



**FDA Public Hearing:
Approval Pathway for Biosimilar
and Interchangeable Biological
Products**

November 2-3, 2010

The Biotechnology Industry Organization

- Over 1,100 members, including biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations
- 91% of members have <25M annual revenue
- Non-profit trade association founded in 1993
- Close involvement in biosimilars debate since 2002 (www.bio.org/fobs)

Key Issues

- 1. Biosimilarity**
- 2. Interchangeability**
- 3. Patient Safety and Pharmacovigilance**
- 4. Maintaining Incentives for Innovation**

Biosimilarity

- **Comparative analytical, nonclinical, and clinical studies are necessary to protect patient safety**
 - In particular, clinical immunogenicity testing is necessary
 - Should compare active ingredients and compare formulated drug products
- **Structural requirements for identity should be stringent**
- **The scope of clinical studies depends on factors including the findings and limitations of analytical and nonclinical studies, and the state of public knowledge**
- **Differences have to be scientifically justified**

Interchangeability

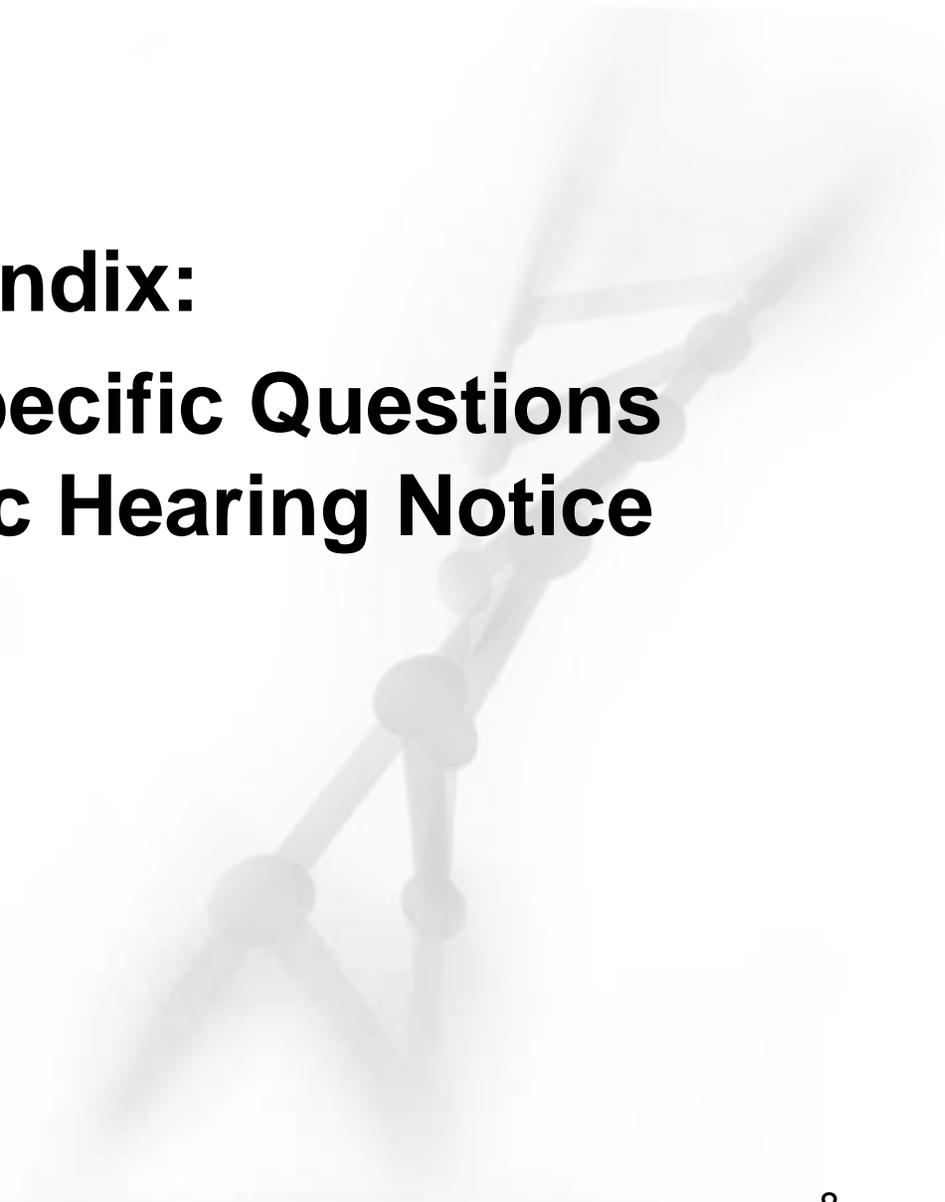
- **“expected to produce the same clinical result as the reference product in any given patient” requires:**
 - No divergence in safety or efficacy profiles in any individual in any relevant patient population
 - No divergence in safety or efficacy profiles when products are substituted or alternated
- **Must demonstrate that alternating between the two products in an individual patient does not negatively impact efficacy or safety**
 - For example, immunogenicity testing is essential to assess risk of a neutralizing antibody reaction that limits or eliminates therapeutic options
- **Patients and their physicians should always be involved when alternation or substitution is considered**

