Update on the Development and Approval of Biosimilar Products:

Where Are We Now
&
Where Are We Headed?

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May 14, 2014

Overview of Presentation

- Review
  - Background, definitions
- Update on Workload
  - Status of biosimilar development programs
- Update on Guidances
- Other Developments
- Ongoing and Future Challenges
  - Key concepts
  - Addressing challenges
- Questions

Biosimilars: Regulatory Background

- Biologics Price Competition and Innovation Act (2009)
  - Created an abbreviated licensure pathway under section 351(k) of the PHS Act for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product
- Permits a biosimilar biological product to be licensed based on less than a full complement of product-specific preclinical and clinical data
- Challenges with an abbreviated pathway for biological products including scientific and technical complexities with larger and typically more complex structure, as well as the processes by which such products are manufactured

Definitions

Biosimilar or Biosimilarity

- 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.

Update on Workload

Workload: Numbers

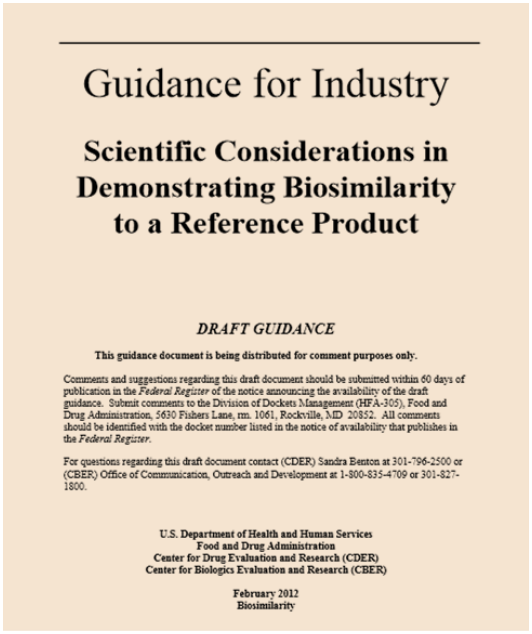
- Biosimilar User Fee Act (BsUFA) authorized a new user fee program for biosimilars
  - Different meeting types to facilitate biosimilar product development
- CDER continues to meet with sponsors interested in developing biosimilar products
- As of April 30, 2014, CDER had received 67 meeting requests for an initial meeting to discuss biosimilar development programs for 14 different reference products and held 55 initial meetings with sponsors
- CDER has received 22 INDs for biosimilar development programs, and additional development programs are proceeding under a pre-IND

Nature of Workload

- CDER is actively engaging with sponsors, including holding development-phase meetings and providing written advice, for ongoing development programs for proposed biosimilar products

- Most meetings currently being held are Biosimilar Development Phase (BPD) meetings
  - 42 programs are in the BPD Program as of March 31, 2014
  - Biosimilar sponsors are
    - Taking advantage of the BPD meetings
    - Engaging in the intended iterative process

Update on Draft Guidances



Guidance for Industry

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

DRAFT GUIDANCE

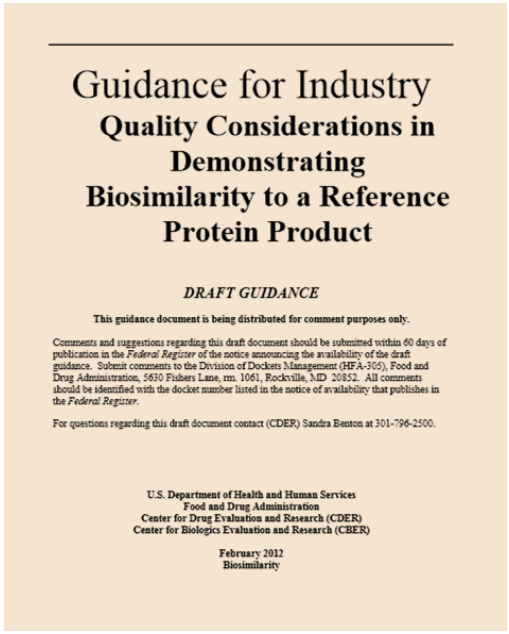
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Sandra Benton at 301-796-2500 or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2012
Biosimilarity



Guidance for Industry

Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

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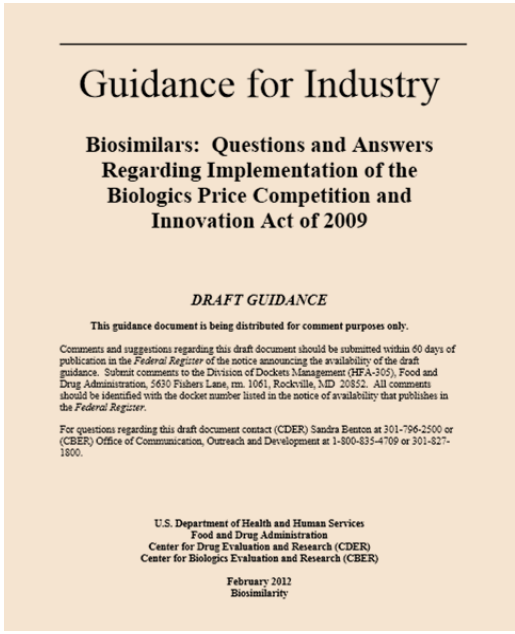

