

Biosimilar and Interchangeable Products in the United States: Scientific Concepts, Clinical Use, and Practical Considerations

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Overview of Presentation

- Overview
 - 2018 Highlights
 - Biosimilar Action Plan
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- Overview of Development Concepts
 - Key Points about IC Products
- Using Biosimilar and Interchangeable Products
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Biosimilars- 2018 Year in Review

- FDA approved a total of 6 biosimilars in 2018 to date
 - **Fulphila** (pegfilgrastim-jmdb)
 - **Retacrit** (epoetin alfa-epbx)
 - **Nivestym** (filgrastim-aafi)
 - **Hyrimoz** (adalimumab-adaz)
 - **Udenyca** (pegfilgrastim-cbqv)
 - **Truxima** (rituximab-abbs)
- FDA released the Biosimilars Action Plan (BAP) July, 2018
- Held Part 15 Hearing to engage in a public dialogue and opened a docket to get feedback from the public on what additional policy steps the FDA should consider as we seek to enhance the biosimilar program – Held September 4, 2018
- Launched Video Series May, 2018

Biosimilars Program



- As of December 1, 2018, 65 programs were enrolled in the Biosimilar Product Development (BPD) Program. CDER has received meeting requests to discuss the development of biosimilars for 33 different reference products.
- Since program inception and as of December 1, 2018, 14 companies have publicly announced submission of 26 351(k) BLAs to FDA.
- As of December 1, 2018, fifteen 351(k) BLAs for biosimilar products have been approved.
 - Zarxio (filgrastim-sndz)
 - Erelzi (etanercept-szzs)
 - Renflexis (infliximab-abda)
 - Mvasi (bevacizumab-awwb)
 - Ixifi (infliximab-qbtx)
 - Fulphila (pegfilgrastim-jmdb)
 - Hyrimoz (adalimumab-adaz)
 - Truxima (rituximab-abbs)
 - Inflectra (infliximab-dyyb)
 - Amjevita (adalimumab-atto)
 - Cyltezo (adalimumab-adbm)
 - Ogivri (trastuzumab-dkst)
 - Retacrit (epoetin alfa-epbx)
 - Nivestym (filgrastim-aafi)
 - Udenyca (pegfilgrastim-cbqv)

Biosimilars Action Plan



- FDA released the Biosimilars Action Plan (BAP) July, 2018 to provide information about the key actions the Agency is taking to encourage innovation and competition among biologics and the development of biosimilars.
- Key Goals:
 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

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**.

“Reference Product”



Reference Product:

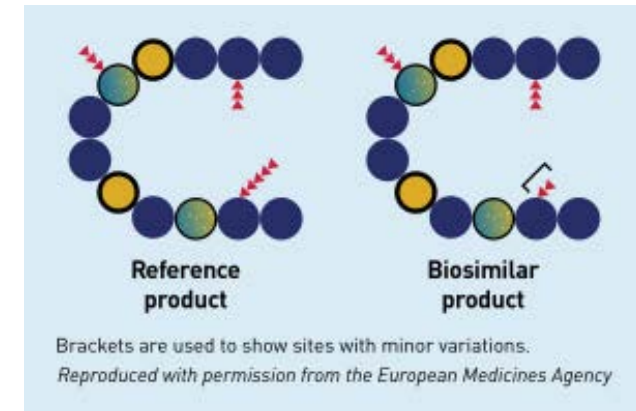
- the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in an application submitted under section 351(k). Section 351(i)(4).
- An application submitted under section 351(a) of the PHS Act is a “stand-alone” application that must contain all information and data necessary to demonstrate that the proposed product is safe, pure and potent (safe and effective).
- In contrast, an application submitted under section 351(k) needs to demonstrate that the proposed product is biosimilar to, or interchangeable with, the reference product.

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.



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.

Overview of FDA's Approach to the Development of Biosimilars

Specific Development Concepts

Development and Approval of Biosimilar Products



- The goal of a biosimilar development program is to establish biosimilarity between proposed product and reference product, not to re-establish safety and effectiveness.
- The manufacturer of a proposed biosimilar product generates an array of data comparing the proposed product to the FDA-approved reference product in order to demonstrate biosimilarity.
- The **data package** required for approval of a biosimilar or interchangeable product is quite **extensive**.
 - As part of the demonstration of biosimilarity, the manufacturer may rely, in part, on FDA's previous determination of safety and effectiveness for the reference product for approval.
 - This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients.

