

Biosimilar Regulatory Policy: Understanding the Landscape and Relevance to Medical Practice

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Disclosure Information

- I have no financial relationships to disclose.
- I will not discuss off label use and/or investigational use in my presentation.

Overview of Presentation

- Biosimilars
 - Data supporting approval
 - Clinical studies and extrapolation
- Interchangeable Products
 - Data supporting approval
 - Switching study design
- Key Points and Practical aspects
 - “Substitution” vs “Switch” vs. “Switches”
- Summary

Biosimilars: Data to Support Approval

General Requirements: 351(k) application

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.

General Requirements: 351(k) application

The PHS Act requires that a 351(k) application include, among other things, **information demonstrating biosimilarity based upon data derived from:**

- **Analytical studies** demonstrating that the biological product is “highly similar” to the reference product notwithstanding minor differences in clinically inactive components;
- **Animal studies** (including the assessment of toxicity); and
- A **clinical study or studies** (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and for which licensure is sought for the biosimilar product

FDA may determine, in its discretion, that an element described above is unnecessary in a 351(k) application.

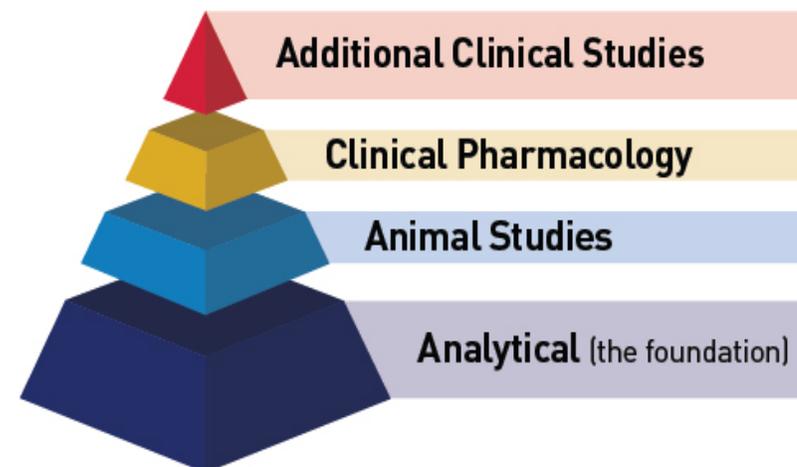
Biosimilar Product: Data for Approval

Adequate data in the 351(k) application to support that the proposed product is **biosimilar** to the US-licensed reference product

- Proposed product must be **highly similar** to the US-licensed reference product notwithstanding minor differences in clinically inactive components
 - Comparative analytical data - the foundation
 - Analytical data is more **sensitive** than clinical data 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) in a clinical setting.

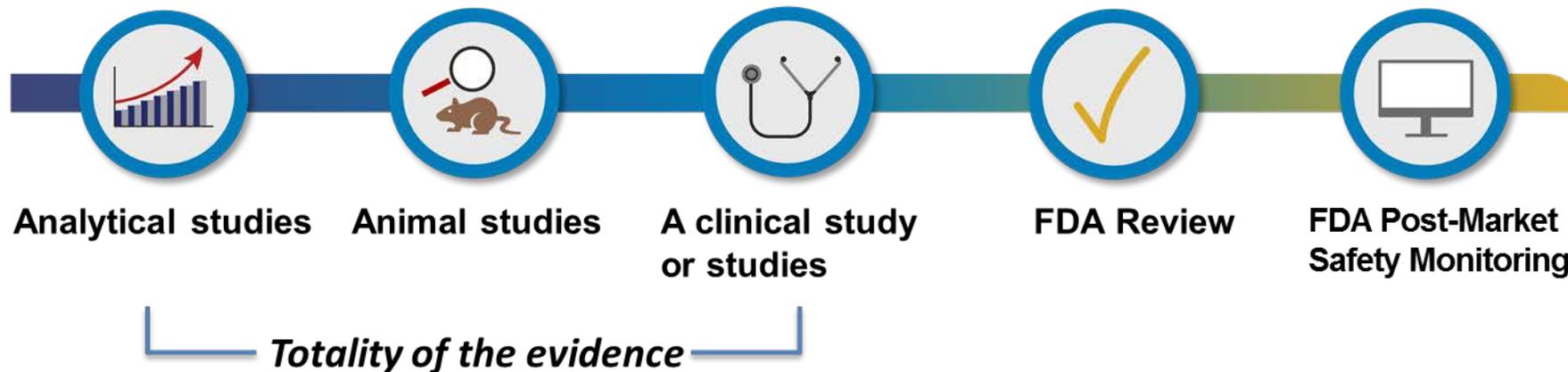
There are **no clinically meaningful differences** between the proposed product and US-licensed reference product in terms of safety, purity and potency