Guidance for Industry

Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

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Guidance Documents

- The four draft guidances were well received as the initial biosimilar guidances from FDA
  - Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
  - Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product
  - Q&As Regarding Implementation of the BPCI Act of 2009
  - Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants

- A public hearing was held on May 11, 2012 to receive public input on the draft guidance documents and solicit input on topics for future policies regarding biosimilars. Comments received at the public hearing indicated that FDA should consider additional guidance on interchangeability, naming, and labeling

Guidance Documents

- FDA is currently reviewing and considering all comments received from the public hearing docket and those from the draft guidance dockets as we move forward to
  - Finalize the four draft guidances
  - Determine plans for developing future policies on biosimilars

Guidance Documents

- FDA has identified additional guidances that they plan to publish in CY 2014:
  - Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009
  - Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product
  - Considerations in Demonstrating Interchangeability to a Reference Product
  - Labeling for Biosimilar Biological Products
  - Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act

Other Developments

Education and Outreach

Working Group created

- Sub-group of the Biosimilars Implementation Committee (BIC)
- Includes representatives from Office of Medical Policy, Office of Communications, and Office of New Drugs
- Focuses on public education and outreach around biosimilars

- Activities
  - FDA Basics Webinars directed towards consumers
  - Work with Office of Health and Constituent Affairs - patient education and communication
  - Presentations at professional society and clinical specialty meetings

- Future outreach activities
  - Planned interactions with physicians and pharmacists
  - Additional consumer education

Biosimilars Cluster

- Started as FDA-EMA Biosimilars Cluster
  - Announced June 2011
  - Kick-off meeting July 2011
- Membership from EMA's Biosimilar Medicines Working Party and FDA's Biosimilar Implementation Committee
- Meet ~3 times/year
  - Usually schedule around EMA BMWP meeting
  - Share chairing, agenda, and minutes responsibilities among agencies
- Health Canada joined Cluster as of July 2013
- Under Inter-Agency Confidentiality Agreements

Biosimilars Cluster

- Purpose
  - Promote global development of biosimilars
  - Discuss general scientific review issues
  - Discuss and share policy
  - Share “lessons learned”
  - Identify emerging issues

- Agenda items
  - Put forward by any member agency
  - Items agreed upon prior to meeting
  - Additional attendees (e.g., subject-matter or therapeutic experts) based on agenda items

Current & Future Cluster Activities

- Share and discuss new and emerging scientific and regulatory issues
- Discuss scientific criteria to demonstrate biosimilarity
- Discuss specific study design features
  - Disease
  - Population
  - Endpoint
  - Margin
- Discuss specific development programs
- Joint scientific advice
  - 2 requests to date

Ongoing and Future Challenges

The "cultural and cognitive transformation"

- "Biosimilars represent a paradigm shift in the way we make a finding of safety and efficacy." This requires a "cultural and cognitive transformation…" [1]
- Is proceeding, but still needs work
- New, key concepts with biosimilar development

[1]2012 DIA/FDA Biosimilars Conference: Dr. Janet Woodcock's keynote address

Examples of key concepts and how to address them

Key Concept #1: 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?

Key Concept #2: Analytical Similarity Data - The Foundation of a Biosimilar Development Program

- Extensive **structural and functional characterization** is necessary
- **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.

- Understand the molecule and function
  - Identify critical quality attributes and clinically active components
  - Have support for assessment and approach
- Understand and evaluate the impact of manufacturing changes which occur during product development
  - Introduces uncertainty depending on the extent and timing of change

Key Concept #2: Analytical Similarity Data - The Foundation of a Biosimilar Development Program

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- **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.

- **Before** proceeding with animal and clinical studies, generate sufficient analytical data to:
  - Characterize reference product variability and product quality characteristics
  - Characterize proposed biosimilar product quality characteristics
  - Identify and evaluate impact of differences
    - Don't ignore or dismiss
    - Must be highly similar **and** no clinically meaningful differences
    - The potential effect of the **differences** on safety, purity, and potency should be addressed and supported by appropriate data

Key Concept #3: 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
- Apply a step-wise approach to data generation and the evaluation of residual uncertainty
- When considering designing a study, **evaluate** and **understand** the question you are trying to answer
  - What is the residual uncertainty?
  - What analytical differences have been observed and how best to evaluate the potential impact?
  - What will the data tell you? Will it answer the question?

Key Concept #4: Comparative Clinical Study

- The nature and scope of the comparative 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.

- 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 product and reference product based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.

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 sample size and study duration to **detect differences**
  - The size and duration of the comparative clinical study in some cases may not be adequate for the detection of relevant safety signals and a separate assessment of safety and immunogenicity may be necessary.
- Study population
  - Are the study population characteristics consistent with those of the population studied for the licensure of the reference product?
  - Is the study population different from that in the clinical trials that supported the licensure of the reference product?

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
- Evaluate plan to support extrapolation early in development
- Ensure totality of the evidence, including scientific justification for extrapolation, supports approach

*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
  - Understand and evaluate the impact of manufacturing changes during product development
  - Consider the risk of introducing additional uncertainty depending on the extent of the manufacturing change, and stage/timing of implementing the change

Summary of Key Concepts

- Understand and evaluate content of development program
  - Stepwise development; totality of the evidence
  - Know why you are doing a study or studies
  - Adequately support "outside the box" proposals
- 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

Thank you