

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

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Overview of Presentation

- Overview
 - Background
 - Definitions
 - Approval Pathway for Biosimilars – General Requirements
- Development of Biosimilars
 - FDA Guidance Documents
 - Approach to Development
 - Specific Development Concepts



Overview

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.

What is an Abbreviated Licensure Pathway for Biological Products?

- A biological product that is demonstrated to be “*highly similar*” to an FDA-licensed biological product (the reference product) may rely for licensure on, among other things, publicly-available information regarding FDA’s previous determination that the reference product is safe, pure and potent.
- 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.

Definition: 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.

Definition: Reference Product

Reference Product means:

- 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.

Note: A biological product, in a 351(k) application, may not be evaluated against more than 1 reference product.

Definition: 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.

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.

Standard for Licensure

- FDA shall license the biological product under section 351(k) of the PHS Act if—
 - FDA determines that the **information submitted in the application (or supplement) is sufficient to show** that the biological product—
 - (i) is **biosimilar** to the reference product; or
 - (ii) meets the standards described in 351(k)(4), and therefore is **interchangeable** with the reference product; and
 - Applicant (or other appropriate person) consents to inspection of the facility, in accordance with section 351(c).
- **Note:** BPCI Act does not require that FDA promulgate guidance or regulation before reviewing or approving a 351(k) application.

Non-US-Licensed Comparator Products

- The PHS Act defines the “reference product” for a 351(k) application as the “single biological product licensed under section 351(a) against which a biological product is evaluated.”
- Data from animal studies and certain clinical studies comparing a proposed biosimilar product with a non-US-licensed product may be used to support a demonstration of biosimilarity to a US-licensed reference product.
- Sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product.

Support for Use of Non-US-Licensed Comparator

- Type of bridging data needed would include:
 - Direct physico-chemical comparison of all 3 products (proposed biosimilar to US-licensed reference product; proposed biosimilar to non-US-licensed comparator product; US-licensed reference product to non-US-licensed comparator product)
 - Likely 3-way bridging clinical PK and/or PD study
- All three pair-wise comparisons should meet the pre-specified acceptance criteria for analytical and PK and/or PD similarity.

Overview of FDA's Approach to the Development of Biosimilars - Specific Development Concepts

FDA Biosimilars Draft Guidances

1. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (2012)
2. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (2012)
3. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (2012)
4. Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (2013)
5. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (2014)

FDA Guidance

- Focus on therapeutic protein products
- Discusses general scientific principles
- Outlines a stepwise approach to generating data and the evaluation of residual uncertainty at each step
- Introduces the *totality-of-the-evidence* approach



Key Development Concepts

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

- The goal of “stand-alone” development is to demonstrate that the proposed product is safe and efficacious
- Drug development starts with preclinical research, moves to Phase 1, 2 and culminates in Phase 3 “pivotal” trials to show safety and efficacy
- The goal is to **demonstrate biosimilarity** between the proposed product and a reference product
- The goal is not to independently establish safety and effectiveness of the proposed 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
- *Totality-of-the-evidence* approach in evaluating biosimilarity
 - There is no one “pivotal” study that demonstrates biosimilarity
- Apply a step-wise approach to data generation and the evaluation of residual uncertainty
- When considering designing a study, **evaluate** and **understand** the question being answered
 - What is the residual uncertainty?
 - What differences have been observed and how best to evaluate the potential impact?
 - What will the data tell you? Will it answer the question?

Totality of the Evidence

- No “one size fits all” assessment
- FDA scientists will evaluate the applicant’s integration of various types of information to provide an overall assessment that a biological product is biosimilar to a US-licensed reference product.

Analytical Similarity Data - The Foundation of a Biosimilar Development Program

- Extensive **structural and functional characterization** is necessary
- **Understand** the molecule and function
- Identify **critical quality attributes** and clinically active components
- **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.