- Comparative clinical data (clinical pharmacology, additional clinical studies)



Biosimilar Product: Data for Approval

- Goals of “standalone” biological product vs. biosimilar product development differ
 - Standalone: *de novo* safety and efficacy
 - Biosimilar: biosimilarity (highly similar, no clinically meaningful differences)
- Use a totality-of-the-evidence approach in consideration all the data and information in a 351(k) application
 - No “pivotal” study in biosimilar development
 - Additional clinical studies are not “pivotal” in the way Phase 3 clinical trials are for standalone development



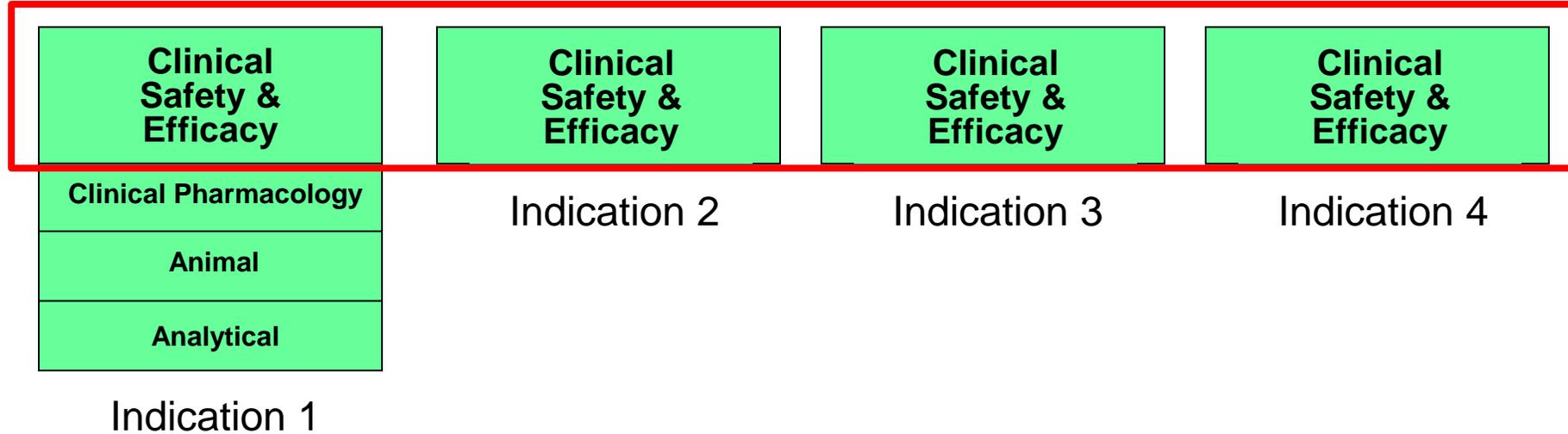
Biosimilar: Comparative Clinical Study

- A comparative clinical study should be designed to investigate whether there are **clinically meaningful differences** in safety and efficacy between the proposed product and the reference product.
 - Not establishing *de novo* safety and efficacy
- Population, endpoint, sample size and study duration should be **adequately sensitive to detect differences between products**, 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 depending on product-specific and program-specific considerations.
- Assessment of immunogenicity

