Regulation of Protein Products Including Follow-On Biologics

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Legal Basis

- Federal Food, Drug and Cosmetic Act
  - Drugs include biological products
- 21CFR 312 Investigational drugs
- 21CFR 314 Drugs
- 21CFR 211 cGMP

Legal Basis

- Public Health Service Act, Section 351
  - Biological products only
  - Provides for the biologics license
  - Permits suspension and revocation of licenses
  - Review of the manufacturing facility is integral to review of the product
- 21CFR 312 Investigational drugs
- 21CFR 600 Biological products
- 21CFR 211 cGMP

Biological Product

- Virus
- Therapeutic serum
- Toxin
- Antitoxin
- Vaccine
- Blood, blood component or derivative
- Allergenic product
- Trivalent organic arsenic compound
- Analogous product

Examples

- Drug
  - Small molecule
  - Organ derived product
- Biological product
  - Vaccine
  - Plasma fractionation product

Product Evolution

- Recombinant technology
- Source material concerns
- Synthetic molecules
- Progress in health care

Recombinant Technology

- Monoclonal antibodies
  - Biologic, analogous to blood
- Antibody conjugates
  - Biologic if radiolabeled
  - Biologic if toxin conjugate
  - Drug if chemical conjugate
- Enzymes
  - Biologic
  - Drug if predicate is organ – derived

Source Material Concerns

- Emerging health issues
  - Recombinant growth hormone - Drug
- Supply concerns
  - Recombinant clotting factor - Biologic
  - Recombinant glucocerebrosidase - Drug

Guidance for Protein Products

- ICH technical documents
  - Q5A and Q5D for cell substrate / virus
  - ICH Q5B for the genetic construct
  - ICH Q5C for stability
  - ICH Q5E for comparability
  - ICH Q6B for specifications
- ICH general quality documents

- ICH clinical documents
- ICH multidisciplinary documents
- FDA Points to Consider
- FDA product / indication specific guidance documents

Impact

- Variable expectations
  - Product understanding
  - Clinical program
  - Type of application
  - Regulatory requirements
- Transfer of most of the therapeutic proteins from CBER to CDER
- Increasing pressure on FDA regarding follow-on protein products

Drug

- Innovator company files a 505(b)(1) application as a NDA under 21CFR 314
- Generic company files a 505(j) application as an ANDA under both 21CFR 314 and 21CFR 320
- A 'paper NDA' pathway is available under 505(b)(2), relying on data from clinical studies not performed by the applicant and for which no right of reference was given

Biologics

- While,
  - FD&C Act mechanisms are not available for biological products as these mechanisms require 'sameness'
  - PHS Act does not provide a mechanism for approving a follow-on biologic product
- Historically, FDA has approved several "follow-on" biological products on a case by case basis

Basis for approvals

- 'Similarity' rather than 'sameness'
- Clinical data were included
- Comparability data in some cases
- A finding of safety and effectiveness is not the same as a finding of substitutability

- Woodcock J *et al.* The FDA's assessment of follow-on protein products: a historical perspective. *Nature Reviews Drug Discovery.* 6, 437 - 442 (2007).

Factors

- Consistency of manufacturing process
- Conformance to existing regulations
- Consistency with reference standards or comparators, including comparative PK and PD data
- Ability to rely on existing clinical data for approved product

Non-recombinant Product

- Human Serum Albumin
  - Mechanism of action well understood
  - Manufacturing process well understood
  - Extensive clinical experience with established safety and efficacy
  - Conformance to manufacturing standards in the regulations
  - Small safety trials

Recombinant Products

- Glucagon
  - Replacement for pancreatic product
  - Extensive clinical experience
  - Clinical data
    - PK and PD
    - Safety and Immunogenicity
  - Thorough analytical package

- Epoetin alfa
  - Use of common MCB with tech transfer of manufacturing process
  - Right of cross-reference to clinical data, with reliance on both clinical and preclinical data
  - Manufacturing review and analytical package
  - PK / PD data
  - Similar clinical safety profile
  - However, formulation and presentation change in one of the two subsequent to approval appeared to correlate with increases in PRCA

- Omnitrope
  - Approved according to Section 505(b)(2)
  - Physicochemical data
  - Product-specific non-clinical pharm/tox data
  - PK, PD and bioavailability data
  - Direct clinical comparison to comparator product, including immunogenicity
  - Supportive clinical studies
  - Allows reliance on comparator safety and efficacy data and published literature
  - Not substitutable to any other growth hormone product

Impasse

- Pathway charted by Omnitrope is very extensive … but …
- Omnitrope is a drug and not subject to the provisions of Section 351 of the PHS Act
- Biologics Price Competition and Innovation Act of 2007 (BPCIA)

Provisions of BPCIA

- Compromise position
- Amends Section 351 of the PHS Act
- Provides a regulatory pathway for safe and interchangeable follow-on biological products
- Tacit acknowledgment that it may not be possible to dissociate the product from the process

Approval Process

- Applicant must demonstrate no clinically meaningful differences in safety, purity and potency between products
  - Analytical data
  - Animal testing
  - One or more clinical studies, unless FDA deems this not necessary

New clinical data requirement

- For a demonstration of safety and effectiveness, the amount and type will be influenced by the extent to which the follow-on product can be shown to be sufficiently similar to the comparator to rely on the safety and effectiveness of the comparator
- Influenced by clinical use of product, and the amount and type of clinical experience from the comparator and related products

- "Follow-on protein products: Statement of Janet Woodcock, MD, Deputy Commissioner, Chief Medical Officer, FDA before the Committee on oversight and government reform US House of Representatives, 26 March 2007. *FDA web site* [on line]. http://www.fda.gov/ola/2007/proteins32607.html (2007).

- For a designation of interchangeable, applicant must provide evidence that, in any given patient, the follow-on product yields the same clinical result as the comparator and that it presents no risk to safety or efficacy if the patient alternates or is switched between products

- FDA may, but is not required to, issue guidance documents with respect to standards and criteria that will be applied to follow-on products
- Applications may be submitted prior to issuance of any guidance documents

Status of BPCIA

- Approved by the Senate Health, Education, Labor and Pensions Committee
- Expected to be taken up by the House Energy and Commerce Subcommittee on Health in early 2008
- Could see approval by the end of the congressional session