General Requirements

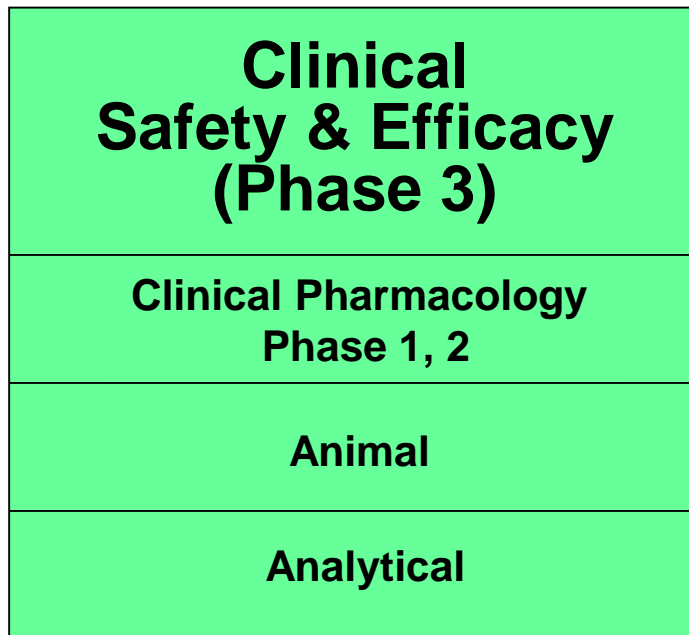
A 351(k) application must include information demonstrating that the biological product:

- 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.

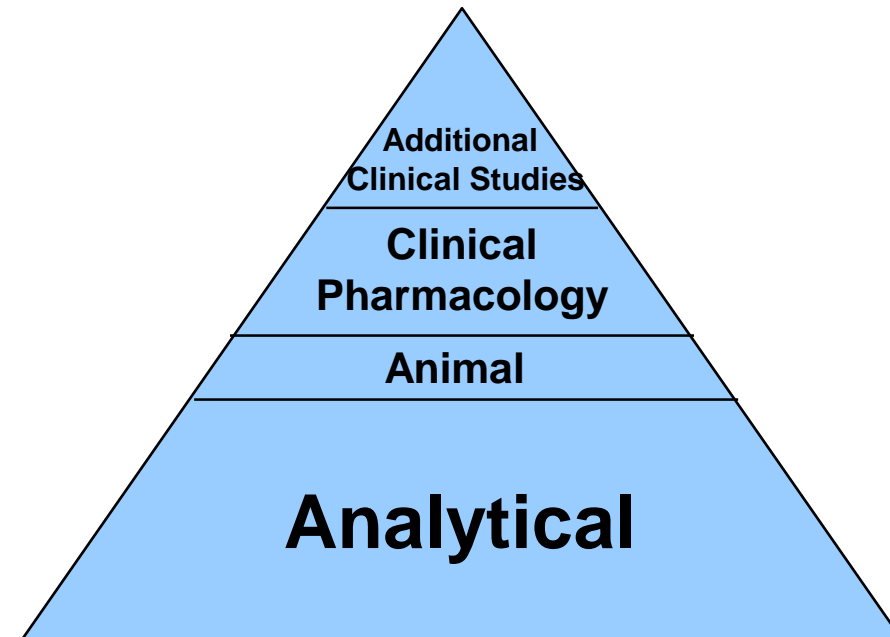
Goals of “Stand-alone” and Biosimilar Development are Different



“Stand-alone” Development Program, 351(a)
Goal: To establish *de novo* safety and efficacy of a new product



“Abbreviated” Development Program, 351(k)
Goal: To demonstrate biosimilarity (or interchangeability) to a reference product