Patient Safety and Pharmacovigilance

- **Robust post-marketing data collection and evaluation are essential to assuring patient safety**
- **Pharmacovigilance activities must be guided by an understanding of the unique nature of biologics/biosimilars**
 - Biosimilar products are not identical to the reference product
- **Identification of the exact product received by the patient, via unique trade and nonproprietary names, is essential to recognizing safety issues quickly and limiting risks to patients**

Maintaining Incentives for Innovation

- **351(a) v. 351(k) Pathways**
 - To preserve the statute's careful balancing of interests, applications for biosimilar products must proceed under the 351(k) pathway
- **Protection of Innovator Rights to Notice and Content of Biosimilar Applications**
 - Adoption of proper procedures is imperative to ensure proper functioning of the statutory scheme
- **FDA Reliance on Reference BLA/Protection of Confidential Info**
 - In 351(k) review, FDA may rely only on publicly-available information about the reference product
- **Significant Product Modifications**
 - A biologic that is modified structurally, resulting in a change to safety, purity, or potency, is a distinct product that obtains its own 12-year period of exclusivity
- **User Fees**
 - Biosimilars workload should not undermine review of new drugs & biologics



Appendix:
**Responses to Specific Questions
Posed in Public Hearing Notice**

A. Biosimilarity Question 1: Determining whether a product is “highly similar”

- **Side-by-side analytical comparison should occur for active protein molecules and for formulated drug products**
 - Technical factors include primary sequence, higher order structure, post translational modifications, bioactivity, stability, purity and product/process related impurities, heterogeneity, and other chemical/physical properties
- **Structural requirements for identity should be stringent**
 - Same primary amino acid sequence (except for certain N- or C-terminal post-translational modifications/fraying if these are known to have no significant impact on efficacy or safety for a specific molecule in a specific indication)
 - No evidence of mutation or mRNA splicing
- **Use of multiple orthogonal analytical methods is essential**
 - Single measures for any given attribute could be lacking in quantitation, specificity, or scientific content

A. Biosimilarity Question 1 (continued)

- **Other manufacturing and quality aspects of the biosimilar should also be assessed in relation to what is publicly known about the reference product**
 - May include formulation excipients, equipment, primary packaging material, delivery device, the raw materials used in the manufacturing process for the active ingredient, the container closure system, the cold chain distribution system
- **Proof of biosimilarity should also be demonstrated by comparative nonclinical and clinical studies**
- **The scope of clinical studies depends on factors including the findings and limitations of analytical studies, nonclinical studies, and state of public knowledge about product structure and function**

