Innovation: Biosimilars & Biobetters

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Learning Objectives

- What is a biosimilar product?
- Are biosimilar products generics?
- How are biosimilars regulated?
- What is the US regulatory approval pathway?
- What challenges are there in establishing a high degree of similarity?
- What data are needed to successfully achieve regulatory approval?
- What are Biobetters?
- What are biologic novel delivery systems?
Definitions

US BPCIA

- A biological product may be demonstrated to be “biosimilar” to an already-licensed FDA biological product (the “reference product”) if data show that the 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 safety, purity and potency of the product. (FDA Website)

EMA

- A similar biological medicinal product, also known as “biosimilar”, is a product which is similar to a biological medicine that has already been authorized, the so-called “reference medicinal product”. The active substance of a similar biological medicinal product is a known biological active substance and similar to the one of the reference medicinal product. A similar biological medicinal product and its reference medicinal product are expected to have the same safety and efficacy profile and are generally used to treat the same conditions. (EMA "Procedural advice for users of the centralised procedure for similar biological medicinal products applications", November 2011)

What is a “biosimilar”?

- A copy of a reference biological product that shares the same primary amino acid sequence with that of the reference

- Differences in critical quality attributes (such as purity, impurities, stability profile, higher order structure, biological activity, etc.) are close enough to achieve a designation of similarity following an assessment of safety and efficacy

- A regulatory pathway allows the manufacturer to reference the innovator’s data package to some degree in order to encourage development and commercialization of more affordable biologic therapies

Changing the order of just one amino acid creates a different primary protein structure (ex. Humalog which is an NME vs. a “biosimilar” of Human Insulin Regular)
What other names do biosimilars have?

- Subsequent entry biological products (Canada)
- Follow-on Biologics/Biosimilars (US)
- Similar biological medicinal products (aka “biosimilars”) (EU)
- Follow-on Biologics (Japan)
- Similar Biotherapeutic Products (WHO)

The fact that policymakers and regulators have not used the term “biogenerics” clearly indicates that the standards expected for these molecules is distinct from the standard small molecule generic approval pathway.

Differences Between Biosimilars and Generics

<table>
<thead>
<tr>
<th>Size &amp; Complexity – Small Molecule Drugs &amp; Proteins</th>
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<tbody>
<tr>
<td><strong>Small Molecule Drug</strong></td>
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<tr>
<td>Aspirin 21 atoms</td>
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<tr>
<td><strong>Large Molecule Drug</strong></td>
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<tr>
<td>hGH ~ 3000 atoms</td>
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<tr>
<td><strong>Large Biologic</strong></td>
</tr>
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<td>IgG Antibody ~ 25,000 atoms</td>
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Source: Genentech Website, Biosimilars
Differences Between Biosimilars and Generics

Due to their size and complexity, Biosimilars are similar...

...but not identical (i.e., small molecule generics)

Impact of small differences in either biological or manufacturing process could lead to different clinical efficacy and safety for patients\(^1,2\)

\(^1\)Roger SD. Nephrology. 2006;11:341-346; 

Innovator Industry Positions: For approval, cannot rely on simple bioequivalence; pre-clinical and clinical data required; not interchangeable at launch; different names necessary for safety monitoring

Modified from EuropaBio
### Product Characteristics

<table>
<thead>
<tr>
<th>Generics</th>
<th>Biosimilars</th>
</tr>
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<tbody>
<tr>
<td>• Small molecules</td>
<td>• Large, complex molecules</td>
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<tr>
<td>• Mostly without a device</td>
<td>• Device is often a key differentiator</td>
</tr>
<tr>
<td>• Predominately oral delivery</td>
<td>• Predominantly parenteral delivery</td>
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<tr>
<td>• No endogenous counterpart</td>
<td>• Potential for endogenous equivalent</td>
</tr>
<tr>
<td>• Immunogenicity not an issue</td>
<td>• Immunogenicity must always be evaluated</td>
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### Development and Production

#### Chemically-Synthesized Drugs

- Produced by chemical synthesis
- Well characterized by validated analytical methods
- Manufacturing changes easily validated
- Relatively low cost to manufacture

#### Biosimilars

- Produced by genetically modified living organisms
- Multiple methods used to characterize
- Highly sensitive to manufacturing changes
- Often comparatively high costs