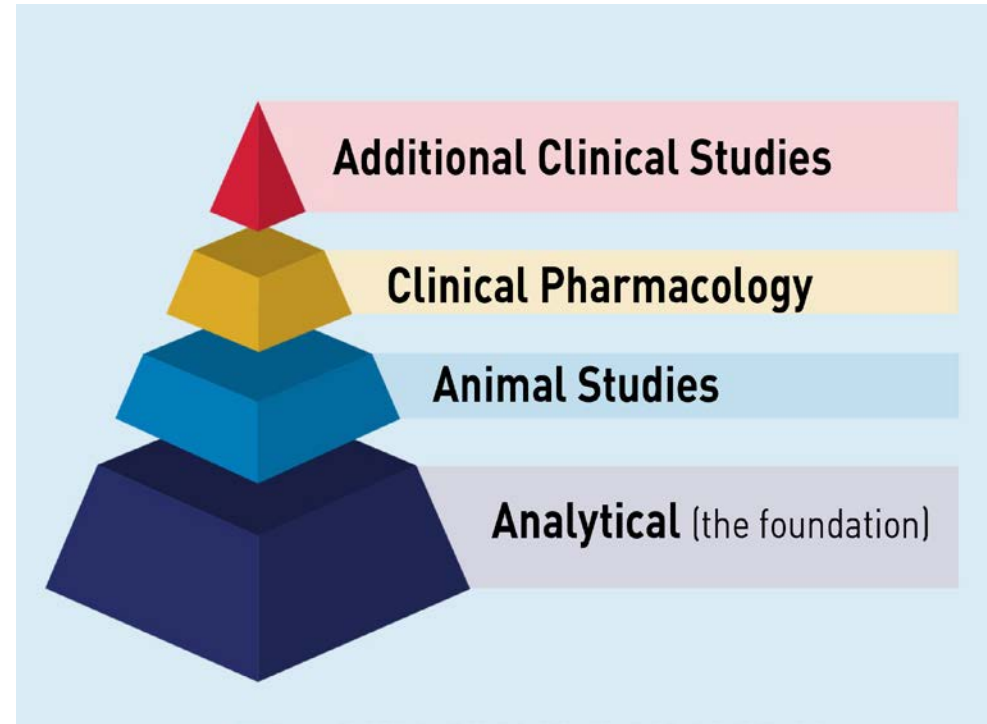


What does this difference mean from a development perspective?

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**

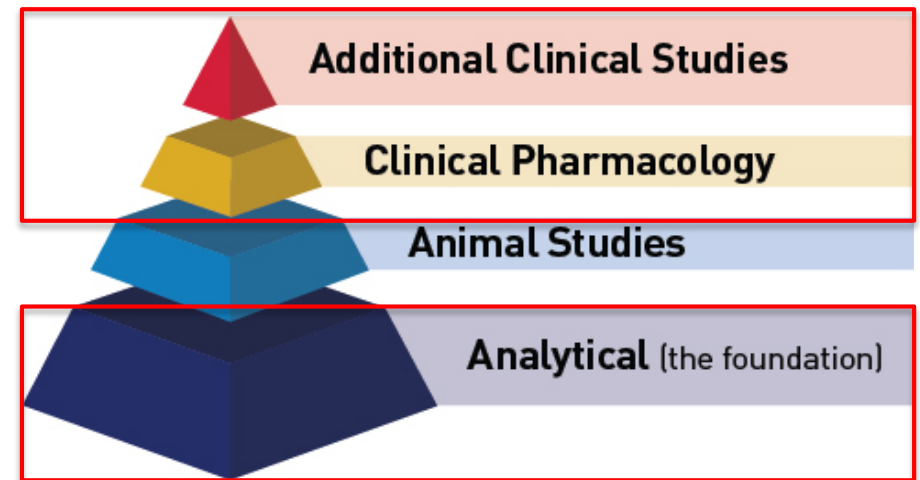


Biosimilar Product: Data for Approval



Adequate data in the marketing 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 (**structural and functional analysis/characterization**) - 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)
- 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.
- This is generally demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies.



Are Minor Differences OK?

