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Monday, 12:45 pm – 2:15 pm

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Overview of the Regulatory Pathway and FDA's Guidance for the Development and Approval of Biosimilar Products in the US

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Overview of Presentation

- Overview
  - Background and BPCI Act
  - Terminology
  - Approval Pathway for Biosimilars – General Requirements

- Development of Biosimilars
  - Overview of FDA Biosimilar Guidances
  - Approach to Development
  - Specific Development Concepts

Overview

Background and BPCI Act

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 passed as part of health reform (Affordable Care Act) that President Obama 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.

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

- 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 contains **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 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 and effective.

Interchangeability

Interchangeable or **Interchangeability** means**:**

- 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.

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

Abbreviated Licensure Pathway for Biological Products

- For licensure, a biosimilar applicant submits (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 and effective.

- This licensure pathway permits a biosimilar biological product to be licensed under 351(k) of the Public Health Service Act (PHS Act) based on **less than a full complement of product-specific preclinical and clinical data → abbreviated licensure pathway.**

What is Meant by Abbreviated Licensure Pathway?

- 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 abbreviated licensure pathway does not mean that a lower approval standard is applied to biosimilar or interchangeable products than to originator biological products approved under 351(a).
- The **data package** required for approval of a biosimilar or interchangeable product is quite extensive; biosimilar applicants submit data from analytical, nonclinical, and clinical studies to support a demonstration of biosimilarity with the reference product.
- Once a biosimilar or interchangeable has been approved by FDA, patients and health care providers will be able to rely upon the safety and effectiveness of an FDA approved biosimilar just as they would for the reference product that the biosimilar was compared to.

INFORMATION NEEDED FOR A 351(K) BIOLOGICS LICENSE APPLICATION (BLA)

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.

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.

Development of Biosimilars

Overview of FDA Biosimilar Guidances
Approach to Development
Specific Development Concepts

FDA Guidances - Final

1. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (2015)
2. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (2015)
3. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (2015)
4. Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (2015)
5. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (2015)
6. Nonproprietary Naming of Biological Products (2017)

FDA Guidances - Draft

1. Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (2015)
2. Labeling for Biosimilar Products (2016)
3. Considerations in Demonstrating Interchangeability with a Reference Product (2017)

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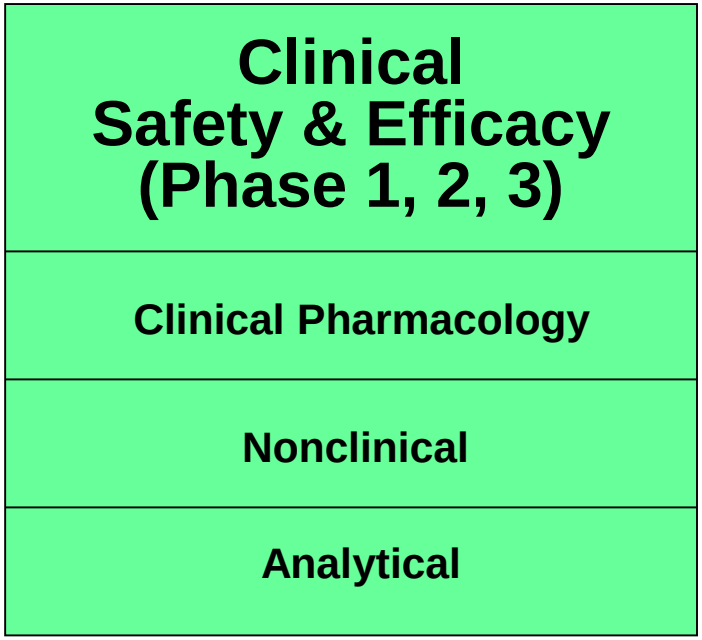
4. Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (draft, 2014)

