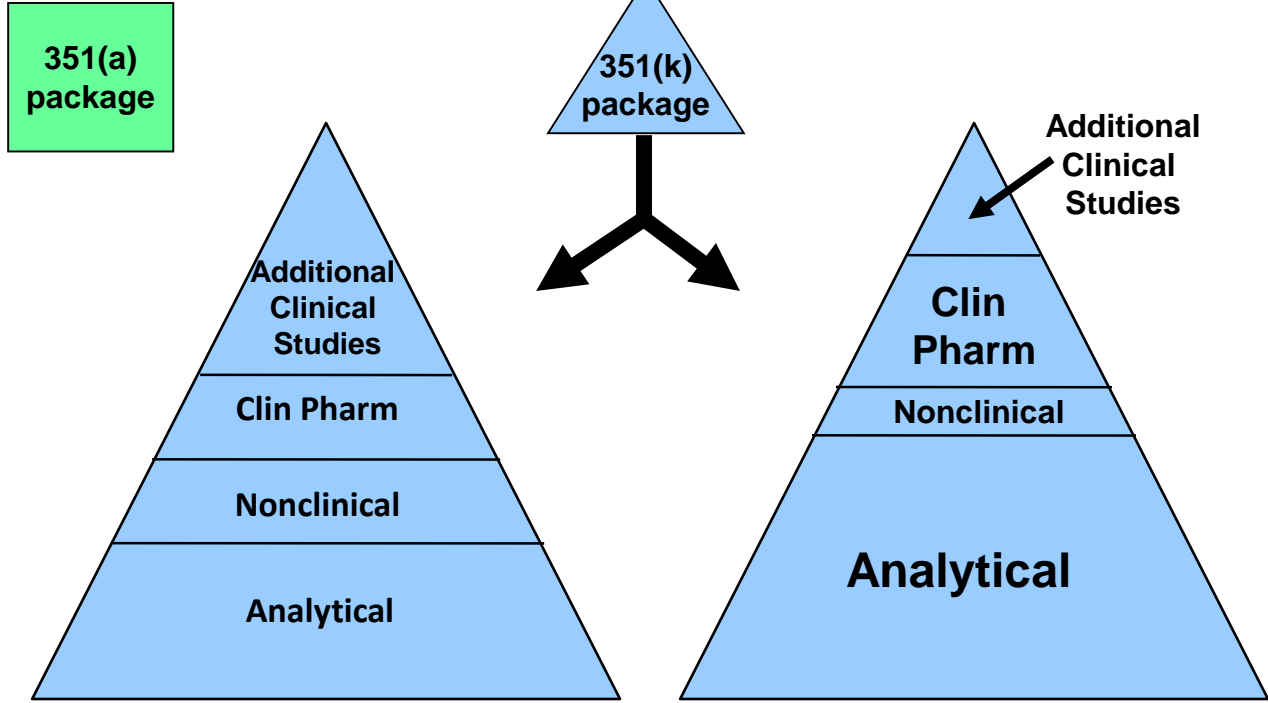
Comparative Human PK and PD Data

- PK and/or PD is generally considered the most sensitive clinical study/assay in which to assess for differences between products, should they exist
- Demonstrate **PK similarity** in an adequately sensitive population to detect any differences, should they exist
- **Similar PD** using PD measure(s) that reflects the mechanism of action (MOA) or reflects the biological effect(s) of the drug
- Clinical PK data generally will be expected; PD data desirable (case by case)
- **PK and PD similarity** data supports a demonstration of biosimilarity with the assumption that similar exposure (and pharmacodynamic response, if applicable) will provide **similar efficacy and safety** (i.e., an exposure-response relationship exists)

Comparative Clinical Study (“Phase 3 trial”)