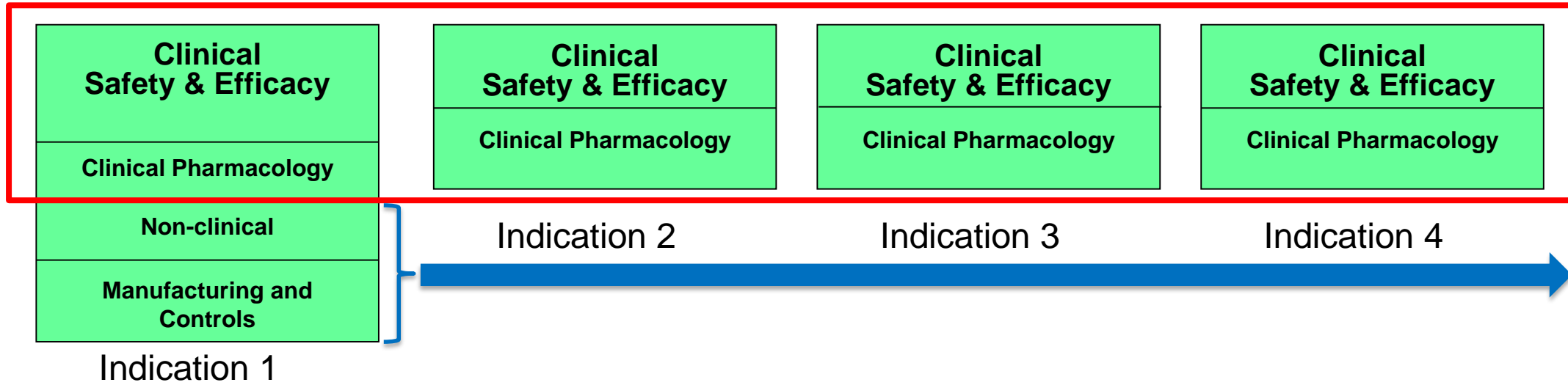
- Minor differences between the reference product and the proposed biosimilar product are acceptable.
- Slight differences are expected during the manufacturing process for biological products, regardless of whether the product is a biosimilar or a reference product.
- Any differences between the proposed biosimilar product and the reference product are carefully evaluated by the FDA to ensure the biosimilar meets FDA's high approval standards.

Extrapolation

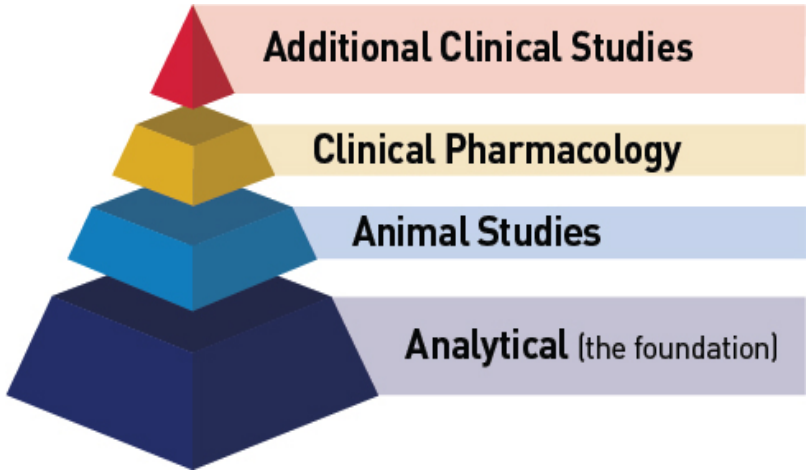
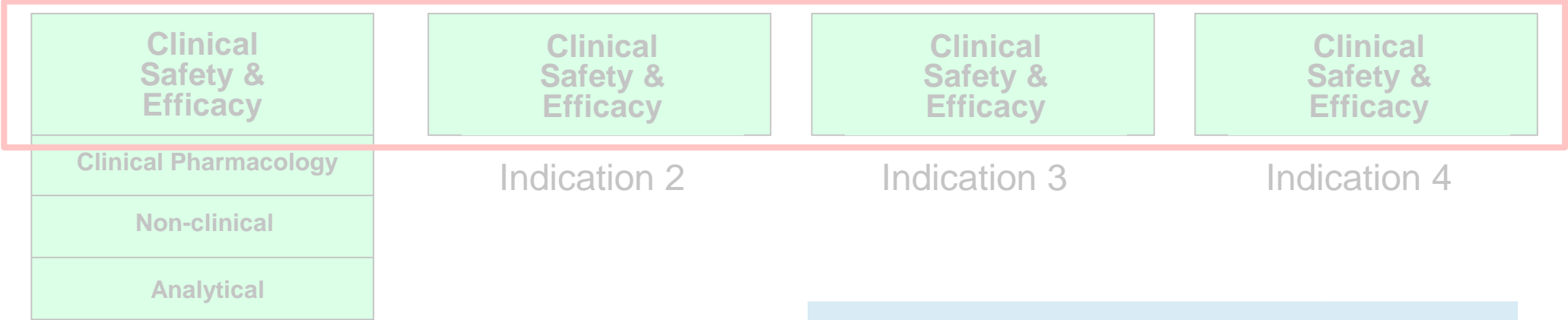


