

SK 9/24/07

FDA ~~Policy~~ on Follow On Biologics

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Steven Kozlowski, M.D.

Director

Office of Biotechnology Products/OPS/CDER

FDA Considerations on Follow on Biologics

Policy is under development

Focus of talk will be on proteins

Overview

- Regulatory Statutes
- Challenges & Similarity Analysis
- Non-clinical & Clinical Studies
- Examples

Proteins: Drugs or Biologics

- Natural source proteins: drugs or biologics
- Late 1970s and early 1980s, recombinant proteins & monoclonal antibodies began to be developed
 - Hormones (e.g. insulin and human growth hormone)
 - Drugs/CDER/FD&C Act
 - Antibodies, cytokines, growth factors, immunomodulators & clotting factors, etc.
 - Biologics/CBER/PHS Act
 - in 2003, many transferred to CDER under the PHS Act
- Some proteins are licensed under the PHS Act, and some are approved under the FD&C Act.

Regulatory Statutes

- PHS Act § 351
 - ...approve...on the basis...that ...the subject of the application is safe, pure and potent...
- FD&C Act
 - 505(b)(1) ...full reports of investigations of safety and efficacy [applicant right of ref]
 - 505(b)(2) ...full reports of investigations of safety and efficacy [some without right of ref]
 - 505(j) ...a duplicate of a previously approved drug

FD&C Generics

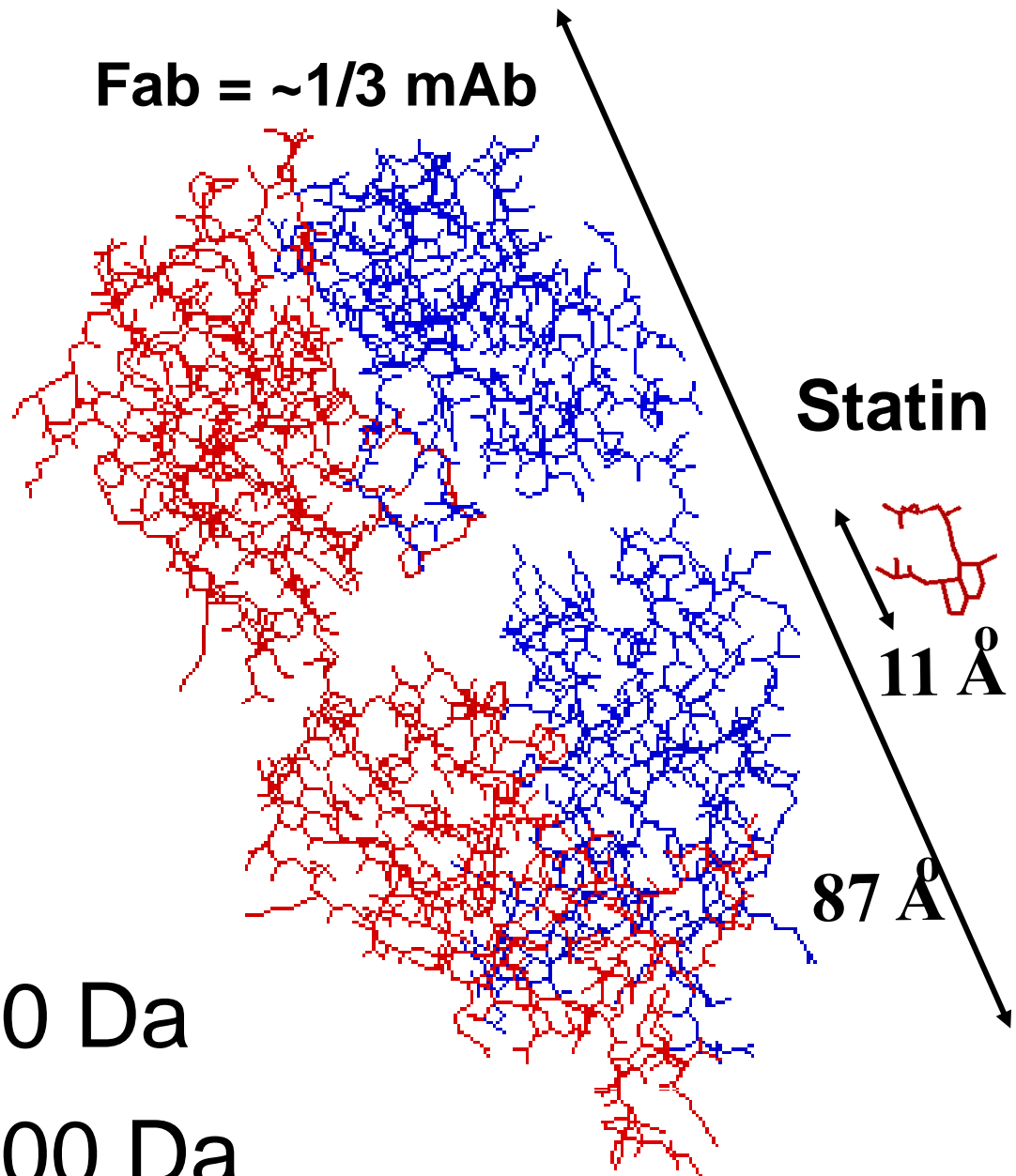
- Pharmaceutical Equivalence (PE): same active ingredients, dosage form, route, strength
- Bioequivalence (BE): same rate & extent of absorbance & availability at site
- Therapeutic Equivalence (TE) = PE + BE
- Rule for 505(j) need PE + BE without need for clinical or pre-clinical studies beyond BE
- Substitutability needs Therapeutic Equivalence
- Substitutability may also occur under 505(b)(2)