A. Biosimilarity Question 2: Analytical Studies

- **Analytical techniques are increasingly capable of discerning differences between protein structures**
- **Differences observed should be addressed step-wise**
 - What are results of higher order structure, and functional *in vitro* tests?
 - What is the potential clinical relevance of differences, given Mechanism of Action (MoA) and reference drug history?
 - What differences in structure or impurities may have gone undetected?
- **Due to uncertainties in detecting differences, and in associating differences in structure and function, comparative clinical studies should be performed**

A. Biosimilarity Question 2: Animal Studies

- **Animal pharmacokinetics (PK) assessments should:**
 - compare reference product and biosimilar product
 - be conducted in appropriate and relevant animal species
 - be designed considering individual properties of each molecule
 - provide an integrated assessment of PK which may include evaluation of pharmacodynamics (PD) and/or immunogenicity
- **Animal pharmacology assessments should:**
 - compare reference product and biosimilar product
 - be conducted in appropriate *in vitro* and/or *in vivo* model (using a relevant animal species) and may include a disease animal model (if relevant/available)

A. Biosimilarity Question 2: Animal Studies (continued)

- **Animal toxicity assessments should:**
 - compare reference product and biosimilar product (unless otherwise scientifically justified by the sponsor)
 - be consistent with ICH guidelines and conducted in an appropriate, pharmacologically relevant animal species
 - be repeat-dose
 - use scientifically justified dosage level(s)
 - incorporate relevant specific safety and PD endpoints into the study design, including collecting and measuring samples for toxicokinetics (TK) and anti-drug antibody (ADA)
 - be of sufficient duration to measure such endpoints

A. Biosimilarity Question 2: Clinical Studies

- **Clinical studies are necessary**
 - Differences in potency and safety between the innovator and biosimilar products pose potential risks for patients
 - Clinical testing is necessary to demonstrate there are no clinically meaningful differences between the biosimilar and reference product
- **Immunogenicity must be assessed in clinical studies**
 - Minor differences in product quality can have major impact on immunogenicity
 - At present, analytics and nonclinical studies have limited predictive value with regard to immunogenicity, particularly across indications
- **Potency of biosimilar must be similar to that of reference**
 - Resolution of efficacy & mechanism-based safety concerns depends in part on robust clinical demonstration that potency of the biosimilar and innovator is similar
 - Degree of similarity in potency may vary with the drug type; any differences must be justified by biosimilar applicant
 - Biologics may have multiple aspects of activity other than that reflected in the potency assay

A. Biosimilarity Question 2: Clinical Studies (continued)

- **Clinical PK assessments should:**
 - compare reference product and biosimilar product
 - be conducted in population(s) where PD can also be evaluated, and use scientifically justified dosage level(s)
 - be designed considering individual properties of each molecule (e.g., non-linear behavior such as target mediated disposition)
 - provide an integrated assessment of PK which may include evaluation of PK/PD, PK/Safety, PK/Efficacy relationships, and immunogenicity
- **Clinical safety and efficacy studies are necessary, and must be comparative, for all indications for which the biosimilar applicant seeks approval except in cases where extrapolation can be scientifically justified**

A. Biosimilarity Question 3: Acceptable range of structural differences

- **Biosimilar products must have the same amino acid sequence**
 - except, as noted above, for certain N- or C-terminal post-translational modifications/fraying if these are known to have no significant impact on efficacy or safety for a specific molecule in a specific indication
- **Biosimilar products must have highly similar secondary and tertiary structure, bioactivity, and binding**
- **Any structural difference that alters the amount of drug administered would be unacceptable as this reflects a change in pharmacokinetics or in vivo bioactivity**
- **Differences in charge variants and glycosylation have to be justified**

A. Biosimilarity Question 4: Necessity of animal and clinical studies

- **Animal PK and/or toxicity studies are necessary, and should be comparative, unless no pharmacologically relevant species is available**
 - Appropriate nonclinical testing is the standard for minimizing risk to patients in clinical trials using investigational biopharmaceuticals
 - If no pharmacologically relevant species is available, biosimilar applicant must still demonstrate that it can manage the risks of taking the investigational product into humans
- **Clinical study/studies are necessary, and should be comparative**