Generating Analytical Similarity Data

- Characterize reference product variability and product quality characteristics
- Characterize proposed biosimilar product quality characteristics
- Identify and evaluate impact of differences
 - The potential effect of the **differences** on safety, purity, and potency should be addressed and supported by appropriate data
 - Must be highly similar **and** no clinically meaningful differences

Assessing Analytical Similarity

- Important factors for consideration in assessing analytical similarity, including:
 - Expression System
 - Manufacturing Process
 - Assessment of Physicochemical Properties
 - Functional Activities
 - Receptor Binding and Immunochemical Properties
 - Impurities
 - Reference Product and Reference Standards
 - Finished Drug Product
 - Stability

Choice of Analytics

- It is expected that appropriate analytical test methods will be selected based on:
 - the nature of the protein being characterized,
 - knowledge regarding the structure, and
 - heterogeneity of the reference product and proposed biosimilar product including
 - known and potential impurities, and
 - characteristics that are critical to product performance

Animal Data

- Animal toxicity data are useful when uncertainties remain about the safety of the proposed product prior to initiating clinical studies.
- The scope and extent of animal toxicity studies will depend on publicly available information and/or data submitted in the biosimilar application regarding the reference product and the proposed biosimilar product, and the extent of known similarities or differences between the two.
- A comparison of PK/PD in an animal model may be useful.

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 extensive structural and functional characterization and, where relevant, animal studies.

Type of Clinical Data

- As a scientific matter, FDA expects an adequate clinical PK, and PD if relevant, comparison between the proposed biosimilar product and the reference product.
- As a scientific matter, at least 1 clinical study that includes a comparison of the immunogenicity of the proposed and reference product generally will be expected.
- As a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there are **residual uncertainties** about whether there are clinically meaningful differences between the proposed and reference products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.

Comparative Human PK and PD Data

- Comparative human PK (and PD) data :
 - Demonstrate PK (and PD) **similarity**
 - Assess clinically meaningful differences between the proposed biosimilar and the reference product
- PK and/or PD is generally considered the most sensitive clinical study/assay in which to assess for differences, should they exist
- Support a demonstration of biosimilarity with the assumption that similar exposure (and pharmacodynamic response) provides similar efficacy and safety (i.e., an exposure-response relationship exists)
- Clinical PK data generally will be expected; PD data desirable (case by case consideration)

Human PK and PD Study Considerations

- **Study Design**

- Study population: an adequately sensitive population to detect any differences, should they exist
- PD endpoint: Reflect the biological effect(s) of the drug, they may (or may not) be on mechanistic path of MOA or disease process
- Route of administration: all routes vs. a single route

- **Data analysis plan**

- Acceptance range: 80-125% (90% CI for PK and PD), scientifically justify use of other ranges
- Choice of primary endpoints (e.g., PK—AUC, $C_{\max}$; PD—AUEC)

