US Regulatory Perspectives on Biologics Evaluation and Control

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Legal Basis

- Federal Food, Drug and Cosmetic Act
- Public Health Service Act
  - Section 351

Jurisdiction

- FD&C Act
  - Drugs
  - Devices
  - Biological products
- Public Health Service Act
  - Biological products

PHS Act

- Requires a biologics license
- Permits suspension and revocation of licenses
- Review of the manufacturing facility is integral to review of the product

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
- Device
  - Blood supply test kit
  - Antibody based cell sorter

Code of Federal Regulations

- 21CFR 312 Investigational drugs
- 21CFR 314 Drugs
- 21CFR 600 Biological products
- 21CFR 812 Investigational Devices
- 21CFR 814 Devices
- 21CFR 1271 Cells and Tissues
- 21CFR 211 cGMP
- 21CFR 820 Device Quality Systems

Product Evolution

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

Combination Product

- Two or more regulated components that are combined or mixed and produced as a single entity
- Two or more separate products packaged together into a single package or unit

Recombinant Technology

- Monoclonal antibodies
  - Biologic, analogous to blood
- Enzymes
  - Biologic
  - Drug if predicate is organ – derived

Synthetic

- Peptides
  - Drug
  - Biologic
- Nucleic acids
  - Drug

Source Material Concerns

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

Health Care

- Antibody conjugates
  - Biologic if radiolabeled
  - Biologic if toxin conjugate
  - Drug if chemical conjugate
- Paired treatments
  - Coated implants
  - Interferon and ribavarin

Product Jurisdiction

- 1990 amendment to FD&C Act
  - Concept of combination products
  - Clarification of product jurisdiction
- 1991 Intercenter Agreements
  - CDER/CBER
  - CDER/CDRH
  - CBER/CDRH

Intercenter Agreements

- Intended to clarify product review assignments
- For biological products, potential for inconsistencies
- Variable expectations
  - Product understanding
  - Clinical program
  - Type of application
  - Regulatory requirements

Governing regulations

- Investigational products
  - 21CFR 312 for Drugs and Biologics
  - 21CFR 812 for Devices
- Market applications
  - 21CFR 314 for Drugs
  - 21CFR 600 for Biologics
  - 21CFR 814 for Devices
- Quality
  - 21CFR 211 for Drugs and Biologics
  - 21CFR 820 for Devices

Current thinking

- Office of Combination Products
  - Central role in regulation
  - Decisions on product jurisdiction
- 2005 Final Rule
  - Defines Primary Mode of Action
  - Provides algorithm for assignment of lead center for product review

- CDER / CDRH and CBER / CDRH
  - Guidance to clarify distinction between drug and device (PMOA)
  - Additional guidance in areas not envisioned by original documents
- CBER / CDER
  - Account for transfer of therapeutic biological products
  - Clarify assignment of single entity products
  - Intention to rescind agreement as obsolete

Changing Paradigms

- Focused collaborations
  - Regulatory science
    - Improved manufacturing methodologies
    - Tools for effective drug development
    - Delivery systems
    - Contaminant detection systems
  - Medical science
    - Predicting safety and efficacy
    - Biomarkers
    - Clinical trial design
    - Data collection

- Quality systems and risk management
  - Harmonize pharmaceutical and device requirements
  - Incorporate advances in manufacturing science
  - Six system inspection model
  - Quality by design

Practicalities

- Today at FDA
  - Increasing responsibilities in all disciplines
  - Decreasing resources
  - Focused attention on specific items

- Process Validation
  - Greater understanding of process capabilities
  - Greater scrutiny of small scale studies as predictors of commercial scale performance
  - Variability in validation requirements
- Specifications
  - Data on which justifications are based

- Test methods
  - Formal study to identify stability indicating assays
  - Appropriateness of host cell protein assay reagents
  - Methods to assess immunogenicity

- Product comparability
  - Appropriateness of methods used
  - Correlation with clinical data
- Greater scrutiny of clinical data
  - Endpoints chosen
  - Measurements of success