#### Production

- Able to prove identical to innovator compound through analytical characterization
- Very limited clinical trials (often only Phase I PK/PD studies)

#### Development

- Significant R&D to develop (cell line, mfg, process, formulation, etc.)
- Significant challenges in fully characterizing the molecule
- Difficult to “copy” innovator manufacturing process
- Clinical trials including Phase I - Phase III studies
- Post marketing surveillance required
The EU was an Early Adopter of Biosimilars

EU timeline of initial regulatory activity

Current EU regulatory pathway for biosimilars
- Legislation specifically distinguishes between biosimilars and generic drugs
- Case-by-case approval process requires extensive testing before approval and post-marketing monitoring (like biologics)
- General guidelines address quality, pre-clinical and clinical issues; numerous product-specific annexes define specific comparability tests
- Comparability to reference compound is required for quality, safety and efficacy

EU Guidelines for Biosimilars

Overarching Guideline
Similar biological medicinal products (CHMP/437/04 Rev1)

General Guidelines
On Quality, Non-Clinical and Clinical

Quality
Non-clinical
Clinical

Non-clinical
Clinical

Non-clinical
Clinical

Non-clinical
Clinical

Non-clinical
Clinical

Non-clinical
Clinical

Product class
Specific guidelines
LMWH
EPO
GCSF
hGH
Insulin
FSH

All guidances in blue are currently under revision
Biosimilar Product Experience in EU

19 Marketing Authorization Applications reviewed for biosimilars
   • 18 positive, 4 withdrawn, 1 refused

17 biosimilar medicinal products currently holding a valid marketing authorization
   • 1 somatropin, 5 epoetins, 7 filgrastims, 2 Mabs, 2 follitropin alfas

Other biosimilar Marketing Authorization Applications are currently under review including 3 human insulin products

EMA Scientific advices (first and follow-up advices)
   • 2003-2007 less than 10 advices per year
   • 2008-2010 around 15 advices per year
   • 2011 over 30 advices
US Regulatory Landscape

- Biotechnology and biologic products are approved primarily under the PHS Act. Only endocrine drugs and other hormones are approved under FD&C Act. The FD&C Act has some provision that has permitted the approval of certain biosimilars through the 505(b)2 route. Biosimilars cannot be approved under the 505(j) statute of the Act.

- Therapeutic proteins, vaccines, and monoclonal antibodies, are approved under the PHS Act. Until the passage of the Biologics Price Competition and Innovation Act, FDA had no authority to approve biosimilars based on a reduced data package.
Overview of “Biologics Price Competition and Innovation Act” (BPCIA)

- BPCIA now provides a clear regulatory pathway for approval of “biosimilars”
  - Enacted as part of the Affordable Care Act
  - BPCIA establishes a biosimilar regulatory pathway under Section 351 of the Public Health Service Act (PHSA), 42 U.S.C. § 262.
  - FDA now has the authority, and obligation, to implement the legislation
  - FDA has discretion to develop implementing regulations and/or guidance
- In very general terms, BPCIA authorizes FDA to approve “biosimilars” based on
  - Similarity to an already-approved biologic (reference product);
  - Reliance on the safety and efficacy findings of the reference product (subject to Data Package Protection, if applicable); and
  - A reduced package of clinical and non-clinical safety and efficacy data for the biosimilar

US Regulatory Approval Pathways

“Drugs” Approved under Section 505 of the Food, Drug and Cosmetic Act (FDCA)
1. NDA – 505(b)(1): Full application
2. NDA – 505(b)(2): Hybrid application; relies on previous approvals, but also may include clinical trials
3. ANDA – 505(j): Abbreviated application; no clinical trials other than bioequivalence

“Biologics” Approved under Section 351 of the Public Health Service Act (PHSA)
4. BLA – 351(a): Full application
5. BLA – 351(k): Biosimilar application (added by BPCIA)
   a. Biosimilar
   b. Interchangeable
Revised Definition of a “Biological Product”

- “Biological Product” is "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."
- Approvals for products that do not meet this definition are governed by Section 505 of the Food, Drug and Cosmetic Act (FDCA)
- Under BPCIA, products (innovators or biosimilars) that meet the definition of a "biologic" must be submitted as part of a Biologics License Application (BLA) under Section 351 of the Public Health Service Act (PHSA)

**Exception:**
- For a period of ten (10) years post-enactment, some biological products can be submitted under 505 if a product in the same class is already approved under 505.
- However, if there is an already-approved § 351 product that could serve as a reference product for the product being submitted, then it must be submitted under 351.
- After the 10-year period, all “505 biologics” will be deemed approved under § 351, and from that point all future biologics will be submitted/approved under 351.