- A comparative clinical study for a biosimilar development program should be designed to investigate whether there are **clinically meaningful differences** in safety and efficacy between the proposed product and the reference product.
- Population, endpoint, sample size and study duration should be **adequately sensitive to detect differences**, should they exist.
 - Population can be novel/unapproved but justifiable to use as a test assay because of sensitivity, e.g., neoadjuvant breast cancer for biosimilar to Herceptin – biosimilar does not subsequently receive approval for that novel population/indication
 - Endpoint can be novel/unapproved if it reflects activity of the product, e.g., VEGF for biosimilar to Avastin (anti-VEGF MAb)
 - Sample size and duration generally similar or less than in the original clinical trials; no need to re-establish efficacy (e.g, mortality) or long term safety
- Typically, an equivalence design would be used, but other designs may be justified
- Assessment of safety and immunogenicity expected in **all** clinical studies

Totally-of-the-Evidence

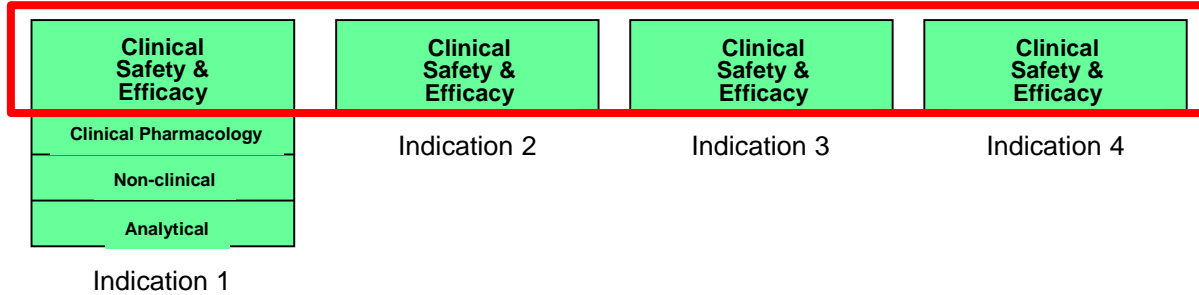


Totally of the evidence to demonstrate biosimilarity

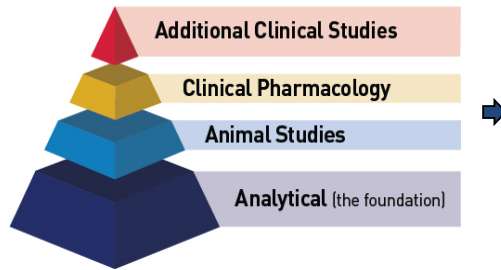
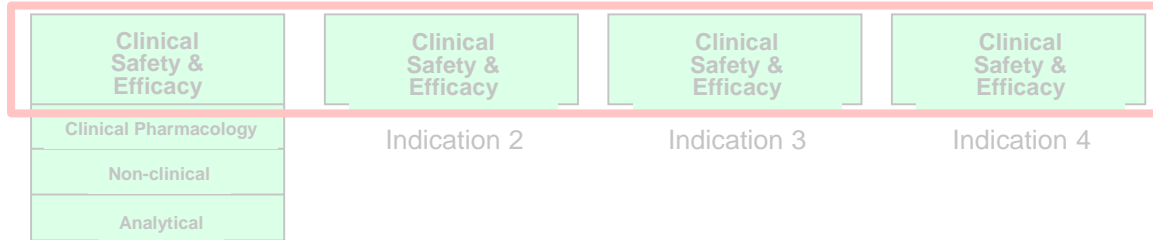
Extrapolation

- The potential exists for a biosimilar product to be approved for one or more conditions of use for which the reference product is licensed based on extrapolation
- Sufficient scientific justification for extrapolation is necessary
- Differences between conditions of use (e.g., indications) do not necessarily preclude extrapolation
- FDA guidance outlines factors to consider, including:
 - MoA in each condition of use
 - PK and biodistribution in different patient populations
 - Immunogenicity in different patient populations
 - Differences in expected toxicities in each condition of use and patient population

Extrapolation Considerations: “Stand-alone” Drug Development



Extrapolation Considerations: “Stand-alone” vs. Biosimilar Development



The concept of extrapolation is based on:

- ✓ All available data and information in the biosimilar application
- ✓ FDA’s previous finding of safety and efficacy for other approved indications for the reference product
- ✓ Knowledge and consideration of various scientific factors for each indication



Biosimilar extrapolation is based on all available data in the 351(k) BLA and FDA’s finding for the reference product, not from the indication(s) studied for the biosimilar to other non-studied indications