B. Interchangeability Question 1: “expected to produce the same clinical result ...”

- **Consider the Product, the Patient, and Experience**
 - Product: complexity, similarity, immunogenicity profile, benefit/risk profile, route of administration, acute vs. chronic, therapeutic index, treatment combination
 - Patient: age, gender, ethnic factors, stage of disease, co-morbidities, other medications
 - Experience: clinical trial and post-marketing experience with the reference and proposed interchangeable products in each approved indication
- **“expected to produce the same clinical result as the reference product in any given patient” requires:**
 - No divergence in safety or efficacy profiles when used by any individual in any relevant patient population
 - No divergence in safety or efficacy profiles when products are substituted or alternated
 - Study endpoints same as reference product (or current standard)
 - Clinical data must be provided for each indication

B. Interchangeability Question 2: Evaluating risk of alternating or switching

- **Clinical studies must address the potential for an individualized response to a biologic product (typically, greater potential than with small molecules)**
- **Must demonstrate that alternating between the two products in an individual patient does not negatively impact efficacy or safety**
 - Cross-over studies with multiple switches; to protect patient safety, size of initial study population should be carefully considered and appropriately limited
 - Design of studies should reflect expected length of therapy
 - Must provide assurance that immunogenic responses that arise as a result of switching will not render reference and other products ineffective or unsafe, and narrow patients' therapeutic options.
- **Patients and their physicians should always be involved when any alternation or substitution is considered**

C. Patient Safety and Pharmacovigilance

Questions 1-5

- **Robust post-marketing data collection and evaluation are essential to assuring patient safety**
- **Pharmacovigilance standards and post market data collection, including requirements for REMS, should be equally rigorous for reference, biosimilar, and interchangeable biologics; specific requirements may vary**
- **Pharmacovigilance activities must be guided by an understanding of the unique nature of biologics/biosimilars**
 - Biosimilar products are not identical to the reference product.
 - Biologics are complex molecules and/or mixtures, and may be affected by manufacturing methods, delivery system, and supply chain conditions
 - Biologics can produce highly individualized safety and efficacy responses and unique immunogenic responses
- **Design of post-marketing studies should reflect expected length of treatment**

C. Patient Safety and Pharmacovigilance

Questions 1-5 (continued)

- Pharmacovigilance programs should be capable of distinguishing among adverse events associated with reference, biosimilar, and interchangeable biologics, and capturing switching information
- Identification of the exact product received by the patient via unique trade and nonproprietary names is essential to recognizing safety issues quickly and limiting risks to patients
- Current information about the “status” of biologic products (*i.e.*, whether biosimilar and/or interchangeable) is important to ensure safe use
 - Product labeling (package insert and patient labeling)
 - Database for reference by dispensers
- Physicians and patients should be educated to be vigilant in reporting product adverse events

E. Definition of a Biological Product

- **Regulatory definition for “protein” (vs. peptide/polypeptide)**
 - Proteins are a subset of polypeptides; no settled “bright-line” distinction between protein polypeptides and non-protein polypeptides exists
 - Many experts regard a polypeptide to be a protein if the polypeptide has a stable higher order structure that when absent renders the product inactive
 - Consequently, in developing a regulatory definition for the category of “protein”, FDA should consider incorporating the concept of a *polypeptide in a stable conformational state with a higher order structure that is integral to its function*
 - All such protein polypeptides should be regulated as biologics
 - Treating products differently based on whether they were chemically synthesized or fermented will lead to confusion and should be avoided if possible

F. Guidances

- **The Secretary should issue guidance governing the review and approval of biosimilars**
- **The guidance development process, which includes public input, will facilitate the development of biosimilars**
 - provides for transparency with respect to agency decision-making, which is extremely important to public confidence in the safety of biosimilars
 - facilitates the entrance of biosimilars to the market by providing an added degree of regulatory predictability
 - allows innovators to contribute specific information gained from their lengthy experience in biologics manufacturing
 - permits physicians, academics, and patients to provide valuable insights and data on the innovator product that might be relevant to the biosimilar
- **Because of the wide variety among biologics, such guidance should be specific to product types**