42 U.S.C. § 262(b)(1); BPCIA § 7002(e)

Basic Approval Standards under BPCIA

**“Biosimilar”**

Applicant demonstrates that

1. Product is “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and
2. Product has no clinically meaningful differences from the reference product in terms of safety, purity and potency.

**“Interchangeable”**

Applicant demonstrates that

1. The product is biosimilar;
2. The product is “expected to produce the same result as the reference product in any given patient”;
3. The risks of switching between use of biosimilar and reference product during a course of therapy are no greater than using reference product without switching.
Additional Approval Requirements Under § 351(k)

- Biosimilar applicant must demonstrate the biosimilar is safe, pure and potent as to one or more indications of the reference product
- Biosimilar application must include the following data (unless FDA determines such data element is unnecessary):
  - Analytical studies to demonstrate biosimilar is “highly similar” to reference product;
  - Animal studies (including toxicology assessment); and
  - Clinical studies (including immunogenicity and PK/PD)
- Biosimilar must have the same mechanism of action, to the extent known
- Labeled “conditions of use” must have been previously approved in reference product label
- Biosimilar must have same route of administration, dose form and strength
- Manufacturing facility meets approval requirements

Biosimilar Application: Reference Product

- A biosimilar application must list a single “reference product” against which the biosimilar is evaluated
  - Reference product must be subject of an approved BLA under Section 351(a)
  - A biosimilar application shall include publicly available information regarding the reference product’s approval
  - A biosimilar application may include additional information, including publicly available information, regarding the reference product or another biologic
- In FDA’s view, “reliance” on the reference product means taking into account the scientific findings and conclusions from the earlier approval, as opposed to directly relying on the innovator product’s raw safety and efficacy data.
  - Some innovators will argue that reliance on safety/efficacy data, or explicit or implicit use of CM&C data, amounts to unauthorized use of trade secrets and confidential commercial information. See Genentech Citizen Petition (April 8, 2004); FDA Response (May 30, 2008)
- To facilitate resolution of patent issues, a biosimilar applicant also must follow the complex rules in BPCIA for providing notice and information about the application to the reference product sponsor. [patent provisions of BPCIA are not covered in this presentation]
Overview of Data Package Protection

- In general, an application that earns data package protection (DPP) is protected, for a set period of time, from the use of safety and efficacy data or findings from that application to support approval of a competing application from a different sponsor/manufacturer:
  - After the set period of time, reliance is permitted (may be subject to patent protection)
  - DPP runs in parallel with patent terms, not consecutively
  - DPP does not prevent a competitor from developing its own data package to support approval of the same molecule, even during the DPP period (again, may be subject to patents)
  - In the U.S., DPP is not lost by public disclosure of data or analyses, but this is not the case in some other countries

Data Package Protection For Biologics Under BPCIA

- The BPCIA provides a base data protection period (DPP) of 12 years.
  - This means that a biosimilar application cannot be approved until the date that is 12 years after the date that the innovator biologic product on which it relies was first licensed under Section 351(a) of the PHSA
  - This DPP also provides that a biosimilar may not file an application relying on a reference product until 4 years after the reference product was first licensed.
  - The 12-year and 4-year periods are extended by 6 months each if the reference product has met the requirements for pediatric exclusivity.
  - In general, BPCIA does not provide DPP for supplemental approvals such as new indications or formulations. However, orphan approval for a second indication could extend DPP beyond 12 years for that particular orphan use
    - For example, if a BLA product obtains approval of a 2nd indication that is designated as orphan indication 10 years after its initial marketing approval, the product’s DPP would expire at 12 years for its first indication, but its second orphan indication would be protected until year 17.
    - Pediatric exclusivity would extend each of these DPP and orphan time frames by 6 months.
Data Package Protection: “Anti-evergreening”

The BPCIA includes rules intended to deny DPP for innovator products that represent what some view as being based on a non-meaningful modification from a previously-approved product.