- The potential exists for a biosimilar product to be approved for one or more conditions of use for which the reference product is licensed based on extrapolation
- Sufficient scientific justification for extrapolation is necessary
- FDA guidance outlines factors to consider, including:
 - MoA in each 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

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 the biosimilar was compared to.
- 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 an important component in ensuring the safety and effectiveness of all biological products, including biosimilar products.

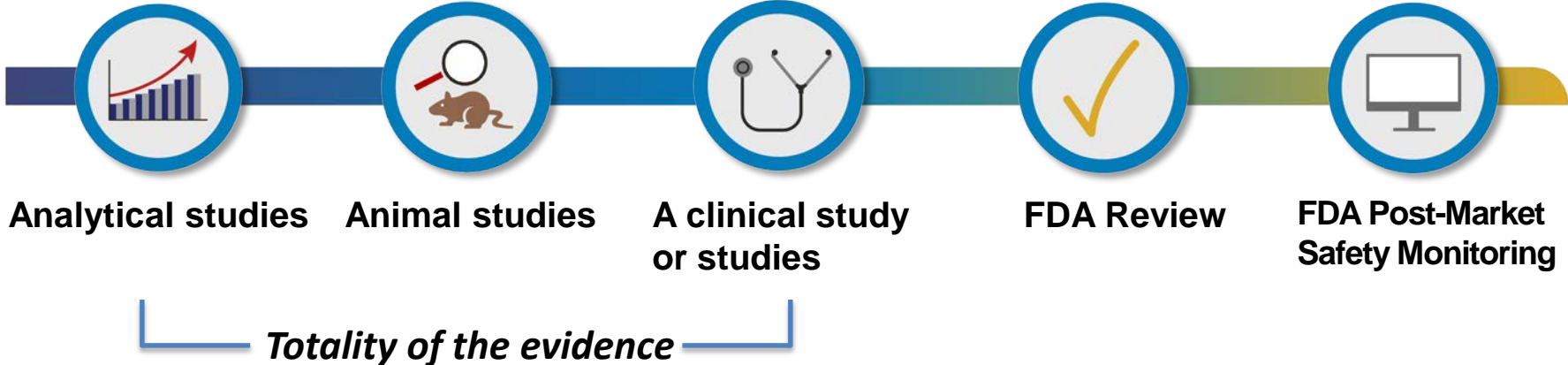
Biosimilar and Interchangeable Products: Key Points



- Interchangeable products, like biosimilars, must meet the same **highly similar** standard
- Products first approved as a biosimilar generally will not be manipulated or changed to “become” an interchangeable (IC) product
- Regardless of whether an Applicant is developing a biosimilar or IC product, extended characterization through additional methods and orthogonal testing can reduce uncertainty about potential clinical impact stemming from any minor differences between the biosimilar or IC and the reference product
- The same manufacturing and facility standards apply to biosimilar and IC products (and reference products)
- A switching study intended to support a demonstration of interchangeability is recommended to evaluate changes in treatment that result in two or more alternating exposures (switch/alternation intervals) to the proposed interchangeable product and to the reference product.

Summary

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



- Approval of a biosimilar product is based on the **integration of various information and the totality of the evidence submitted** by the applicant to provide an overall assessment that the proposed product is biosimilar to the reference product.

Using Biosimilar and Interchangeable Products

Using Reference Products and Biosimilars



- 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.
- All reference products and biosimilar products meet FDA's **rigorous standards** for approval for the indications described in product labeling.
- Although there are distinct approval requirements for reference products and biosimilars, the approval standards that apply to each type of biological product ensure the **safety and effectiveness** of each type of product.
- The FDA's high standard for approval of biosimilars means that patients and health care providers **can be confident of the safety and effectiveness of a biosimilar product**, just as they would for the reference product.

