The Future of Biosimilars

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The Future of Biosimilars

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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 -- only to the extent known for the reference product;
- **Condition(s) of use** proposed in labeling **have been previously approved** for the reference product; and
- Has the **same route of administration, dosage form, and strength** as the reference product.
Biosimilar or Biosimilarity means

- 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.
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 administered more than once, the **safety and reduced efficacy risks of alternating or switching** are not greater than with repeated use of the reference product without alternating or switching.

Note: The interchangeable product may be substituted for the reference product without the authorization of the health care provider.
Biosimilarity?

- How close do the proposed biosimilar products (figures B-E) compare to the reference product (figure A)?
- Advances in current state-of-the art analytical methods enhance the likelihood that a product will be highly similar to another product by better targeting the original product’s physicochemical and functional properties.

Totality-of-the-Evidence

- Describes stepwise approach to evidence development, ensuring that development includes only those elements necessary to address residual uncertainty.
- Introduces concept that only after a thorough review of data from structural and functional analyses can FDA provide meaningful advice on scope and extent of necessary animal and human testing.
- Explains general expectations for human clinical trials:
  - At least one study will be expected (immunogenicity/PK-PD).
  - Comparative safety and effectiveness data may be necessary if residual uncertainty exists.
Residual Uncertainty

Comparative safety and effectiveness data may be needed to address residual uncertainty:

- Complexity of larger proteins. Scope of structural and functional characterization.
- Understanding the MOA based on publicly available information.
- Extent to which human PK/PD predicts clinical outcomes.
- Extent of clinical experience with the reference product and its therapeutic class.
- Extent of any clinical experience with the proposed product.
Filgastrim-sndz – What it does and doesn’t tell us about key biosimilars implementation issues

• Naming
• Labeling
• Evidentiary basis for biosimilarity determination
• Extrapolation to other indications
• Interchangeability
Extrapolation and Naming

John T. Vaughan, Vice President, Chief Regulatory Counsel, Hospira, Inc.
How do we define biologic and biosimilar?

**BIOLOGIC**

“virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product … applicable to the prevention, treatment or cure of a disease or condition of human beings.”

**BIOSIMILAR**

“The biological product (351(k)) is **highly similar** to the reference product (351(a)) **notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between the biosimilar product and the reference product in terms of the safety, purity and potency of the product.”

Biosimilar development will require a mindshift in the purpose and design of the clinical program

“Biosimilars represent a paradigm shift in the way we make a finding of safety and efficacy.” This requires a “cultural and cognitive transformation.”

2012 DIA/FDA Biosimilars Conference: Dr. Janet Woodcock’s keynote address

- Apply new, key concepts with biosimilar development including requirements for clinical development
- The goal of a biosimilar development program is to establish biosimilarity between the biosimilar product and reference product. It is **NOT** to independently establish safety and effectiveness of the proposed biosimilar product
- Apply stepwise approach to data generation and evaluation of residual uncertainty. The clinical data should answer the residual uncertainty question.
- **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 biosimilar product and reference product based on structural and functional characterization, animal testing, human PK and PD data and clinical immunogenicity assessment**

Sue Lim, May 2014, FDA: [http://www.fda.gov/downloads/ForHealthProfessionals/UCM397133.pdf](http://www.fda.gov/downloads/ForHealthProfessionals/UCM397133.pdf)
FDA has adopted robust biosimilar regulation

The FDA regulatory approach to biosimilars has developed from pre-existing knowledge and experience


EMA: European Medicines Agency

FDA guidance covers key quality and scientific issues in demonstrating biosimilarity … but gaps exist

Draft Guidances on Biosimilars

Implementation of the BPCI Act and the regulatory approval process for biosimilar medicines

Stepwise approach/residual uncertainty
General scientific principles for comparative research
Analytical studies – structure and function
Chemistry, manufacturing and controls
Clinical pharmacology (behavior in humans)
- clarification on level of similarity
Immunogenicity
Sensitive population
Extrapolation to other disease states
“Totality of evidence”

Guidances Needed:

Interchangeability
Labelling and promotion
“Lifecycle management”
Naming / INN
Other areas …

Hints exist in the Zarxio approval…

BPCI: Biologics Price Competition and Innovation
FDA will evaluate biosimilars based on a “Totality of Evidence” approach\textsuperscript{1,2}

It is not scientifically beneficial to repeat the entire development program of the reference product\textsuperscript{3,4}

A robust analytical characterization and preclinical foundation reduces the need for extensive animal and clinical testing\textsuperscript{1}
Scientific justification will need to support extrapolation to indications and uses not clinically studied

Convincing non-clinical evidence to support extrapolation to a reference biologic's approved indications

Note: If the Mechanism Of Action (MOA) for clinically studied indication(s) potentially differs from that of indications not studied clinically with the biosimilar, compelling evidence must be provided that any detectable differences will not result in differences in safety or efficacy in the indication(s) not clinically studied.

