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
  – 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

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.

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.

Follow-on Protein Products

- 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.”

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.

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)

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.

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