Regulatory Issues and Drug Product Approval for Biopharmaceuticals

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Regulatory Authority Mission

"Assure that SAFE and EFFECTIVE drugs are marketed in the country and are available to the People"

Drug Approval Process

- New drug
  - Safety: Preclinical studies in animals and controlled clinical studies in human
  - Efficacy: Clinical studies in patients
  - CMC: Full characterization, description of manufacturing process and test methods and stability data.
  - Manufacturing under cGMP conditions to ensure identity, potency, purity, quality and safety of the final product.
- Generic
  - Generic product is a copy of the brand name product, same active ingredient, different inactive ingredients.
  - PE + BE = TE

Biotech Drug Products

- **Difference between**
  small and large molecule drugs

  – **Small molecule drugs are chemically pure synthetic molecules and can easily be formulated.**
  – **Biotech drug products are Large complex molecules, heterogeneous mixtures, and vary from batch to batch and difficult to formulate.**

Biotech Products

FDA

- **Follow-on-Protein**

EMEA

- **Biosimilar**

"Not Biogenerics"

Follow-on Protein Products

- Unlike small-molecule generic products, follow-on protein products can exhibit a range of structural similarities to the original product. The follow-on might be
  - precisely identical (some peptides)
  - highly similar (some recombinant proteins)
  - generally similar (natural products)
- Second-generation products: structural differences designed to improve performance while maintaining the same mechanism of action

J Woodcock et. al. Nature Reviews Drug Discovery. 2007: 6(6), 437-442.

FDA Regulations

- **Science based policy**
- **It is dynamic and has evolved over many years and continues to evolve – based on the ability of the analytical techniques to characterize the products, manufacturing practices and controls, clinical and regulatory experience.**
- **Rigorous standards of ensuring product Safety & Efficacy must be maintained, at the same time unnecessary and/or unethical duplication trials must be avoided.**

FDA Regulations

- **505(b)(1) – Full reports of investigations of S & E; full NDA, with right of reference. This means that information about S & E can be used by others.**
- **505(b)(2) – Some without right of reference, require clinical studies, NDA for rDNA.**
- **505(j) – For ANDA applications – need PE + BE. No need for clinical or pre-clinical studies beyond BE.**

Follow-on-Proteins
The Problem / Issues

- Inadequate definition of the molecular complexity associated with the structure and function of protein pharmaceuticals
- Barriers to understanding the complexity
  - Analytical methods
  - Definition of process space
  - Understanding the relationship between the structure and function

Points to Consider
Scientific Issues

Understanding of molecular complexity, manufacturing process, characterization, safety and clinical data

- **Comparative Qualitative analysis**
  - Identity, structure, bioassay, purity, impurities, stability
- **Pre-clinical Studies**
  - Animal toxicity, animal PK/PD
- **Clinical Safety**
  - Immunogenicity
- **Clinical studies**
  - Efficacy, biomarkers, surrogate endpoints, PK/PD, Immunogenicity

A Perspective on the state of Follow-on Proteins Today

- Multiple processes and manufacturers for
  - Insulin, Human Growth Hormone, Erythropoietin
- Multiple locations for manufacturing
- Processes for follow-on products may be different because
  - Freedom to operate
  - Use of differing analytical methods
  - Introduction of new process technology
  - Incorporation of prior knowledge into new process

Follow-on Proteins

- Follow-on Protein manufacturers might use better methods than innovator
- Generics are not privy to current innovator methods
- Innovator may continue to find ‘new characteristics’ over time

Risk vs Benefit

- **Potential Risks**
  - **Lower efficacy**
  - **Different adverse events**
- **Potential Benefits**
  - **Decreased cost to patients**
  - **Increased availability of drugs**
  - **Increased Quality of drugs**

Follow-on Proteins

- **Reduce Uncertainty:**
  - **Structural features – Primary, secondary, tertiary and quaternary structures, size and mass, hydrophobicity**
  - **Purity – Active component and impurity**
  - **Biological attributes**
    - **Primary activity**
    - **Immunogenicity – focus on aggregation,**
    - **Product and process related impurities,**
    - **Potentially immunogenic glycans**
    - **Pharmacokinetics**
    - **Toxicity**

Follow-on Protein Pharmaceuticals
Characterization

- Physical-chemical characterization
- Protein characterization
- Biological characterization
- PK/PD studies, preclinical, pharmacological, toxicological, clinical
- Immunogenicity
- Clinical safety and efficacy
- BE of biopharmaceuticals

Protein Characterization

- Complete characterization of the protein (structural properties) provides the foundation for supporting product changes and comparison
  - Primary, Secondary, Tertiary and Quaternary
- State-of the-art analytical techniques allow investigation of protein of physicochemical and biochemical properties
- 35% of the proteins can be glycans – thorough characterization of glycans is essential

Glycans

Glycans play critical role in biology and chemistry of proteins

- **Glycans modulate**
  - **Protein folding and stability**
  - **Binding activity to receptors, influencing S & E**
  - **Immunogenicity through folding**
  - **Clinical profile/activity**
  - **Pharmacokinetics**
  - **Tissue Distribution**

  Contributions of glycans to clinical profile are similar in importance to amino acid sequence and protein structure

Biological Characterization

- **Bioassays – Biomarkers needed for clinical relevance**
- **Biological characterization (BC) is not usually predictive of clinical efficacy.**
- **BC + PD parameters can be used to justify limited clinical studies**

