Regulation of Biopharmaceuticals in the United States of America

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Overview

• FDA Organization
• Laws Relevant to Biotechnology Drugs for Humans
• Follow-on Biologics (Biosimilars)
• Complexity of Protein Pharmaceuticals
U.S. Food and Drug Administration

Center for Drug Evaluation and Research
- Synthetic Drugs
- Biotechnology Products

Center of Biologics Evaluation and Research
- Blood & Blood Products
- Vaccines
- Cellular, Tissue, and Gene Therapies
Center for Drug Evaluation and Research

Office of New Drugs
  • Clinical Trial Review
  • Six Review Offices

Office of Pharmaceutical Science
  • Product Quality Review
    • Office of Biotechnology Products
    • Office of New Drug Quality Assessment
    • Office of Generic Drugs
Laws for Human Drugs

**LAW**
- U.S. FOOD DRUG & COSMETIC ACT (1938)
- U.S. PUBLIC HEALTH SERVICE ACT (1944)

**PRODUCTS**
- “TRADITIONAL” DRUGS AND PROTEIN HORMONES
- BIOLOGICAL DRUG PRODUCTS
APPLICATIONS

LAW

U.S. FOOD DRUG & COSMETIC ACT

U.S. PUBLIC HEALTH SERVICE ACT

APPLICATION

NEW DRUG APPLICATION (NDA)

ABBREVIATED NDA (ANDA)

BIOLOGIC LICENSE APPLICATION (BLA)

ABBREVIATED BLA
Categorical Examples

**NDA**
- h-GROWTH HORMONE
- INSULIN
- CALCITONIN

**BLA**
- MONOCLONAL ANTIBODIES
- INTERFERONS
- INTERLEUKINS
- GROWTH FACTORS
What is a Follow-on Product?

A product for which a sponsor relies to some extent on the finding of safety and efficacy of an approved reference product.
What is a Follow-on Product?

Not a single answer…

• Product intended to be interchangeable with comparator product
  – High degree of similarity

• Product intended to be similar to comparator product
  – Similar, but not interchangeable
  – Improved (e.g., 2nd Generation Product)
Examples of Approved Follow-on Products

Approved under 505(b)(2):

• Hyaluronidase
• Glucagon
• Calcitonin
• Human Growth Hormone
Janet Woodcock’s Congressional Testimony

• Because of the variability and complexity of protein molecules…it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product.

• Therefore, the section 505 (j) generic drug approval pathway, which is predicated on a finding of the same active ingredient, will not ordinarily be available for protein products.
COMPLEXITY

- COMPLEXITY IS MULTIFACTORIAL
- INTRINSIC PRODUCT COMPLEXITY
  - SIZE
  - SHAPE
  - NUMBER OF SUBUNITS
  - POST-TRANSLATIONAL MODIFICATIONS

- HETEROGENEITY

- IMPURITIES & CONTAMINANTS
FUNCTIONAL COMPLEXITY

• MECHANISM OF ACTION
  – ANTAGONIST
  – AGONIST
  – ENZYMATIC ACTIVITY
  – MULTIPLE FUNCTIONS

• CORRELATIONS TO SAFETY & EFFICACY

• MULTI-INDICATION PRODUCTS
PRODUCT AND MANUFACTURING CHALLENGES

- COMPLEXITY OF COMPARATOR
  - STRUCTURAL
  - FORMULATION
  - BIOACTIVITY

- MANUFACTURING PROCESS DEVELOPMENT
  - ‘REVERSE ENGINEERING’

- AVAILABILITY OF ANALYTICAL TECHNOLOGIES
Regulatory Path vs. Complexity

![Graph showing the number of products across different molecular weight ranges for NDA, BLA, and ANDA.]
Examples of Approved Follow-on Products

Approved under 505(b)(2):

- Hyaluronidase
- Glucagon
- Calcitonin
- Human Growth Hormone
Regulatory Path vs. Complexity

![Bar Chart]

- **Number of Products**
- **Molecular Weight (kiloDaltons)**: <3, <10, <30, <100, <300

**Legend**:
- NDA
- BLA
- ANDA

505(b)(2)
PK/PD COMPLEXITIES

PK:
• THE USUAL ‘TARGET’ DEFINING EQUIVALENT PK IS NOT VERY PRECISE
• SERUM LEVELS MAY NOT RELATE TO CLINICAL ACTIVITY

PD:
• MEANINGFUL INTERPRETATION OF PD STUDIES REQUIRES AN UNDERSTANDING OF THE CLINICALLY RELEVANT MECHANISM OF ACTION OF THE PRODUCT.
Waiting for new laws...

Four laws have been written, but, until one is passed, we cannot approve biosimilar biological products in the USA.
FDA Policy

• Science-based
  – Avoid precepts (i.e., what can’t be done.)
  – Data-driven
  – Flexible to changing technologies

• Focus on public health
  – Patient safety
  – Therapeutic efficacy
  – Drug availability
Thank You
For Additional Information

CDER –
http://www.fda.gov/cder/regulatory/applications/default.htm

CBER –
http://www.fda.gov/cber/guidelines.htm