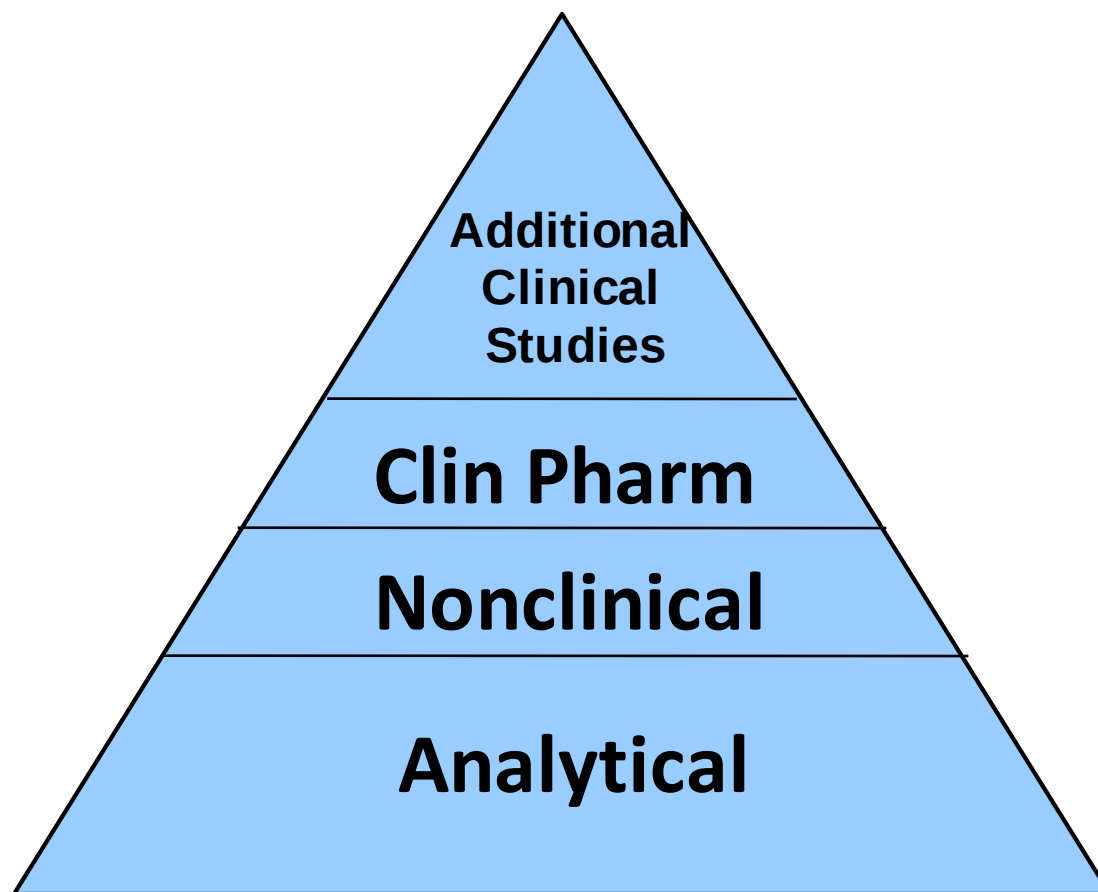
- **Others**

- Incidence of immunogenicity

Comparative Clinical Study Considerations

- A comparative clinical study for a biosimilar development program should be designed to investigate whether there are clinically meaningful differences between the proposed product and the reference product.
- Consider the adequacy of population, sample size and study duration to detect differences, should they exist.
- The goal of the study is to support a demonstration of no clinically meaningful differences.
 - Typically, an equivalence design with symmetric inferiority and superiority margins would be used, but other designs may be justified depending on product-specific and program-specific considerations.

Highly Similar Analytical and PK/PD Data Assumes Lower Risk of Clinical Differences



Totality 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 US-licensed reference product is licensed based on extrapolation of data intended to demonstrate biosimilarity in one condition of use.
- Sufficient scientific justification for extrapolating data is necessary.

Extrapolation Considerations

- FDA guidance outlines factors/issues that should be considered when providing scientific justification for extrapolation including, for example*,
 - The MOA(s) in each condition of use for which licensure is sought
 - The PK and bio-distribution of the product in different patient populations
 - The immunogenicity of the product in different patient populations
 - Differences in expected toxicities in each condition of use and patient population
- Differences between conditions of use do not necessarily preclude extrapolation

*This list is a subset of the issues outlined in the FDA guidance document

Summary of Key Concepts

- Demonstrating biosimilarity is different from “stand-alone” product development
 - A “stand-alone”-like program will **not** demonstrate biosimilarity
 - The approach and the development program should and will be different based on the intended outcome to demonstrate biosimilarity
- **Analytical similarity data is the foundation** of biosimilar development
 - **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.

Summary of Key Concepts

- The nature and scope of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products **after** conducting an extensive analytical similarity assessment.
- Comparative clinical study(ies) will be necessary to support a demonstration of biosimilarity if there are **residual uncertainties** about whether there are clinically meaningful differences between the proposed biosimilar and reference product
- Scientific justification must be provided to support extrapolation to other conditions of use
- The content of a biosimilar development program is based on stepwise development and approvability is based on the totality of the evidence submitted by the sponsor



Thank you for your attention.