Under these rules, DPP does not apply to the following types of approved applications:

- A supplement to an existing BLA approval;
- A subsequent application by the same sponsor or manufacturer (or licensor, predecessor in interest, or other related entity) for
  - A change, not including structural modification, that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or
  - A modification to the structure that does not result in a change in safety, purity or potency

42 U.S.C. § 262(k)(7)(C)

Content of this slide is for educational purposes only.
Pediatric Requirements and Exclusivity

- Prior to BPCIA, biologics had been subject to the mandatory pediatric requirements of the Pediatric Research Equity Act (PREA), but not eligible for pediatric exclusivity under the Best Pharmaceuticals for Children Act (BPCA).
- Under BPCIA, products that are approved as biosimilar but without a determination of interchangeability, are considered to have a “new active ingredient” and therefore subject to PREA.
  - Biosimilars that are determined to be interchangeable are not considered to have a new active ingredient and therefore not subject to PREA.
- In general, BPCIA provides that pediatric exclusivity under BPCA is available to biologics, which if earned will extend data package protection against biosimilar approval and filing by 6 months each (see earlier slides on DPP).
  - BPCIA includes the new BPCA provisions that effectively require submission of pediatric studies 15 months in advance of the date exclusivity will expire.

Other Regulatory Provisions

- Automatic Substitution: BPCIA provides that interchangeable products may be substituted for the reference product without the intervention of the prescriber
  - Q as to effect of this provision: Will FDA build on its current practice under Hatch Waxman to communicate its scientific determinations, and then leave it to states, and other stakeholders, to decide the criteria for automatic substitution of biosimilar and interchangeable biologics? Or will FDA assert authority beyond just communicating its scientific determination?
- FDA has explicit REMS authority as to biosimilars
- First interchangeable biosimilar earns one year exclusivity as against other interchangeable approvals for the same reference product
- FDA may issue guidance documents, general or specific, relating to licensing of biosimilar products
  - Public comment (Q – how will innovators handle confidential commercial information and trade secrets?)
  - May include approval criteria, or determination that approvals not possible at this time
- Biosimilar application will be reviewed by same FDA Division that approved the reference product
- BPCIA contains user fee provisions applicable to biosimilar applications
Does Application Qualify To Be Filed As A Biosimilar Under the BPCIA?

1. Biologic?
   - yes

2. Reference product is the subject of an approved BLA under Section 351(a) of the PHSA?*  
   - yes

3. Development plan will rely on previous approval to include less than a full safety and efficacy data package?  
   - yes

4. Molecule has same mechanism of action, if known, as the reference product?  
   - yes

5. Compared to reference product, molecule has the same route of admin., dosage form and strength?  
   - yes

6. Proposed label conditions of use have been previously approved in reference product label?  
   - yes

Biosimilar Application
PHSA § 351(k)

NDA
FDCA § 505(b)(1) or (b)(2)

Full BLA under PHSA § 351(a)

* Ten (10) years after enactment of BPCIA, all “biologics” previously approved under FDCA 505 will be deemed to be approved under Section 351(a) of the PHSA.

Biosimilar Pathway: Chronology of Events

May 30, 2006  
FDA approves Omnitrope under 505(b)(2) (precedent)

March 23, 2010  
Enactment of BPCIA as a part of the PPACA, establishing biosimilar pathway under 351(k)

November 2-3, 2010  
FDA public meeting on biosimilar pathway in ACA

February 9, 2012  
FDA issues three draft guidances on biosimilars

May 11, 2012  
FDA public meeting on draft guidances

June 28, 2012  
U.S. Supreme Court Decision on PPACA

July 9, 2012  
Biosimilar User Fee Agreement Enacted

March/May 2014  
Two additional draft FDA Guidances released (clinical pharmacology studies and industry/FDA meeting guidelines)
Legal Challenges to Biosimilar Pathway

- **Abbott Citizens Petition**
  - **Risk:** FDA decides or a court rules that the biosimilar law only applies to reference products approved after enactment of PPACA (March, 2010)
  - **Legal Basis:** (1) Interpretation of BPCIA as prospective or (2) Constitutionality (takings clause) of retroactive application
  - **Impact:** Would result in no biosimilar approvals for biologics approved prior to March, 2010. Unlikely that Congress could do anything to resurrect biosimilar pathway for BLA biologics already approved. However, even under such a ruling, supplemental FDA approvals by the originator biologics that occur after March, 2010 could change the status of these biologics and open them up to the biosimilar pathway.

