

Biosimilars: Are We There Yet?

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OUTLINE

WORKING DEFINITIONS

POLICY

CURRENT ACTIVITIES

What is a Follow-on Product?

Products intended to be sufficiently similar to an approved product to permit the applicant to rely on certain existing scientific knowledge about the safety and efficacy of an approved reference product.

What is a Follow-on Product?

Not a single answer...

- Product intended to be interchangeable with the reference product
- Product intended to be similar to the reference product
 - An alternative therapeutic

FDA Policy

- Focus on public health
 - Patient safety
 - Therapeutic efficacy
 - Drug availability
- Science-based
 - Avoid precepts (i.e., what can't be done.)
 - Data-driven
 - Flexible to changing technologies

Regulatory Paths

STATUTE

U.S. FOOD DRUG &
COSMETIC ACT



U.S. PUBLIC
HEALTH SERVICE
ACT



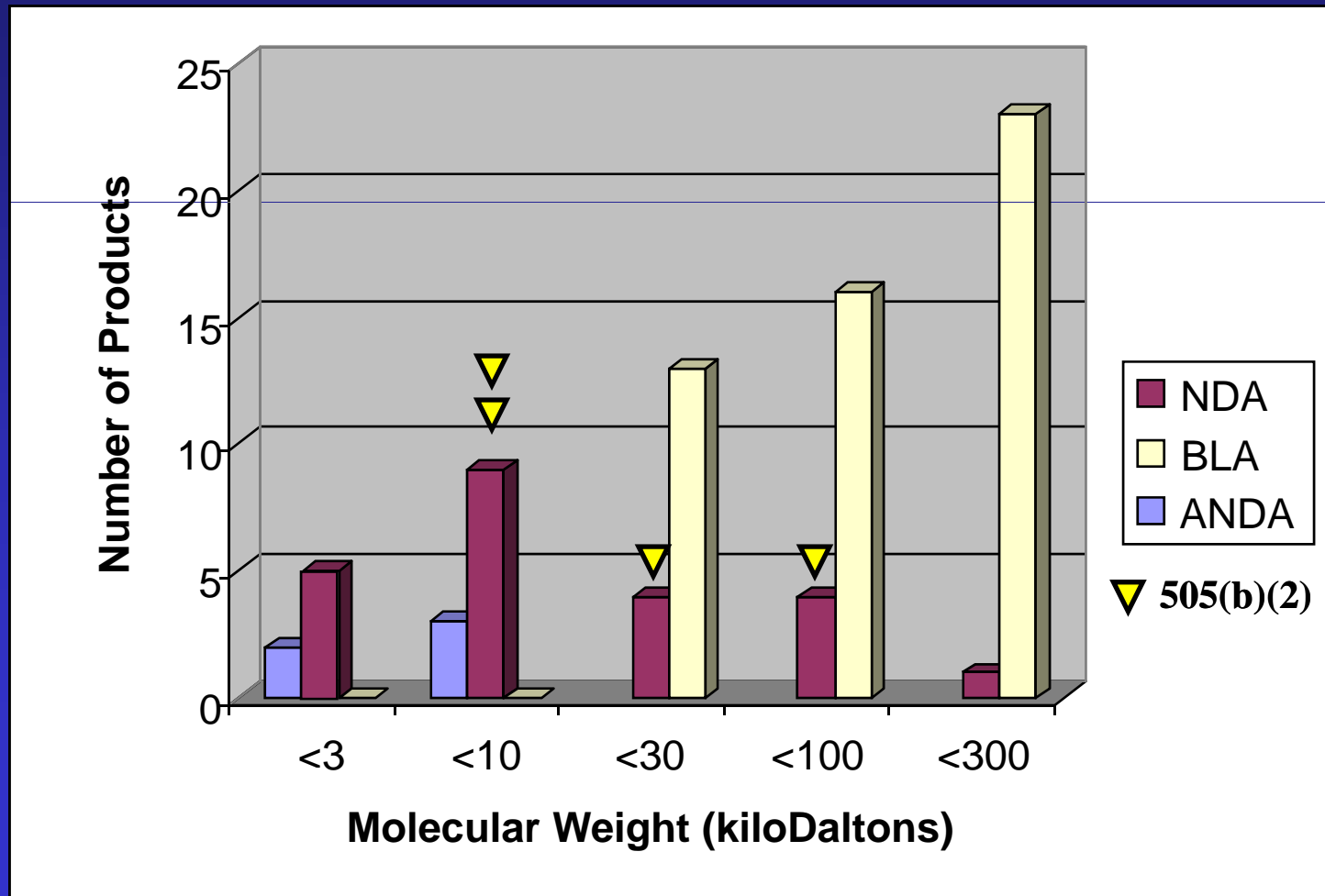
APPLICATION

NEW DRUG
APPLICATION (NDA)
AND 505(b)(2) NDA
ABBREVIATED NDA
(ANDA)

BIOLOGIC LICENSE
APPLICATION (BLA)

ABBREVIATED
BLA

Regulatory Path vs. Complexity



Current Activities

- FDA's Assessment of Follow-On Protein Products—An Historical Perspective on Scientific Evaluations – Nature Reviews April 13th, 2007
- Guidance for industry on scientific considerations in **demonstrating the safety and effectiveness** of follow-on protein products (under development)
- Guidance for industry on **CMC issues** for follow-on protein products (under development)
- Guidance for industry on **immunogenicity** studies (under development)

Proposed Legislation

PHS Act -- Section 351(k)

- **Access to Life-saving Medicines Act of 2007**
 - H.R. 1038 & S. 623
 - Waxman (D), Schumer (D), + 28 others
 - In Health, Education, Labor, & Pensions (HELP) Committee
- **Affordable Biologics for Consumers Act of 2007**
 - S. 1505
 - Gregg (R), Burr (R), Coburn (R)
 - In HELP Committee
- **Biologics Price Competition and Innovation Act of 2007**
 - S. 1695
 - Kennedy (D), Enzi (R), Clinton (D), Schumer (D), Hatch (R)
 - In HELP Committee

Relevant Questions to Consider

Product Quality Attributes

- What quality attributes are relevant to the product's use and function?
