The Future has Arrived: Biosimilars

Overview of the Regulatory Framework and FDA’s Guidance for the Development and Approval of Biosimilar and Interchangeable Products in the US

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Sue Lim declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.
Overview of Presentation

- Overview
  - Background
  - Terminology
  - General Requirements
- Development and Approval of Biosimilars
  - Specific Development Concepts
- Using biosimilar and interchangeable products
- Overview of Demonstrating Interchangeability
- Using biosimilar and interchangeable products
Learning Objectives

At the completion of this knowledge-based activity, participants will be able to:

1. List five differences between generic drugs and biosimilar agents related to their chemical structure, manufacturing process, and regulatory evaluation.

2. Explain the differences among reference, biosimilar, interchangeable, non-innovator, and follow-on biologic agents.

3. Describe the FDA approval process of originator, biosimilar, and interchangeable biologic products.
Self-Assessment Questions

Question 1
► What is a biosimilar product?

Question 2
► True or False: The abbreviated licensure pathway for a biosimilar product means that lower approval standards are applied to biosimilar or interchangeable products than to “originator” biological products.

Question 3
► True or False: Biosimilar development is a different development paradigm with different goals than the development of a “standalone” biological product.
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**

- Biological products are generally large, complex molecules
- May be produced through biotechnology in a living system (e.g., microorganism, plant cell, animal cell)
- Often more difficult to characterize than small molecule drugs
- Complexity:
  - Post-translational modifications and other product-related variants
  - 3D structure is complex, can vary, and is difficult to precisely characterize
  - Can change during manufacture and storage
  - Minor lot-to-lot variability is expected and monitored; An “ensemble of molecules”

Pyro-Glu (2)
Deamidation (3 x 2)
Methionine oxidation (2 x 2)
Pentose phosphate (2 x 2)
Glycation (2 x 2)
High mannose, G0, G1, G2 (5)
Sialylation (5)
C-term Lys (2)

Total variants \((9600)^2 \approx 10^8\)

\[2 \times 6 \times 4 \times 4 \times 5 \times 5 \times 2 = 9600\]
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:

- 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.
Overview of FDA’s Approach to the Development of Biosimilars

Specific Development Concepts
Biosimilars Approved in the US¹

- Zarxio (filgrastim-sndz)
- Inflectra (infliximab-dyyb)
- Erelzi (etanercept-szss)
- Amjetiva (adalimumab-atto)
- Renflexis (infliximab-abda)
- Cyltezo (adalimumab-adbm)
- Mvasi (bevacizumab-awwb)
- Ogivri (trastuzumab-dkst)
- Ixifi (infliximab-qbtx)
- Retacrit (epoetin alfa-epbx)
- Fulphila (pegfilgrastim-imdb)
- Nivestym (filgrastim-aafi)

¹As of Sept 30, 2018

https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580432.htm
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)
4. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (2016)
5. Nonproprietary Naming of Biological Products (2017)

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm
2. Considerations in Demonstrating Interchangeability With a Reference Product (2017)
3. Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (2018)

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm
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

- Clinical Safety & Efficacy (Phase 3)
  - Clinical Pharmacology Phase 1, 2
  - Animal
  - Analytical

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

- Analytical
- Animal
- Clinical Pharmacology
- Additional Clinical Studies

What does this difference mean from a development perspective?
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.
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).
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)
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.
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

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Indication 1
Extrapolation Considerations: “Stand-alone” vs. Biosimilar Development

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.
Considerations in Demonstrating Interchangeability With a Reference Product

Draft Guidance for Industry
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 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.
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.

Sponsors should evaluate the proposed product’s presentation, including product design and user interface, relative to the reference product.
Additional Data and Information Needed to Support a Demonstration of Interchangeability

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.
Design of a Switching Study (Continued)

- 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

- **Randomization**
  - RP
  - BS
  - RP
  - BS

- **Safety follow-up**

- **Trough PK sampling after each switch**

- **Intensive PK sampling**

- **Endpoint for Intensive PK sampling AUCtau, Cmax (3 half lives)**

- **Safety and immunogenicity assessed throughout Switching period based on appropriate sampling schedule**

- **End of Study**
A sponsor developing an interchangeable product generally should not seek licensure for a presentation for which the reference product is not licensed.

**Differences in the design** of the container closure system or delivery device constituent part between the proposed interchangeable product and the reference product may be acceptable provided that:

- the design differences are analyzed appropriately, and
- data are provided to demonstrate that the changes do not negatively impact the ability of end users, including patient and caregiver end-user groups, to appropriately use these products when the interchangeable product is substituted for the reference product without the intervention of the prescribing health care provider or additional training before use.
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.
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 assure prescribers of 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.
Answers to Self-Assessment Questions

Question 1
➢ What is a biosimilar product?
➢ A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product.

Question 2
➢ True or False: The abbreviated licensure pathway for a biosimilar product means that lower approval standards are applied to biosimilar or interchangeable products than to “originator” biological products.
➢ False

Question 3
➢ True or False: Biosimilar development is a different development paradigm with different goals than the development of a “standalone” biological product
➢ True
Thank you for your attention.

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