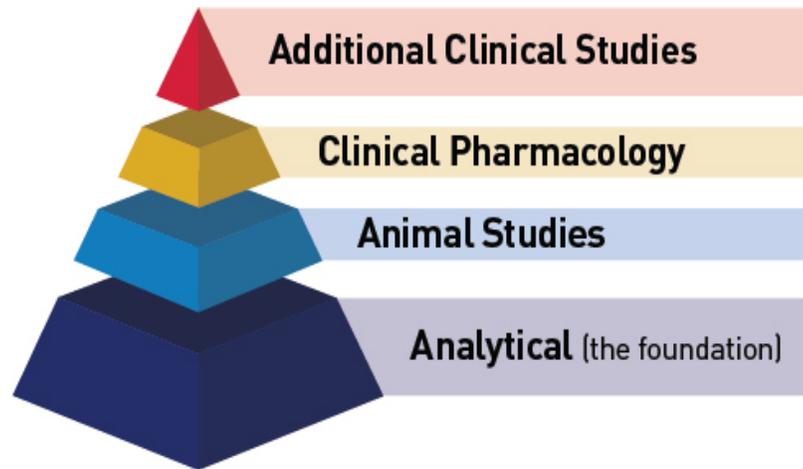
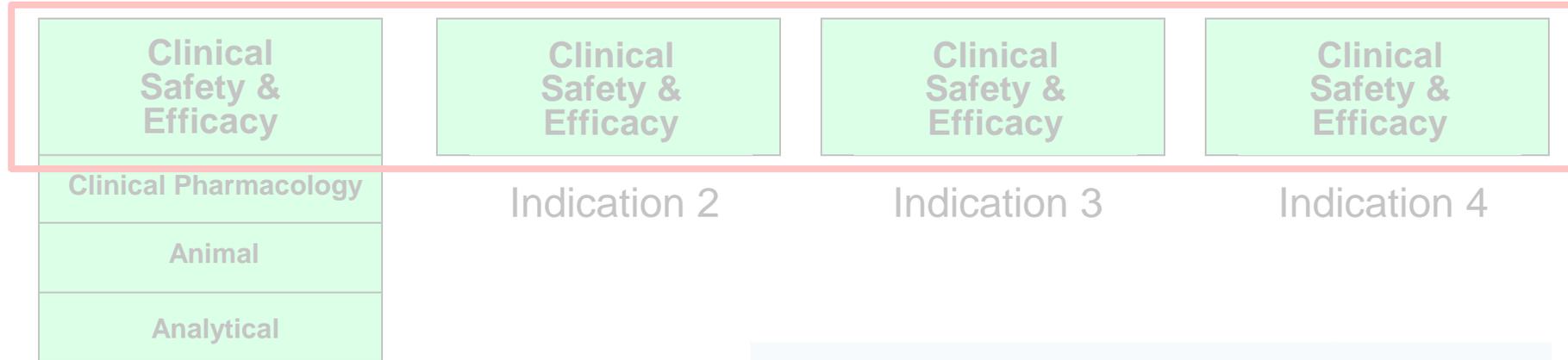
Extrapolation

- 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: Standalone 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

Interchangeable Products: Data to Support Approval

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: 351(k) application

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.

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.

Interchangeability: General Principles

- When a product is first licensed as a **biosimilar**, that licensure may be referenced to support a showing for this statutory criterion for demonstrating interchangeability
- FDA expects that sponsors will submit data and information to support a showing that the proposed interchangeable product **can be expected** to produce the **same clinical result as the reference product** in ***all*** of the reference product's licensed conditions of use
 - The data and information may vary depending on the nature of the proposed interchangeable product.
 - The data and information should include a scientific justification as to why **any differences** that exist between the reference product and the proposed interchangeable product, with respect to the factors described in the guidance, **do not preclude a showing** that the proposed interchangeable product **can be expected** to produce the same clinical result as the reference product in any given patient.