FDA's Approach to the Development of Biosimilars

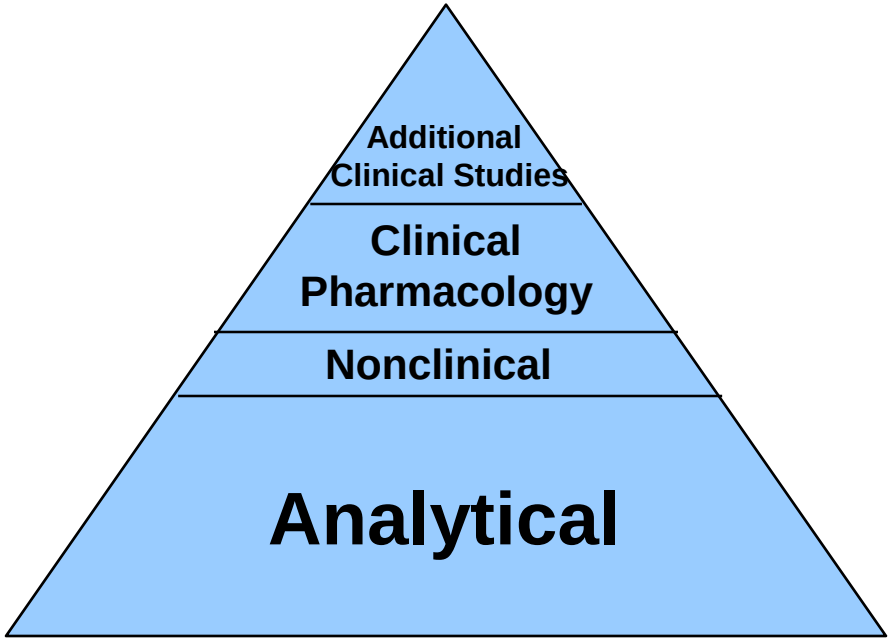
Key Development Concepts

Key Concept #1: 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

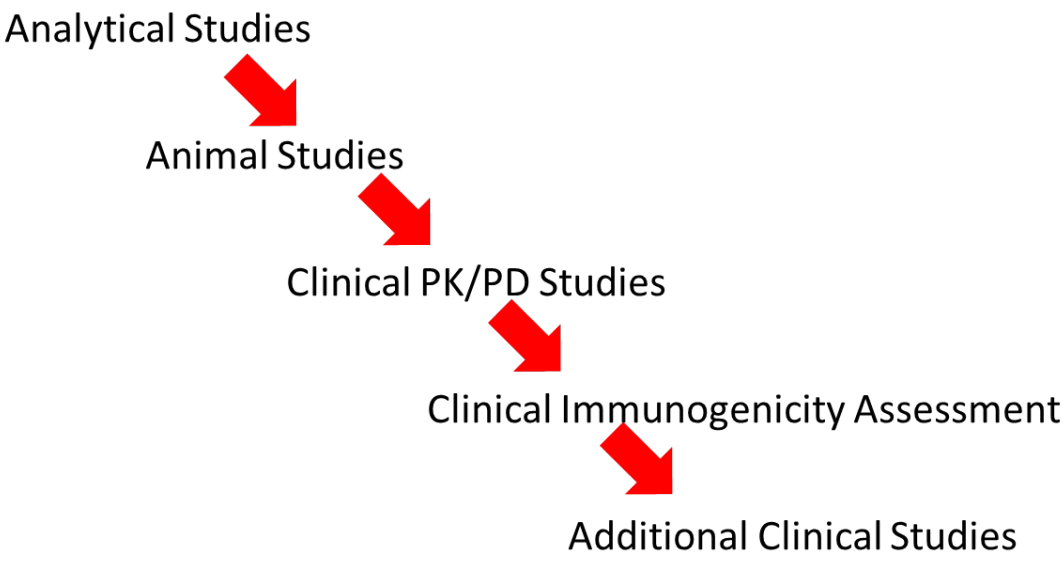


"Abbreviated" Development Program, 351(k)
Goal: To demonstrate biosimilarity (or interchangeability)