Study Design Considerations in Biosimilar Development

(Comparative clinical study)

Biosimilars: Study Design Considerations

	Reference Product	Biosimilar
Comparator	Placebo or active comparator	Active comparator study – reference product (“no clinically meaningful differences”)
Statistical study design	Superiority or non-inferiority	Generally equivalence; non-superior and non-inferior
Endpoint	“Outcome by which the effectiveness of treatment in a clinical trial is evaluated” ²	Traditional efficacy endpoints may not be sensitive to detect differences between similar, active products Endpoints should reflect activity of the product
Time point for assessing endpoint	Adequate time for product to take and maintain clinical effect	Time point(s) when most likely to detect differences between products, e.g., ascending portion of the dose-response curve, (“activity”) rather than at the therapeutic plateau (“efficacy”); look for similarity between “activity” responses

² Follman DA. 2007 Wiley Encyclopedia of Clinical Trials. 1-8

Biosimilars: Study Design Considerations

	Reference Product	Biosimilar
Patient population	Disease population for which licensure is sought	<p>Same or different from the reference product</p> <p>Should be sensitive to detect differences; for example populations in early or late stage disease which may not be confounded by concurrent or previous therapy</p>
Dose	Objective is to obtain clinical efficacy as efficiently and safely as possible	<p>May be therapeutic dose, or a lower dose (if ethical)</p> <p>Dose should produce an effect over a time period that is conducive to detecting differences between products, e.g., therapeutic dose may reach plateau before one can assay for differences between products; lower dose may have a less steep dose-response curve</p>
Sample size	Powered to demonstrate efficacy by detecting treatment difference	Based on the selected endpoint and margins (generally equivalence) under the chosen study conditions
Duration	Adequate to assess efficacy and reasonable safety follow-up	Driven by study design (e.g., endpoint and time point); Generally same or shorter duration because not independently establishing safety and efficacy of the product

Safety

Safety and Immunogenicity

- Concern for biological products
 - Large molecules with complex manufacturing process
- Impact can range from no clinical relevance to loss of efficacy and/or autoimmunity to endogenous molecules (antibody neutralization of a natural protein with biological activity)

Immunogenicity: Biosimilars

General immunogenicity issues with biologics, plus product-specific considerations

- Immunogenicity related to clinically inactive components
 - Proposed biosimilar may have different excipients, impurities and formulation than the reference product; permissible as long as proposed biosimilar meets definition of biosimilarity
- Goal is to evaluate potential differences between the proposed biosimilar and reference product in the incidence and severity of human immune response
- Differences in immune response between a reference product and proposed biosimilar could represent a clinically meaningful difference and therefore preclude licensure as a biosimilar

Immunogenicity: Study Design Considerations

- Comparative assessment between biosimilar and reference product
 - Descriptive evaluation of immune response (e.g., onset, duration, titer)
- Design can be informed by what is publicly known about the reference product
 - Nature of immune response (what is the response, and when does it occur)
 - Clinical relevance (extent of assessment)
 - Incidence of immune response (timing of assessment, i.e., pre- or post-market)

Immunogenicity: Study Design Considerations

- Study design
 - Usually need at least 2 exposures (prime and boost) in a parallel design
- Study population
 - Consider baseline immune status; whether patients could mount an adequate immune response to detect a difference between products
 - If multiple populations available, consider the one where baseline immune status is less compromised
- Prospectively define the clinical immune response criteria
 - Some knowledge about immune profile because of publicly available information from use of the reference product

Summary

- Demonstrating biosimilarity is different from “stand-alone” product development
 - A “stand-alone”-like program (establish efficacy and safety) will **not** demonstrate biosimilarity (highly similar, and no clinically meaningful differences)
- The content of a biosimilar development program is based on stepwise evidence development starting with analytical data and the evaluation of residual uncertainty about biosimilarity between the proposed biosimilar product and the reference product
- Approval of a proposed biosimilar product is based on the integration of various information and the totality of the evidence submitted by the biosimilar sponsor

Thank you for your attention.

**For more information, go to
www.fda.gov/biosimilars**



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