 - API: Physical, Structural, Functional,
 - Components: Excipients; Container-closure; Delivery system
- What are the acceptable ranges for these attributes?

Justification of Specifications

- What is the comparator product?
 - Specify the brand-name product.
- What are the proposed specifications?
- What are the justifications for the proposed specifications?
 - Analysis of comparator product
 - Other relevant information
 - Literature
 - Other products
 - Clinical data

Manufacturing Process

- What is the expression system?
- What are the raw materials?
- What are the purification steps?
- What is the composition of the bulk drug substance?
- How is the product formulated, filled, and finished?

- How is quality controlled throughout the manufacturing process?
 - Assess risks to quality
 - Describe risk mitigation/managment

Stability & Storage Conditions

- What are the impacts of environmental conditions?
 - Temperature
 - Humidity
 - Light
 - Agitation
- What are the recommended storage conditions?
- How long is the shelf-life?

Clinical Studies to Fill the Gaps

- What uncertainties regarding the correlation of clinical effects to CMC information remain?
- How are these uncertainties resolved?
 - PK & PD studies
 - Immunogenicity studies
 - Safety and Efficacy studies?

Omnitrope (Somatropin)

Approved in 2006 under Section 505(b)(2) of FD&C Act

- Physicochemical testing that established highly similar structure to Genotropin
- New non-clinical pharmacology and toxicology data specific to Omnitrope
- Pharmacokinetic, pharmacodynamic, and comparative bioavailability data
- Clinical efficacy and safety data from comparative controlled trials and from long-term trials with Omnitrope
- Vast clinical experience and a wealth of published literature concerning the clinical effects (safety and effectiveness) of human growth hormone

Biosimilars: Are There Yet?

- Scientifically:
 - Yes, for some products.
 - The complexity of the protein and knowledge of its structure-function relationships determine the types of information needed to establish similarity.
- Legally:
 - Yes, for NDA-approved products.
 - Not yet for BLA-approved products.

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