Key Concept #2: Stepwise Evidence Development

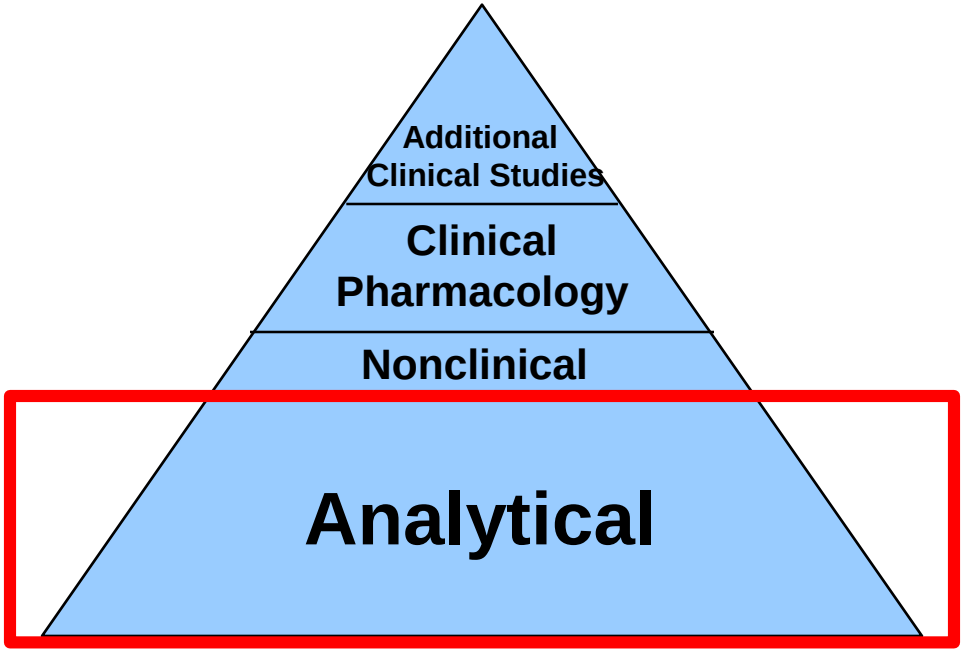
- FDA has outlined a **stepwise approach** to generate data in support of a demonstration of biosimilarity
  - Evaluation of residual uncertainty at each step
- *Totality-of-the-evidence* approach in evaluating biosimilarity



* The list is not intended to imply that all types of data described here are necessary for any given biosimilar development program. FDA may determine, in its discretion, that certain studies are unnecessary in a 351(k) application.

Key Concept #3:
Analytical Similarity Data is the Foundation of a Biosimilar Development Program

- Extensive structural and functional characterization



"Abbreviated" Development Program, 351(k) BLA

Assessing Analytical Similarity

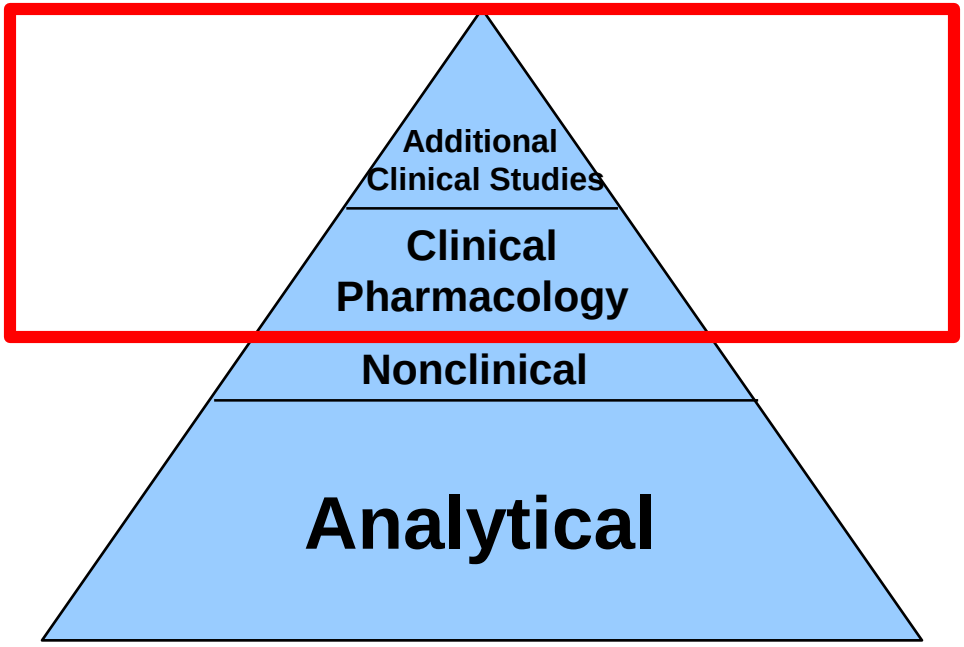
- Comparative assessment of attributes including:
  - Amino acid sequence and modifications
  - Folding
  - Subunit interactions
  - Heterogeneity (size, aggregates, charge, hydrophobicity)
  - Glycosylation
  - Bioactivity
  - Impurities
- If a molecule is known to have multiple biological activities, where feasible, each should be demonstrated to be highly similar between the proposed biosimilar product and the reference product
- **Understand** the molecule and function and identify **critical quality attributes**

Generating Analytical Similarity Data

- Characterize reference product quality characteristics and product variability
- Manufacturing process for the proposed biosimilar product should be designed to produce a product with minimal or no difference in product quality characteristics compared to the reference product
- Identify and evaluate the potential impact of differences observed and what study(ies) will address the residual uncertainty
- **Understanding the relationship** between quality attributes and the clinical safety & efficacy profile aids ability to determine **residual uncertainty** about biosimilarity and to predict expected “clinical similarity” from the quality data.

