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

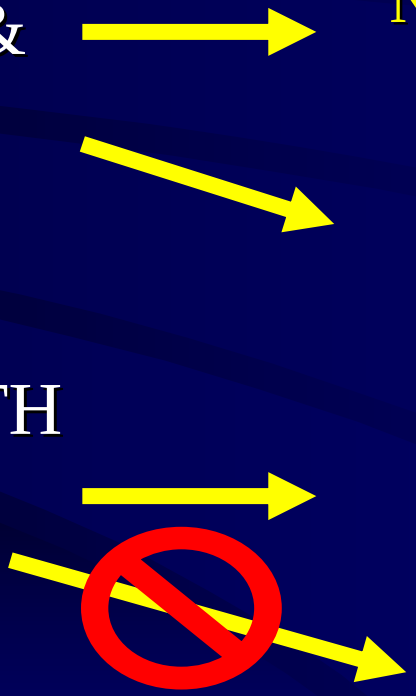
- Product Quality Review
  - Office of Biotechnology Products
  - Office of New Drug Quality Assessment
  - Office of Generic Drugs

Laws for Human Drugs

LAW	PRODUCTS
U.S. FOOD DRUG & COSMETIC ACT (1938) →	"TRADITIONAL" DRUGS AND PROTEIN HORMONES
U.S. PUBLIC HEALTH SERVICE ACT (1944) →	BIOLOGICAL DRUG PRODUCTS

APPLICATIONS

LAW	APPLICATION
U.S. FOOD DRUG & COSMETIC ACT	NEW DRUG APPLICATION (NDA)
	ABBREVIATED NDA (ANDA)
U.S. PUBLIC HEALTH SERVICE ACT	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