Characterization - Immunogenicity

- Human proteins are usually immunogenic
- Immunogenicity must always be addressed by clinical data – clinical studies
- Immune system can detect alterations in products missed by analytical methods
- Immunogenicity may have serious clinical consequences
- Testing for antibody response is essential

Comparability, PE, BE

- **Comparability Protocol: For changes in manufacturing process within *the same* manufacturer's product (Guidance – 1996)**
- **Pharmaceutical Equivalent: Products from different manufacturers, same active ingredient**
- **Bioequivalence: Between two batches**
  - **Test and Reference OR Two processes**
  - **when comparability studies are carried out**
- **PE + BE → TE**

Comparator Studies

Comparator studies may reduce preclinical testing, dose ranging and phase 3 studies

Comparator studies Can NOT substitute for

- **CMC development**
- **Full physicochemical characterization**
- **Full biological characterization**
- **Full release testing**
- **Basic non-clinical testing**
- **Clinical trials**

May need to evaluate intermediates and bulk drug substance in addition to drug product

Follow-on Protein Pharmaceuticals

- **No amount of non-clinical testing of a follow-on protein product can ensure it will have identical effects to the originator product**
  - **A risk of inferior safety and / or efficacy will always remain.**
  - **Clinical testing can limit that risk.**

Follow-on protein products should be able to use appropriate surrogate markers to demonstrate therapeutic equivalence and safety

Follow-on Proteins

- New protein products that are PE and TE
- Do not require full preclinical and clinical studies
- Appropriate surrogate marker can be used to demonstrate TE and S
- 90% C.I. with BE limits (80-125) can be used
- Need for clinical studies beyond PK depends on complexity of the molecule

Regulatory Framework

- Safety
  - Non-clinical studies
- Efficacy
  - Clinical studies
  - Immunogenicity
- Quality
  - Characterization

Biosimilar Products

- The requirements for biosimilar products should be based on structural complexity and clinical knowledge of and experience with the reference biopharmaceutical product.
- Approval should be considered based on product comparisons and demonstration of comparability to the reference product.

Several EMEA Guidances are available

Biosimilar

- Same safety and efficacy profile as brand name product
- Challenge – Identity of the active substance.
- Complex manufacturing process of biopharmaceuticals involves living organisms.
- Production process is very critical. Composition of the product is dependent upon the process
- Comparative analytical characterization of the reference and biosimilar product provide a foundation for determining need of clinical study
- The biggest challenge is to prove PE.

Follow-on Protein Products

The FDA's assessment of follow-on protein products: a historical perspective

J Woodcock et. al.

Nature Reviews Drug Discovery: 2007, 6(6), 437-442.

Follow-on Protein Products

- Because of the difference between protein drug products and small molecule drugs, the development of follow-on version of protein products presents more complex scientific challenges than those presented by the development of generic versions of small molecule drugs.
- Discuss examples of FDA's actions involving the evaluation of various types of follow-on and second-generation protein products within-product manufacturing changes.
- … will evolve as scientific and technological advances in product characterization and manufacturing continue to reduce some of the complexity and uncertainty that are inherent in the manufacturing of protein products.

J Woodcock et. al. Nature Reviews Drug Discovery. 2007: 6(6), 437-442.

Follow-on Protein Products continued

- 10 follow-on biological products discussed in the review article.
- Small scale studies or comparative data
- Clinical studies and immunogenicity studies for Growth hormone – Omnitrope
- Major manufacturing changes such as changes in cell line may require additional tests to assure S & E
- "A range of factors can influence the amount and type of data needed to establish similar or comparable clinical performance" – case-by-case basis to assure S & E.
- "As the analytical technology advances, the evaluation of structural similarity will become feasible for a wide range of products."

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Follow-on Protein Products

Evaluating protein products - Important factors include:

- Evidence of integrity and consistency of the manufacturing process
- Conformance of manufacturing standards to existing regulations (if any)
- Demonstration of product's consistency with appropriate reference standards or comparators including comparative PK and PD data.
- The extent to which the existing body of clinical data and experience with the approved product can be relied on.

J Woodcock et. al. Nature Reviews Drug Discovery. 2007: 6(6), 437-442.

FDA's Assessment of Follow-on Protein Products

- Non-recombinant protein products
  - Albumin
  - Standardized allergenic extracts
  - Mammalian testicular hyaluronidase
  - DigiFab
- Recombinant protein products
  - Glucagon
  - Fortical (salmon calcitonin nasal spray)
  - Omnitrope (somatropin)
  - Eprex (erythropoietin – alpha)
  - Recombivax HB (hepatitis B vaccine)
- Major manufacturing changes
  - Avonex (interferon beta1a)

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FDA's Assessment of Follow-on Protein Products

FDA's approval (case-by-case approach) was based on the knowledge available

- Robustness of manufacturing process
- Degree to which similarity could be assessed
- Extent to which mechanism of drug action is understood
- Existence of valid, mechanically related PD assays
- Comparative PK, immunogenicity and availability of clinical data
- Experience with original product.

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Science must drive …

- Product development
- Product characterization
- Manufacturing
- Need for clinical data
- Regulatory review
- Regulatory approval decisions

Follow-on Proteins
Biosimilar

- **Follow-on Protein, Biosimilar, that are Safe & Effective as the innovator can be developed with the state-of-art science technology if appropriate strategy is selected.**
- **These are copies of already marketed recombinant DNA derived protein products with same mode of action and same indication.**

Follow-on Proteins, Biosimilar products is a reality today!!!

References

http://www.fda.gov/cder/guidance/index.htm

http://www.emea.eu.net

Thank You