How do we compare the development pathway for an originator biologic to a biosimilar?

“**Inverted Pyramid Concept**”

Size of pyramid = “quantity” of effort

- **Reference Biologic Drug**
  - Phase III Clinical Studies
  - Phase II Clinical Studies
  - Phase I Clinical Studies
  - Nonclinical Studies
  - Molecular Characterization

- **Comparability & Biosimilarity Design**
  - Clinical Studies
    - PK / PD (behavioral)
  - Nonclinical Studies
    - Functional (biological) Characterization
    - Physicochemical (structural) Characterization

“High regulatory emphasis”

“Lower regulatory emphasis”
It will take time to achieve equilibrium between regulatory and market requirements

**Regulatory requirements**
- Leverage extrapolation
- Fingerprint analysis model
- Totality of evidence

**Market Needs**
- Data on long-term safety
- Data in several indications
- Dose optimization

- Approval will provide full label, but market will require data in a number of indications to **build confidence**
- Biosimilars will incur additional “sponsor” costs due to **post-launch studies** but, this can be managed through addressing the appropriate scientific and clinical questions
- **Biosimilar adoption** will grow over time: biosimilars use in practice will increase
- Eventually, biosimilars will be broadly used for all the approved indications for patients
Naming

- International Non-Proprietary Name (INN) system
  - 60th World Health Organization Consultation, April 2015
- European experience: biosimilars with the same nonproprietary names as their reference biologics for more than six years in a system that has proved effective
  - Biosimilars have been successfully tracked in the marketplace using their brand name and other identifiers currently in place for product recognition
- US: potential for confusion by variations in nonproprietary names
- Different nonproprietary names for a biologic and the biosimilar medicine patterned on that biologic could create confusion among the clinicians who rely on international and local standards to fill prescriptions for patients
Reference Product Exclusivity

Krista Carver, Partner, Covington & Burling LLP
Statutory Provision: Section 351(k)(7)

• **Biosimilar applications may not be:**
  – submitted until 4 years after first licensure of reference product
  – approved until 12 years after first licensure of reference product

• **These exclusivity periods “shall not apply to”:**
  – supplement for reference product
  – subsequent application filed by same sponsor or “a licensor, predecessor in interest, or other related entity” for:
    • a nonstructural change that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or
    • a structural modification that does not result in a change in safety, purity, or potency
“This guidance is intended to assist sponsors who are developing biological products, sponsors of biologics license applications (BLAs), and other interested parties in providing information that will help the Agency determine the date of first licensure for a reference product”

“FDA recommends that a sponsor include information such as that described in this guidance at the time the 351(a) application is submitted or, in the case of an already licensed 351(a) application, as correspondence to the application.”
Draft Guidance: Recommended Content of Exclusivity Submissions

1. List of “all licensed biological products that are structurally related” to product for which exclusivity is sought
2. Identify products listed in #1 for which the sponsor or any related entities are the “current or previous license holder”
3. Describe structural differences between products identified in #2 and product for which exclusivity is sought
4. Include evidence of change in safety, purity, or potency between products identified in #2 and proposed product, including a description of how described structural differences “relate to” these changes
Draft Guidance: “Related Entity”

• FDA proposes to interpret “licensor” to include that “entities that continue to retain... rights to intellectual property that covers the biological product”

• FDA will determine “related entity” status based on:
  – Ownership and control of companies, or
  – Engagement in “certain commercial collaborations” relating to development of the product(s) at issue
Draft Guidance: Other Key Provisions

• **Structural Modification**: Draft refers to “any” differences in amino acid sequence, glycosylation patterns, tertiary structures, post-translational events (including pegylation), and infidelity of translation or transcription

• **Results in a Change in Safety, Purity, or Potency**:
  - Determination will be made on case-by-case basis and “generally” will need to be based on data
  - “The supporting information provided should include measurable **effects** (typically demonstrated in preclinical or clinical studies and shown by relevant methods such as bioassays) clearly describing how the modification resulted in a change in safety, purity, or potency compared to the previously licensed product”
“[T]he determination of the date of first licensure and of eligibility for exclusivity may not always be made at the time of licensure, particularly if the determination presents complicated scientific, legal, or factual issues; if the information to support such a determination is submitted late in the review cycle; if such information is incomplete; or if FDA requests additional information to make its determination.”
The Purple Book

- CBER and CDER lists
  - Date of licensure
  - Date of first licensure (i.e., exclusivity start date)
  - RP exclusivity expiry data
  - Interchangeable/biosimilar status

- “FDA will generally make a determination of date of first licensure for reasons of regulatory necessity and/or at the request of the 351(a) application license holder”
Questions?