Interchangeability: General Principles

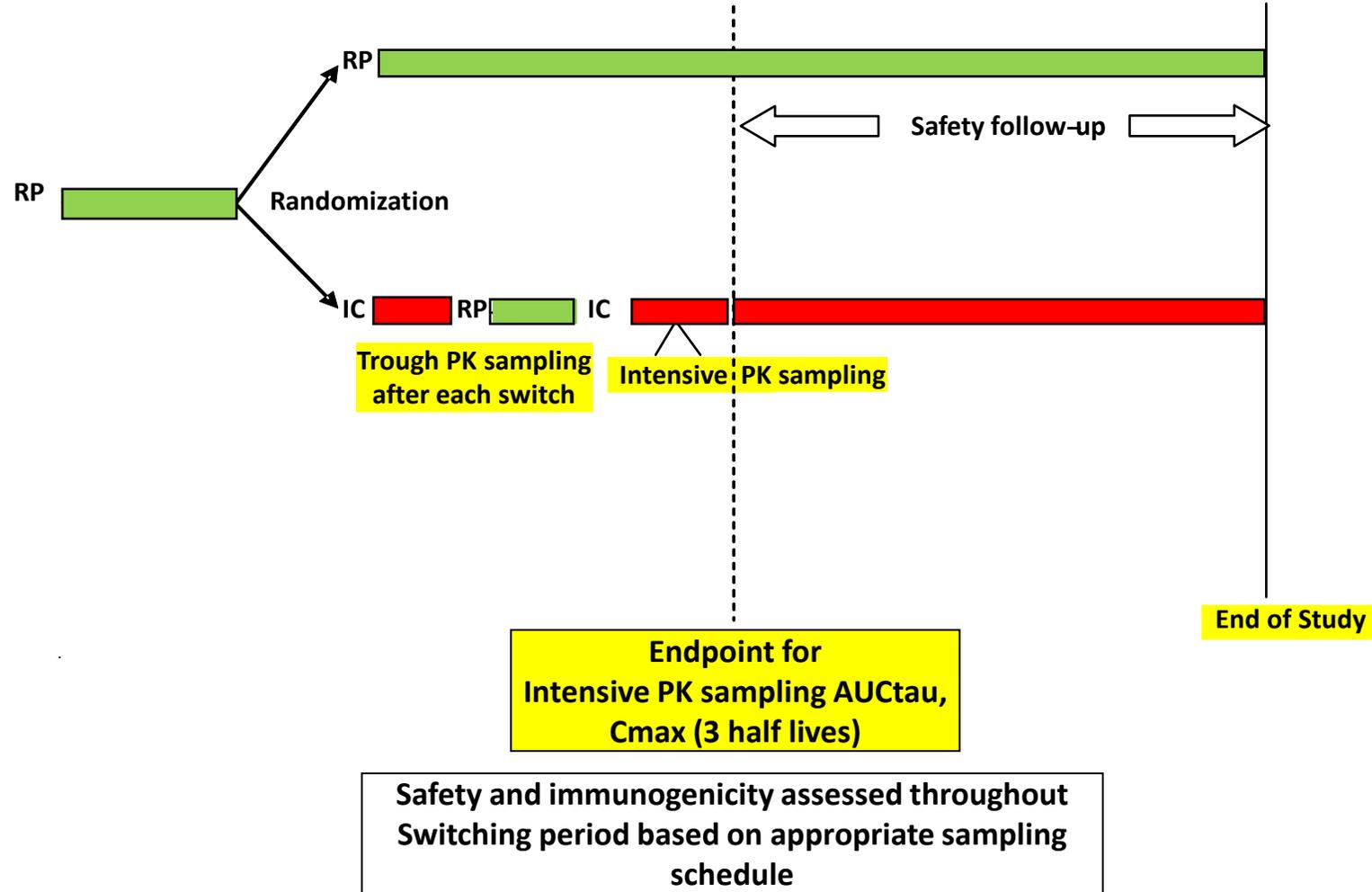
- FDA expects that applications for a product administered more than once to an individual generally will include data from a **switching study or studies** in one or more appropriate conditions of use
- **Switching Study** to demonstrate that **the risk in terms of safety or diminished efficacy of alternating or switching** between use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

Design of a Switching Study

Considerations will be product-specific and should generally consider the scenario of switching where there is the **most clinical concern for patients**. Sponsors should consider:

- **Study Endpoints**- primary endpoint should assess the impact of switching on **clinical PK, and PD** if available as these endpoints are generally most likely to be sensitive to changes in immunogenicity and/or exposure that may arise as a result of alternating or switching; **immunogenicity and safety** should be descriptively analyzed as secondary endpoints
 - **Study Population**- adequately sensitive to allow for detection of differences in PK and PD, common AEs, and immunogenicity
 - **Condition of Use to be Studied**- should be one for which the reference product is already licensed and should support extrapolation for other conditions of use
 - **Route of Administration**- should study the route that will best assess how a patient's immune response will impact clinical performance
- A switching study should **evaluate changes in treatment that result in two or more alternating exposures (switch intervals)**
 - Sufficient scientific justification for **extrapolation** is necessary.