Using Biosimilar and Interchangeable Products

- Biosimilar and interchangeable products can be used in patients who have previously been treated with the reference product (treatment-experienced), as well as in patients who have not previously received the reference product (treatment-naïve).
- Biosimilar and interchangeable products may be approved for all or a subset of the same indications as the reference product.
 - The products may have fewer indications than the reference product if, for example, a reference product has unexpired exclusivity for an indication that prevents other manufacturers from obtaining approval for that particular indication.
 - Health care providers should read the prescribing information to know what the product is approved to treat.
- Once interchangeable biological products are available in the United States, some states may permit a pharmacist to substitute an interchangeable product for the reference product without consulting the prescriber—a practice commonly called pharmacy-level substitution.

Labeling



- Approved prescribing information summarizes the essential scientific information needed by health care practitioners for the safe and effective use of a drug.
- The labeling reflects FDA’s finding of safety and effectiveness for the drug under the labeled conditions of use and facilitates prescribing decisions, thereby enabling the safe and effective use of drugs/biological products and reducing the likelihood of medication errors.
- The Highlights Section contains a “Biosimilarity Statement” describing the biosimilar product’s relationship to its reference product.
- For the Full Prescribing Information, FDA recommends that biosimilar product labeling incorporates relevant data and information from the FDA-approved labeling for the reference product, along with any appropriate modifications specific to the biosimilar product.

Labeling



- A biosimilar product is not required to have the same labeling as its reference product, and so biosimilar product labeling may differ from the reference product labeling for a variety of reasons.
 - For example, a biosimilar applicant may seek licensure for fewer than all of the indications for which the reference product is approved, and this difference would be reflected in product labeling.
- FDA generally does not recommend that comparative data supporting the demonstration of biosimilarity be included in biosimilar product labeling.
- Health care professionals should review the labeling of the biosimilar product to determine what conditions of use and routes of administration are approved for the biosimilar and to make the appropriate prescribing decision for their patient.
- Product-specific data supporting a demonstration of biosimilarity, including the comparative clinical data, can be found in FDA's product reviews at the [Drugs@FDA](#) website.

Pharmacy Level Substitution



- 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.
- A product approved as an interchangeable biosimilar means that FDA has concluded it meets the standards for interchangeability, meaning the product may be substituted for the reference product without consulting the prescriber
- 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. Many states have laws that address pharmacy-level substitution, and the specific laws vary from state to state. For more information, check with your state pharmacy board.
- Prescribers and patients can expect that the interchangeable product will have the same clinical result as the reference product. An FDA-approved interchangeable product will be thoroughly tested and will meet FDA's high standards for approval.

Resources for Health Care Professionals



Education, Outreach, and Stakeholder Support

- FDA is committed to developing effective communications to improve understanding of biosimilars among patients, health care providers and payors.
- Launched Current Campaign October 23, 2017
 - www.fda.gov/biosimilars
 - Offers a variety of outreach materials, including Fact Sheets, Graphics, Social Media Content, Stakeholder Tools, a Video Series and more to help promote understanding of biosimilars and interchangeable products.
- Education is an undertaking that requires multi-stakeholder engagement and each stakeholder plays a key role in reaching the target audiences
- FDA engages with stakeholders each month to continue momentum and interest in the campaign

Future Communication and Research Plans



- Test materials with health care providers (HCP) audiences (*in process*)
- Research with HCP to assess needs for communicating about biosimilars to their patients (*in process*)
- Research with patient and professional society stakeholder groups
 - Knowledge and attitude research
 - Communication needs
 - Materials needs

The Purple Book



- FDA has published the “Purple Book” www.fda.gov/purplebook as an online resource for healthcare professionals and patients to
 - locate information about currently approved biological products, and
 - if a biological product of interest is a reference product, biosimilar, or interchangeable product
- FDA is in the process of developing a database to support the purple book and make it more user-friendly.

Thank you for your attention.

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

For the Biosimilars Action Plan, go to <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm613761.pdf>