Other Legal Biosimilar Issues

- FDA’s protection of trade secrets and confidential information of the reference product in the course of a biosimilar review/approval
  - Ostensibly, statute only authorizes use of publicly available information
- ‘Skinny BLA’
  - Will biosimilars attempt 351(a) approval in order to avoid patent and exclusivity provisions?
  - How will reliance be defined and avoided under 351(a)?
- ‘How will data package protection be determined?’
  - Presumed, or innovators must ‘request’ in BLA?
  - Guidance on related molecules and sponsors
- OUS-sourced Comparator Products
  - Draft FDA Guidance endorses a bridging approach
  - BPCIA requirement for a single U.S. reference product: requires all pivotal trials to use U.S.-sourced comparator? Trade secret concerns?
  - Impacts active comparators for innovator trials?
Scientific Considerations in Demonstrating Biosimilarity to a Reference Product:
The draft guidance is intended to assist companies in demonstrating that a proposed therapeutic protein product is biosimilar to a reference product for the purpose of submitting an application, called a “351(k)” application, to the FDA. This draft guidance describes a risk-based “totality-of-the-evidence” approach that the FDA intends to use to evaluate the data and information submitted in support of a determination of biosimilarity of the proposed product to the reference product. As outlined in the draft guidance, FDA recommends a stepwise approach in the development of biosimilar products.

Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product:
The draft guidance provides an overview of analytical factors to consider when assessing biosimilarity between a proposed therapeutic protein product and a reference product for the purpose of submitting a 351(k) application. This includes the importance of extensive analytical, physico-chemical and biological characterization in demonstrating that the proposed biosimilar product is highly similar to the reference product notwithstanding minor differences in clinically inactive components.

Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009:
The draft guidance provides answers to common questions from people interested in developing biosimilar products. The question and answer format addresses questions that may arise in the early stages of product development, such as how to request meetings with the FDA, addressing differences in formulation from the reference product, how to request exclusivity, and other topics.

Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product:
The guidance is intended to assist sponsors with the design and use of clinical pharmacology studies to support a decision that a proposed therapeutic biological product is biosimilar to its reference product. This guidance pertains to those products—such as therapeutic biological products—for which pharmacokinetic (PK) and pharmacodynamic (PD) data are required as part of a stepwise approach to developing the data and information necessary to support a demonstration of biosimilarity. Specifically, the guidance discusses some of the overarching concepts related to clinical pharmacology testing for biosimilar products, approaches for developing the appropriate clinical pharmacology database, and the utility of modeling and simulation for designing clinical trials.

Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants:
This guidance reflects a unified approach to all formal meetings between sponsors or applicants and the FDA for biosimilar biological product development (BPD) programs. This guidance is intended to assist sponsors or applicants in generating and submitting a meeting request and the associated meeting package to the FDA for biosimilar biological products intended to be submitted under 351(k) of the Public Health Service Act (PHS Act).
A Biosimilar company must first...

- Isolate the reference product from commercial material available in their market
- Conduct a thorough physicochemical characterization of the isolated active ingredient, including assessment in bioactivity assays
- Reverse engineer a copy of the reference product, matching the primary sequence and "tuning" their production system to produce an active ingredient with the same physicochemical attributes as the reference (including process related substances, impurities and process related impurities)
- Conduct non-clinical and clinical studies appropriate to the indications they are seeking in a head to head trial with the reference product

Many potential biosimilar manufacturers don’t know what they don’t know.

Advice from Dr. Woodcock

- "Biosimilar product development represents a paradigm shift in the establishment of safety and efficacy. Clearly, the generic pathway is not appropriate. The efforts leading to a finding of biosimilarity has "created some cognitive dissonance." Industry cannot just do two well controlled clinical studies. The development of a biosimilar begins with comparative characterization. You will need extensive physicochemical evaluation."
- "Do not expect an FDA answer to what a clinical program should look like without sharing the data from the physicochemical characterization first. The clinical program will be based on the degree of difference from the innovator product. The clinical studies will address the "residual uncertainty" that remains from the observed difference. FDA will need to understand what you know."
Biosimilar Development Key Concepts

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?

