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“The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.”

“The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.”

http://www.fda.gov/opacom/morechoices/mission.html
FDA History

- Biologics Control Act (1902)
- Pure Food and Drug Act (1906)
- Food, Drug and Cosmetic Act (1938)
- Food, Drug and Cosmetic Act Amendments (1962)
- Prescription Drug User Fee Act (PDUFA 1992)
- Food and Drug Modernization Act (PDUFA II 1997)
- PDUFA Amendments (PDUFA III 2002)
- Food & Drug Administration Amendments Act (FDAAA 2007)
Definitions

**Biological Product:** defined under Public Health Service Act, Section 351, as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product

- Products derived from viruses, bacteria or blood are biological products

- Products made from cells – including those derived from biotechnology methods – are considered biological products
Biologics License Application (BLA)
- Applicant information
- Product/Manufacturing information
- Pre-clinical studies
- Clinical studies
- Labeling

Public Health Service (PHS) Act
Drugs

New Drug Application (NDA)

➡ Safe and Effective for its proposed use
➡ Benefits outweigh risks
➡ Drug labeling appropriate
➡ Manufacturing methods and controls adequate to preserve drug’s identity, strength, quality and purity
➡ Drugs are approved under Section 505 of the Food, Drug & Cosmetic (FD&C) Act
Section 505(b)(2)

- Allows applicants to create innovative medicines using currently available products without performing a full complement of safety and efficacy studies.
- Permits an applicant to base approval of a drug on information from published scientific literature or on the “finding” that FDA has found a similar drug to be safe and effective.
- Applicant must demonstrate that reliance on previous safety and efficacy data is justifiable and must submit whatever additional nonclinical and clinical data are necessary to establish that the proposed product is safe and effective.
Section 505(j) (ANDA)

- Generic drug must contain the same active ingredient as the innovator product
- Drug must be bioequivalent to the innovator product
- Must have the same dosage form, strength, route of administration, labeling and conditions of use
- Generic manufacturer can rely on FDA’s finding of safety and efficacy for approved innovator product
- Most generic drugs approved under Section 505(j) are therapeutically equivalent to the approved innovator drug
Hatch-Waxman (1984)

- This law covered only drugs approved under section 505 of the FD&C Act.
- It did not cover drugs at that time approved under sections 506 (e.g., insulins) or 507 (e.g., antibiotics) of the FD&C Act.
- It did not cover biologic products approved as BLAs under the PHS Act.
- WHY?
Bioequivalence: FDA Definitions

**Bioequivalence**

- Drug products are considered bioequivalent if they are pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions.
- May be demonstrated through *in vivo* or *in vitro* test methods, comparative clinical trials, or pharmacodynamic studies.

Bioequivalence: FDA Definitions

Bioequivalence

- Product A is bioequivalent to the reference drug; its 90% confidence interval of the AUC falls within 80% to 125% of the reference drug.
- Product B is not bioequivalent to the reference drug; its 90% confidence interval of the AUC falls outside of 80% to 125% of the reference drug.

Drug vs. Biologic Products

- Some natural source biological products and later recombinant forms have been regulated as drugs under the FD&C Act (e.g., hyaluronidase, human growth hormone).

- Certain biological recombinant proteins, such as cytokines, monoclonal antibodies, and clotting factors are regulated under the PHS Act.

- Therapeutic proteins (e.g., monoclonal antibodies, inborn error of metabolism replacement enzymes) regulated by CBER were transferred in 2003 to CDER, but with no change to the regulatory pathway.
What can be a Biological Product?

Proteins, Lipids, Carbohydrates, Combinations

- “Protein only” approach provides the best case for a Well Characterized Product
- Complex Carbohydrate mixtures are more difficult to characterize
- Most difficult component of “glycoprotein” to characterize is the carbohydrate
Antibody formation can result in:
- loss of efficacy (e.g., neutralizing antibodies)
- adverse events (e.g., anaphylaxis), or
- no clinical symptoms at all

The presence or absence of antibodies can also be related to the quality of the in vitro diagnostic assay used to measure these antibodies.
Is Omnitrope a generic biologic?

- No. It is a “follow-on protein product” (FOPP). The product is not rated as therapeutically equivalent to (and therefore not substitutable) for any approved hGH product.

- FOPP refers to protein and peptide products sufficiently similar to a product already approved to permit references to the approved product data.
Drugs that are “Biologic-Like”

- As many as 40 - 50 products fall within this “biologic-like” category

- FDA currently has authority to approve generic versions of “biologic-like” products under the 505(j) pathway if they were approved as drugs under NDA by FDA
Enoxaparin application was approved by FDA as a Drug under NDA, since the Unfractionated Heparins (UFHs) were regulated as Drugs under NDA (New Drug Application) and not Biologics under BLA (Biologic License Application)

Enoxaparin is regulated as a biologic product by EMEA
Each LMWH manufacturing process affects different structural features on the heparin macromolecule.

Enoxaparin has smaller polysaccharid chains and a molecular weight that is 1/3 the average molecular weight of UFH.
Potential Regulatory Concerns

Current standards of Bioequivalence do not ensure Therapeutic Equivalence of products containing Complex Mixtures

“…in patients with acute coronary syndromes without ST-segment elevation, both enoxaparin and UFH produced, starting from the third hour marked and similar reduction of both thrombin generation and activation, which persisted for three days of observation. The greater clinical efficacy of enoxaparin than of UFH in preventing acute cardiac ischemic events could be explained by other unknown mechanisms, such as a different interaction with the platelet function, that deserves further investigation…”

Salvioni A et al; Thromb Haemost 2001; 86: 991–4
Quiz: Which product is safe?

# 1

# 2
Celebrex

# 2
Clinical Trial Data

- The differences in the rates of cardiovascular events, including “Heart Attacks”, were only observed after extensive testing in clinical trials.
- The clinical data led to the withdrawal of VIOXX from the U.S. market in 2004.
- Structural differences between the COX-2 products did not predict the observed clinical differences.
Key Issues for Legislation

- Scope of reference products
- Approval standard
- Data requirements
- FDA approval pathway
- Interchangeability (Orange Book)
- Naming
- Data Exclusivity
- Patent provisions
- Post-Market Surveillance
Update the FDA Regulatory System

When creating a new pathway for Follow-On Biologics under PHS Act, it is an opportunity to make corrections to the current system where certain products with biological-like properties are regulated under the FD&C Act, as well as making appropriate changes to the post-market surveillance system for adequate patient safety monitoring of those products approved through this new abbreviated regulatory pathway.
“Regulation of Follow-on Biologics: Ensuring Quality and Patient Safety”

What can the U.S. learn from the rest of the world regarding the safe regulation of Follow-on Biologics?