G. Exclusivity: Clarifications (relating to Notice of Public Hearing text)

- **Subsequent BLAs that are determined to be subject to the “first licensure” restrictions of Section 351(k)(7)(C) are not “ineligible” for exclusivity**
 - They are covered by any remaining exclusivity of the first licensed BLA
- **There is no “second” 12-year period of marketing exclusivity for any biologic, under any circumstances**
 - A biologic that has been modified structurally resulting in a change to safety, purity, or potency is a distinct product that obtains its own 12-year period
- **“First Licensure” Determinations:**
 - Relevant date for approved products should be identified by FDA through a transparent process, with rights of review
 - FDA should develop a process for advance rulings on R&D targets

G. Exclusivity Questions 1 and 2

- **Scope of “Other Related Entity” Language:**

- The terms “same sponsor or manufacturer,” “licensor,” and “predecessor in interest” with respect to the reference product are clear
- The term “other related entity” should be read in context of the language that surrounds it to mean a subsequent BLA applicant that originally had granted the reference product sponsor exclusive rights to such reference product

- **Factors in Determining that a Modification to the Structure of a Reference Product Results in a Change in Safety, Purity or Potency:**

- A modification to the structure, including but not limited to, the amino acid sequence, critical post-translational features of the active ingredient, or changes in the biologic components, resulting in a product with a change in safety, purity or potency as compared to the reference product

H. Transition Provisions Question 1: “Product Class”

- **Each product class should be sufficiently well-described that manufacturers can easily determine which products are in the class**
 - Each definition of product class should take into account molecular complexity, recombinant or non-recombinant origin, existence of reliable biomarkers, indication, and safety profiles
- **FDA should publish a list of proposed product classes**
- **Consider adopting the product classes used by or similar to those used by the European Medicines Agency (EMA) in connection with biosimilars**

I. User Fees Question 1: PDUFA as a model

- **Biosimilars workload should not undermine review of new drugs & biologics, which should continue to have highest priority**
- **A biosimilars user fee structure should incorporate key elements from existing user fee programs:**
 - Fee rates that are published, grounded by reasonable cost estimates, and adjusted annually for inflation and workload
 - Mechanisms to prevent fee diversion to unrelated FDA or government activities
 - Mechanisms to prevent PDUFA fee diversion to biosimilar review
 - Transparent review processes and publicly reported metrics and annual reports to track program performance and finances.
 - Sunset of the program at specified intervals to provide an opportunity to make course corrections and other related improvements.
 - As stated in statute, user fee rates and performance goals should be determined after technical discussions with regulated industry and consultation with a broad array of stakeholders

I. User Fees Question 2: Use of fees to monitor post-approval safety

- **Careful post-market monitoring of the safety of a biologic, whether innovative or biosimilar, is extremely important and should be funded by user fees.**
- **Biosimilar user fees should also support a lifecycle approach to product evaluation**
 - Enable the monitoring of benefits and risks of products across their marketed lifetime
 - Maximize the public health benefit associated with collecting adverse event information at various points during the product lifecycle

Other Key Implementation Issues

- **Labeling for Biosimilars**
 - Must reflect differences between the products and supporting data
- **Protection of Confidential BLA Information**
 - Need to revise current FDA regulations to account for competitive nature of new pathway
- **FDA Reliance on Reference BLA**
 - FDA may rely, in 351(k) review, only on publicly-available information about the reference product
- **351(a) v. 351(k) Pathways**
 - Ensure that applications for biosimilar products proceed under 351(k) in order to preserve the statute's careful balancing of interests
- **Protection of Innovator Rights to Notice and Content of Biosimilar Applications**
 - Necessary to ensure proper functioning of statutory scheme
- **International Harmonization**
 - Consider, as appropriate, regulatory pathways for approval of biosimilars that exist in other regions