Biosimilar Development Key Concepts

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
**Biosimilar Development Key Concepts**

**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.

**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

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**Biosimilar Development Key Concepts**

**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?
Biosimilar Development Key Concepts

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.

FDA Implementation

- FDA has three main committees working on biosimilars: a CBER/CDER implementation committee (to ensure consistency across the agency), a CBER review committee, and a CDER review committee.
- 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-
FDA Implementation

- 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.

Guidance Documents

FDA has identified additional guidances that they plan to publish in CY 2014:

- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (released on 5/13/14)
- 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
- 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 FDA Activities

- 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 are

- 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
What are Biobetters?

While biosimilars aim to establish similarity to a known biological, biobetters seek superiority in one or various aspects of their clinical profile.

Biobetters include:
- Structural changes
- Improved formulations that may result in an expected improvement in safety and/or efficacy

Example:
- Roche’s obinutuzumab (Gazyvara), an anti-CD20 monoclonal antibody, which has shown superior efficacy in the treatment of chronic lymphocytic leukemia compared to its originator rituximab

Novel Delivery Systems: Nanoparticles

- Nanoparticles (NPs) are novel drug delivery systems and can be used for cancer treatment
- Regarding materials employed for constructing NPs, organic polymers are useful due to the flexibility of design and synthesis and their ease of modification
- For example, application of nanoparticles can be used for drug delivery, gene delivery, photosensitizer deliver, diagnostic imaging and specific ligand-assisted cellular uptake (Liu, Jiang & Hunziker, 2016)

Novel Delivery Systems: Nanoparticles

- One possibility is the delivery of a new cancer drug – the anti-tumor ether lipid edelfosina (ET)
- However, ET has several drawbacks including gastrointestinal problems, and hemolytic toxicity. It also has low oral bioavailability
- To mitigate these problems, ET was encapsulated in Precirol ATO 5 lipid nanoparticles (ET-LN) & its anti-tumor capabilities in vitro tested in breast cancer
- Formulated ET-LN was more effective:
  - Inhibiting cell proliferation
  - Displaying cytotoxic effects
  - Promoting cell cycle arrest at G1 phase (Angelo, Lasa-Saracibar, Mendoza, & Blanco-Prieto, 2013)


FDA’s Approach to Regulation of Nanotechnology:
- FDA will regulate nanotechnology under its existing regulatory divisions
- Industry remains responsible for ensuring that its products meet all applicable requirements including safety standards
- FDA encourages industry to consult with the Agency early and often in the product development process
Novel Delivery Systems: Combination Products

A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. Under 21 CFR 3.2 (e), a combination product is defined to include:

1. A product comprised of two or more regulated components (i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose); or

4. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.
Registration Designation: Orphan Drugs

Novel Delivery Systems: Orphan Drugs

Application for Orphan Drug designation include:

- Specific rare disease or condition for which designation is being requested
- Sponsor contact, drug names and sources
- Description of the rare disease or condition with a medically plausible rationale for any patient subset type of approach
- Description of the drug and the scientific rationale for its use for the rare disease or condition
- Summary of the drug’s regulatory status and marketing history
- For the treatment indication, documentation that the disease or condition affects fewer than 200,000 people in the US (prevalence)
- For a prevention indication, documentation that the disease or condition affects fewer than 200,000 people in the US per year (incidence)
- Alternatively, a rationale for why there is no reasonable expectation that costs of research and development for the indication can be recovered by US sales
Novel Delivery Systems: Orphan Drugs

Number of Approved Orphan Products by Year

Important Web Sites

  - Select “browse by type” to get Biosimilar EPARs
- For more information about BsUFA, please refer to FDA’s website at [http://www.fda.gov/bsufa](http://www.fda.gov/bsufa)
• Outlines FDA's *totality-of-the-evidence approach*
  – Describes stepwise approach to evidence development, ensuring that development include 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

• Nature and complexity of larger proteins
  – Unlikely to be shown to be structurally identical
  – Could require some level of clinical data to resolve whether differences between products could result in clinically meaningful differences
    • Human PK (and PD, if relevant) studies
    • Clinical immunogenicity assessment
    • Clinical safety and effectiveness