Key Concept # 4: 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.



"Abbreviated" Development Program, 351(k) BLA

Clinical Data – PK/PD

- Pharmacokinetic/Pharmacodynamic (PK/PD)
  - PK and/or PD are generally considered the **most sensitive** clinical endpoints for assessing differences between products, should they exist
  - Measure similarity in PK (AUC, Cmax) in a sensitive population able to detect product differences
  - If available, measure PD using a biomarker that reflects a known biological effect of the drug
- PK and PD similarity data support a demonstration of biosimilarity based on the assumption that similar exposure (and PD response, if applicable) will provide similar safety and effectiveness

Clinical Data – Comparative Clinical Study

- 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.
- Assessment of safety and immunogenicity

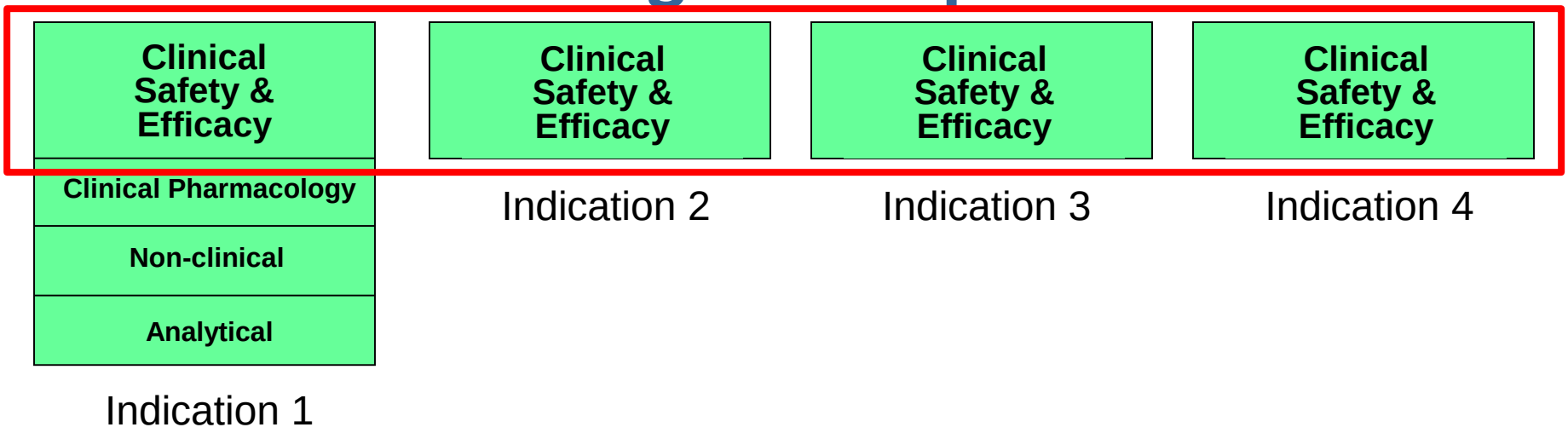
Extrapolation Considerations

- The potential exists for a biosimilar product to be approved for one or more conditions of use (e.g., indication, dosing regimen) for which the reference product is licensed based on **extrapolation of data** intended to support a demonstration of biosimilarity in one condition of use to other conditions of use