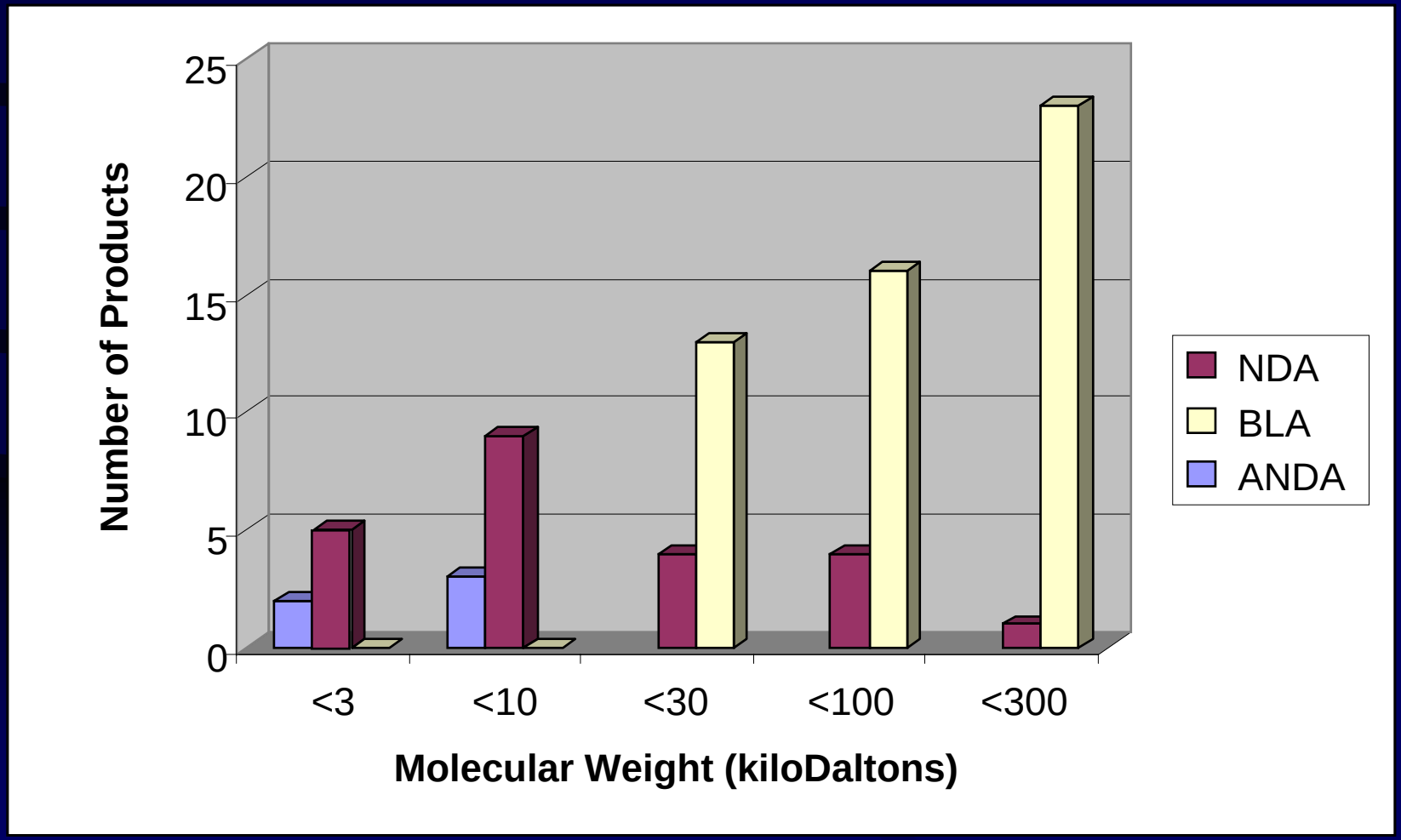
FUNCTIONAL COMPLEXITY

- 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



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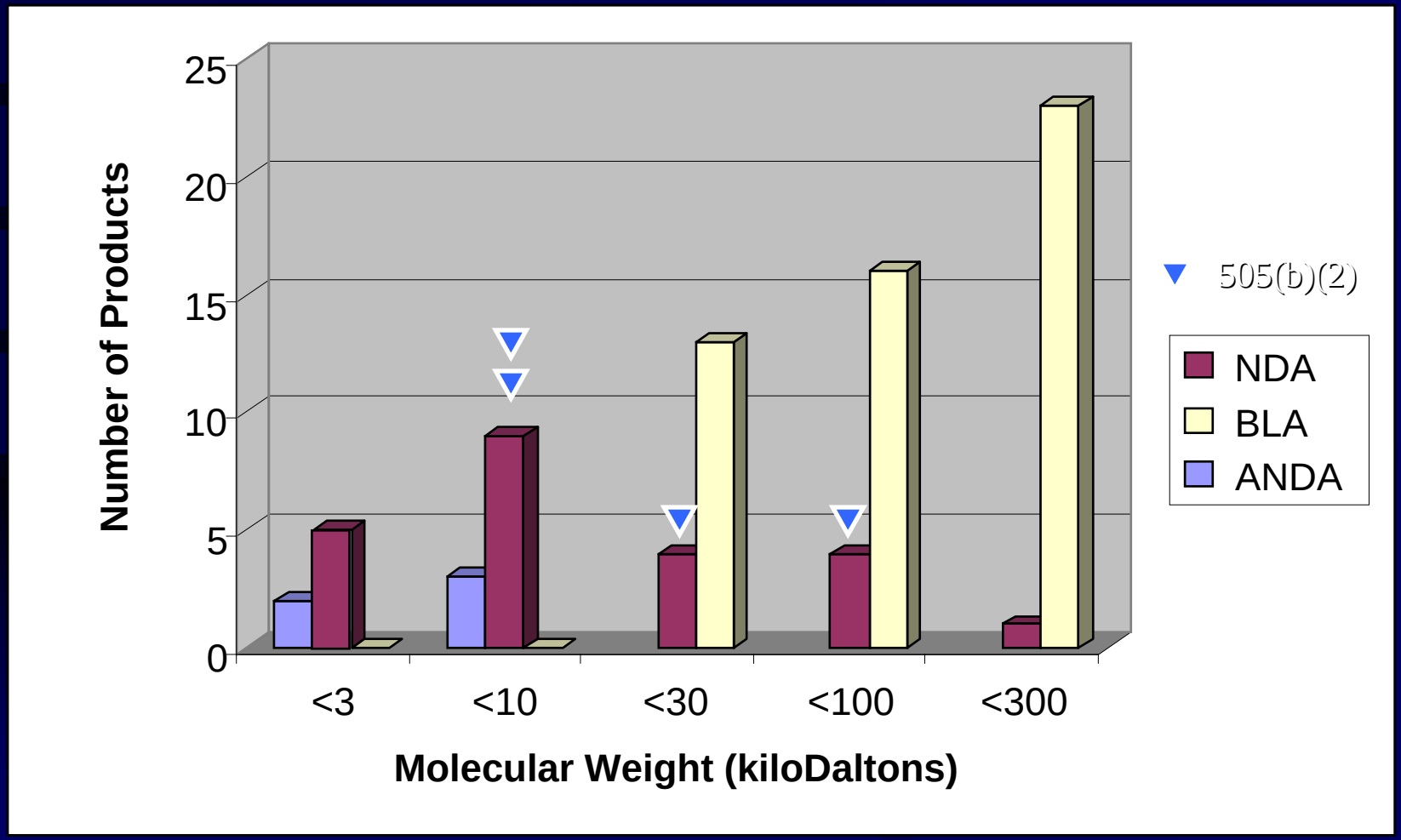


PK/PD COMPLEXITIES

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.

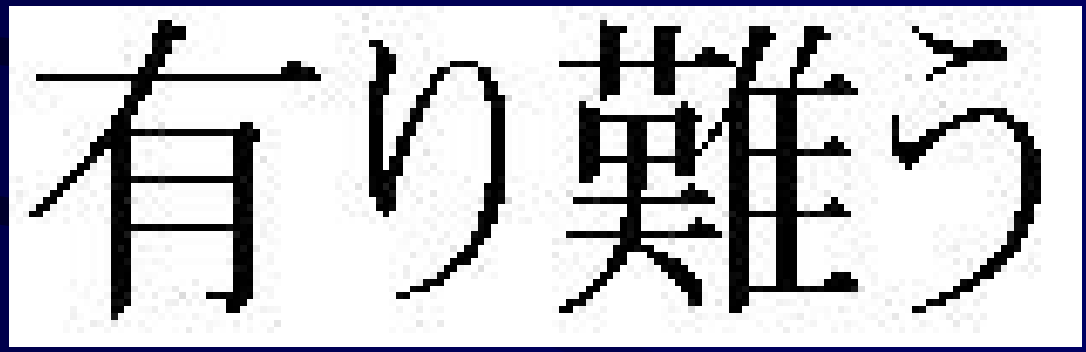
Waiting for new laws…

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