Example of Switching Study Design



Biosimilar and Interchangeable products: Key Points



- There isn't a different analytical standard for biosimilar vs. interchangeable (IC) products – **highly similar**
 - Analytical similarity data in a 351(k) application to support approval of an IC product is **not** more, better or different than the analytical similarity data needed to support a biosimilar product
 - A product that is first approved as a biosimilar is not expected to be manipulated or changed in some manner to “become” an IC product
 - Regardless of whether an Applicant is developing a biosimilar or IC product, extended characterization through additional methods and orthogonal testing **reduces uncertainty** about potential clinical impact stemming from differences between the biosimilar/IC and the reference product (RP)
- Biosimilar and IC products (and RPs) must be manufactured, processed, packed or held in a facility that meets the same standards
- Biosimilar and IC products can be used for the same conditions of use (indications) as previously approved for the RP
 - Treatment naïve and treatment experienced patients

Biosimilar and Interchangeable products: Key Points



- **Different and distinct statutory** approval requirements for biosimilar vs. IC products
 - IC product is **biosimilar**, and has additional data requirements
 - “**Expected** to produce the **same clinical result... any given patient**”
 - “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”
 - These additional data elements allow FDA to evaluate whether the product is **one that may be substituted** for the reference product without consulting the prescriber
- FDA has described its thinking in guidance as to how the IC standards could be addressed though certain showings, data and information
 - Onus is on the Applicant to choose their approach, and provide adequate support for their approach in addressing these additional requirements

Biosimilar and Interchangeable products: Key Points



- By definition, the showings, data and information needed to support approval of a biosimilar differ from that needed to support approval of an IC product
 - What the Applicant **submits** differs between a biosimilar and an IC product
 - What the FDA **evaluates** differs between a biosimilar and an IC product
- A product approved as an interchangeable product means that FDA has concluded it **may be substituted** for the reference product without consulting the prescriber
 - Some states may permit pharmacy-level substitution; laws vary from state to state
 - Prescription and substitution laws overseen by the state pharmacy board
- When FDA carries out a scientific review of a proposed biosimilar, the evaluation does **not** include a determination of whether the biosimilar is interchangeable with the reference product and whether the biosimilar can be substituted for the reference product at the pharmacy
 - Substitution of a biosimilar for a reference product is a matter of state pharmacy law and is a decision that is generally outside of FDA's regulatory role
- Although there are distinct approval requirements for reference products, biosimilars, and interchangeable products, the approval standards that apply to each type of biological product assure prescribers of the **safety and effectiveness** of each type of product

Terminology Matters

- Health care providers should make the prescribing decision that is appropriate for their patient.
- In the context of evaluating whether a product can be licensed as a biosimilar product, depending on the clinical experience of the reference and proposed products (taking into consideration the conditions of use and patient population), FDA may evaluate data from the evaluation of a subset of patients which provides a substantive descriptive assessment of whether a single cross-over from the reference product to the proposed biosimilar would result in a major risk in terms of hypersensitivity, immunogenicity, or other reactions.
- At this time, FDA-approved labeling for **biosimilar products** does not specifically reference a “one-time switch” or “transition” from the reference product to the biosimilar, nor is there a statement recommending that biosimilar products be used only in treatment-naïve patients.
- As part of the demonstration of **interchangeability**, for a product that is administered more than once to an individual, an applicant must demonstrate 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.
 - A **switching study** intended to support a demonstration of **interchangeability** should **evaluate changes in treatment that result in two or more alternating exposures (switch intervals)** to the proposed interchangeable product and to the reference product.
 - An interchangeable product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

Using Reference Products, Biosimilar and Interchangeable Products



- Patients and their physicians can expect that there will be no clinically meaningful differences between taking a reference product and a biosimilar when these products are used as intended
- Patients and their physicians can expect that the interchangeable product will have the same clinical result as the reference product
- The FDA's high standard for approval of biosimilar and interchangeable products means that patients and health care professionals **can be confident of the safety and effectiveness of a biosimilar or interchangeable product**, just as they would for the reference product.

Summary

- Data to support approval of a biosimilar is a demonstration of biosimilarity
 - Highly similar and no clinically meaningful differences
- Data to support approval of an interchangeable product includes demonstrating biosimilarity, and additional requirements as outlined by the statute
 - Data and information to support a showing that the proposed interchangeable product **can be expected** to produce the **same clinical result as the reference product** in **all** of the reference product's licensed conditions of use
 - Generally data from a switching study will also be needed
 - These data are evaluated by FDA and, if adequate, can allow FDA to approve a proposed product as an interchangeable product to the reference product. Some states may permit a pharmacist to **substitute** an interchangeable product for the reference product without consulting the prescriber (pharmacy-level substitution)
 - Lack of clarity around terminology can be confusing
- Biosimilar and interch products are safe and effective when used as intended

Thank you for your attention.

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