- Sufficient scientific justification for extrapolating data is necessary

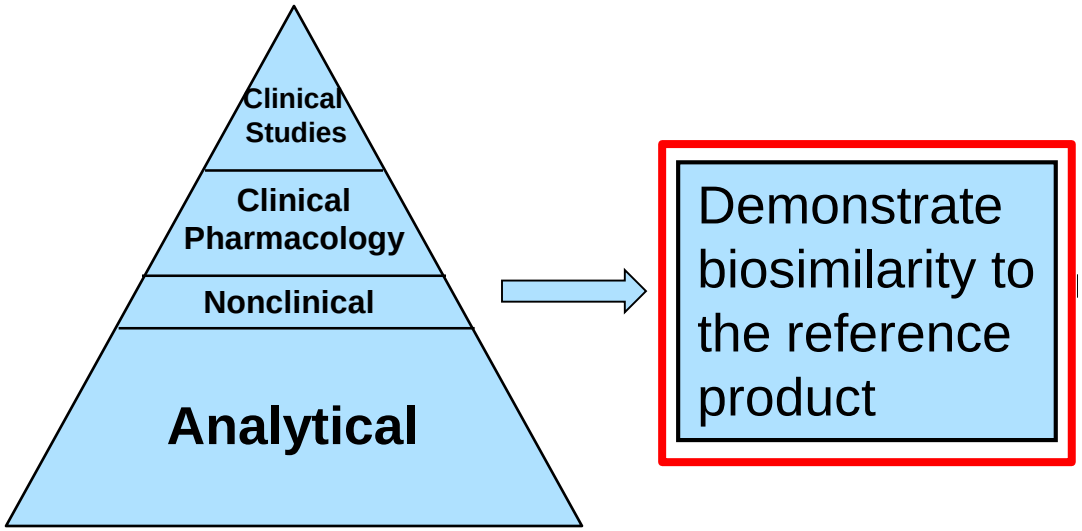
- FDA guidance outlines factors to consider to support justification, including:
  - What are the known and potential MoA in each condition of use?
  - What are the PK and biodistribution in different patient populations?
  - Are there immunogenicity differences in different patient populations?
  - Are there differences in expected toxicities in each condition of use and patient population?
  - Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

Extrapolation Considerations: "Stand-alone" Drug Development



Extrapolation Considerations: "Stand-alone" vs. Biosimilar Development

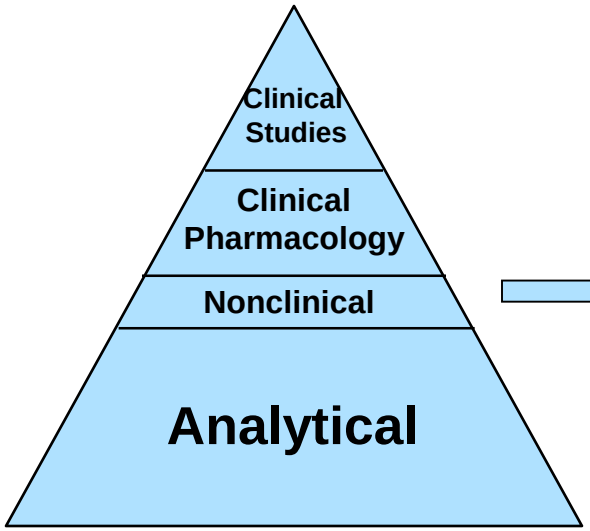
Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy
Clinical Pharmacology	Indication 2	Indication 3	Indication 4
Non-clinical			
Analytical			



Demonstrate biosimilarity to the reference product

Extrapolation Considerations: "Stand-alone" vs. Biosimilar Development

Indication 1	Indication 2	Indication 3	Indication 4
Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy
Clinical Pharmacology			
Non-clinical			
Analytical			



Demonstrate biosimilarity to the reference product

Extrapolate from the reference product to the biosimilar product, considering for each indication:

- MOA(s)
- PK
- Immunogenicity
- Known toxicities

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.

Summary

- Development of a biosimilar product is different from "stand-alone" product development
- Development goal is not to re-establish safety and effectiveness but to demonstrate the biosimilar product is **highly similar** to the reference product, and that there are **no clinically meaningful differences**
  - Analytical comparisons are the foundation for determining whether the products are highly similar
  - Clinical PK (and/or PD) is generally considered the most sensitive endpoint for detecting differences between products
  - An assessment of immunogenicity is needed and comparative clinical data are collected if questions remain
- Approval of a biosimilar is based on the integration of the **totality-of-the-evidence** submitted by the Applicant
  - Biosimilars are approved based on the same high standards as for other therapies
  - Biosimilars are safe and effective when used for their labeled indications

FDA-Approved Biosimilars

Biosimilar	Reference Product	Date
Zarxio (filgrastim-sndz)	Neupogen	Mar 2015
Inflectra (infliximab-dyyb)	Remicade	Apr 2016
Erelzi (etanercept-szzs)	Erelzi	Aug 2016
Amjevita (adalimumab-atto)	Humira	Sept 2016
Renflexis (infliximab-abda)	Remicade	Apr 2017
Cyltezo (adalimumab-adbm)	Humira	Aug 2017
Mvasi (bevacizumab-awwb)	Avastin	Sept 2017

Useful Links

- Information for Healthcare Professionals (Biosimilars):
  - www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm
- FDA CME Course on Biosimilar Products:
  - fdabiosimilars.e-paga.com/
- FDA Guidance on Biosimilars:
  - www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm
- FDA Advisory Committee Meetings:
  - https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/default.htm

Thank you