  More general expectation

  More likely to vary with other factors causing residual uncertainty or concern

Dr. Sarah Yim, CDER, DIA/FDA Biosimilars Conference

Residual Uncertainty

• Other example factors
  – Scope and results of structural and functional characterization
  – Degree of understanding, based on publicly available information and/or data submitted in the biosimilar application, regarding the mechanism of action of the reference product and disease pathology
  – Extent to which human PK or PD predicts relevant clinical outcomes
  – Extent of clinical experience with the reference product and its therapeutic class and the nature of the risk/benefit profile
  – Extent of clinical experience with the proposed product

Dr. Sarah Yim, CDER, DIA/FDA Biosimilars Conference
Impact of Strong Analytical Characterization

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

- Focuses on analytical studies that may be relevant to assessing the similarity between a proposed biosimilar protein product and a reference product
  - General principles: Importance of extensive analytical, physico-chemical and biological characterization
  - Product/process impurities, expression systems
  - Advances in manufacturing science and Quality by Design approaches may facilitate “fingerprint”-like analysis
  - Identification of lots used in the various analyses for biosimilarity determination

Two approaches to demonstrate biosimilarity

Quality Considerations Draft Guidance

- Focuses on analytical studies that may be relevant to assessing the similarity between a proposed biosimilar protein product and a reference product
  - General principles: Importance of extensive analytical, physico-chemical and biological characterization
  - Product/process impurities, expression systems
  - Advances in manufacturing science and Quality by Design approaches may facilitate “fingerprint”-like analysis
  - Identification of lots used in the various analyses for biosimilarity determination
**Need Thorough Characterization**

- **Fingerprinting**
  - Sequence & Modifications
  - Higher Order Structure
  - Bioactivity
  - Glycoforms
  - Impurity Profile

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**DIA/FDA Biosimilars Conference, (9/12/2012)**

**Use of Non-US Comparators**

“Regarding non-US comparator products, their use in biosimilar clinical trials is only "supportive". You will need a scientific bridge to the US approved product to be able to use the data. You must always have a US licensed reference product in your trials. The statute (BPCIA) squares with this. In addition the bridging data would need to have direct physicochemical comparison of all 3 products and bridging clinical PK/PD study. There should be pre-specified acceptance criteria for analytical and PK similarity.”

Dr. Uhl, CDER, DIA/FDA Biosimilar Conference

“Clinical comparison of a biosimilar with a non-US sourced comparator product are unlikely to support a determination of interchangeability.”

Dr. Yim, CDER, DIA/FDA Biosimilar Conference

Scientific Data for bridge between non US licensed product and US licensed RP will likely include:
- Comparative physico-chemical characterization
- Bioassays/functional assays
- Comparative clinical and or non clinical PK and/or PD data
- Data to address any differences in formulation or primary packaging

Source: Guidance for Industry, Quality considerations in demonstrating biosimilarity to a reference protein product, draft guidance February 2012
Three-Way Analytical Bridge to Support Studies with Non-US Comparator

- Biosimilar Product
- US-Licensed Reference Product
- Non-US Licensed Comparator

Q&A Draft Guidance

Topics in the current draft guidance include:

- **Biosimilarity or Interchangeability**
  - Formulation differences
  - Delivery device or container closure system differences
  - Licensure for fewer than all routes of administration (for injectable products), presentations, or conditions of use
  - Comparative data with a non-U.S.-licensed product
  - Sample retention recommendations
  - Extrapolation of clinical data across indications
  - Demonstration of same “strength” for an injectable biosimilar product
  - Submission of “publicly-available information” re: reference product
  - Pediatric Research Equity Act (PREA) requirements

- **Provisions related to requirement to submit a BLA for a “biological product”**
  - Definition of “protein”
  - Definition of “product class”

- **Exclusivity**
  - Requests for reference product exclusivity
Expanded Scope of a Biological Product

• Protein Definition: Any alpha amino polymer with a specific defined sequence that is greater than 40 amino acids in size.

• Chemically synthesized polypeptide definition: Any alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is less than 100 amino acids in size.

• Still to be settled:
  – Naming convention
  – Standards for Interchangeability