Overview

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Structure of Proteins

Fab = ~1/3 mAb



Statin MW ~400 Da

Fab MW ~50,000 Da

PDB 2IG2, 1HW8

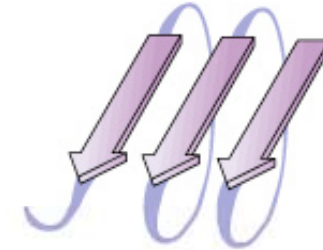
Protein Folding

–Ala–Glu–Val–Thr–Asp–Pro–Gly–

Primary



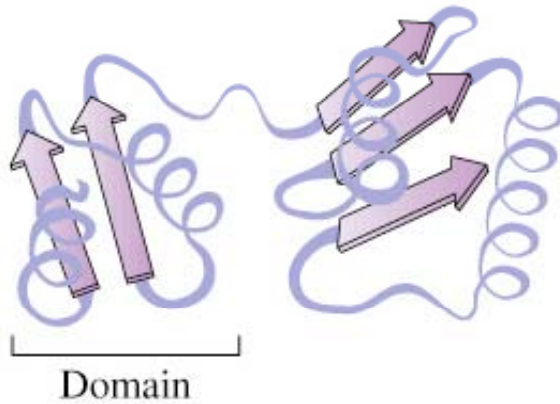
α helix



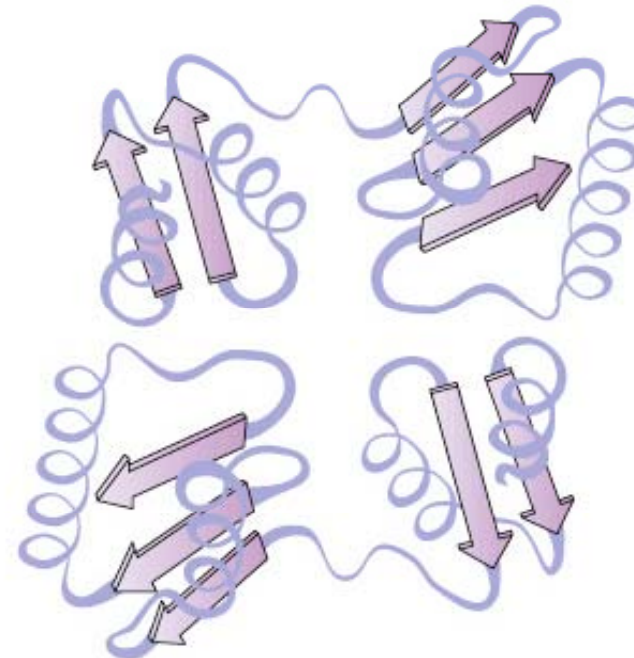
β sheet

Secondary

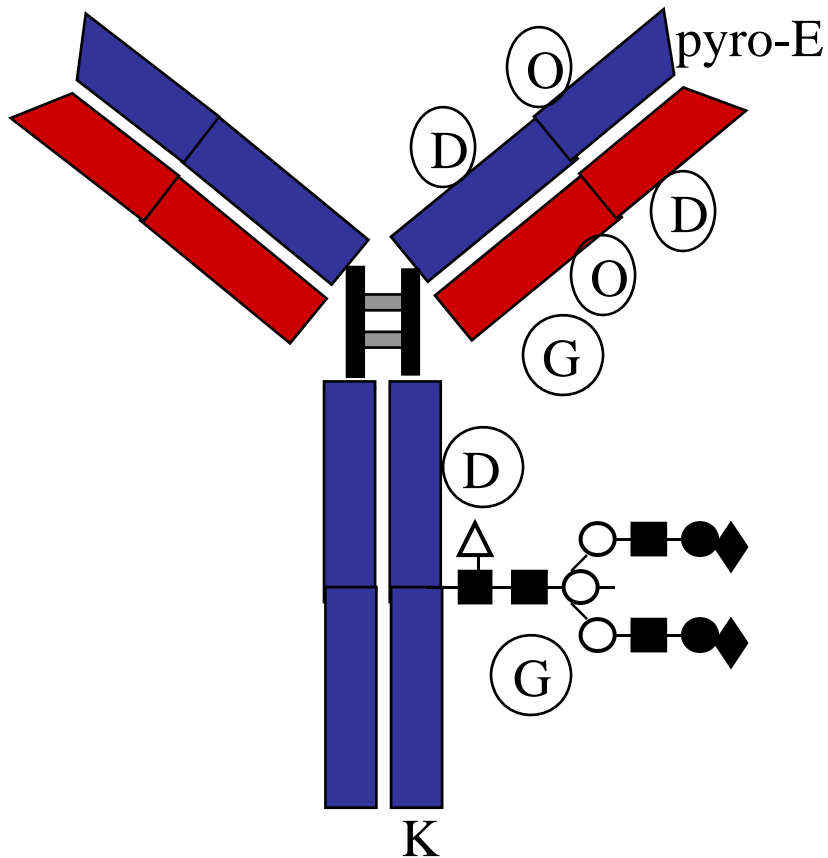
Tertiary



Quaternary



Modifications



- Pyro-Glu (2)
- Deamidation (3 x 2)
- Methionine oxidation (2 x 2)
- Glycation (2 x 2)
- High mannose, G0, G1, G1, G2 (5)
- Sialylation (5)
- C-term Lys (2)

Janet Woodcock

FOPP congressional testimony

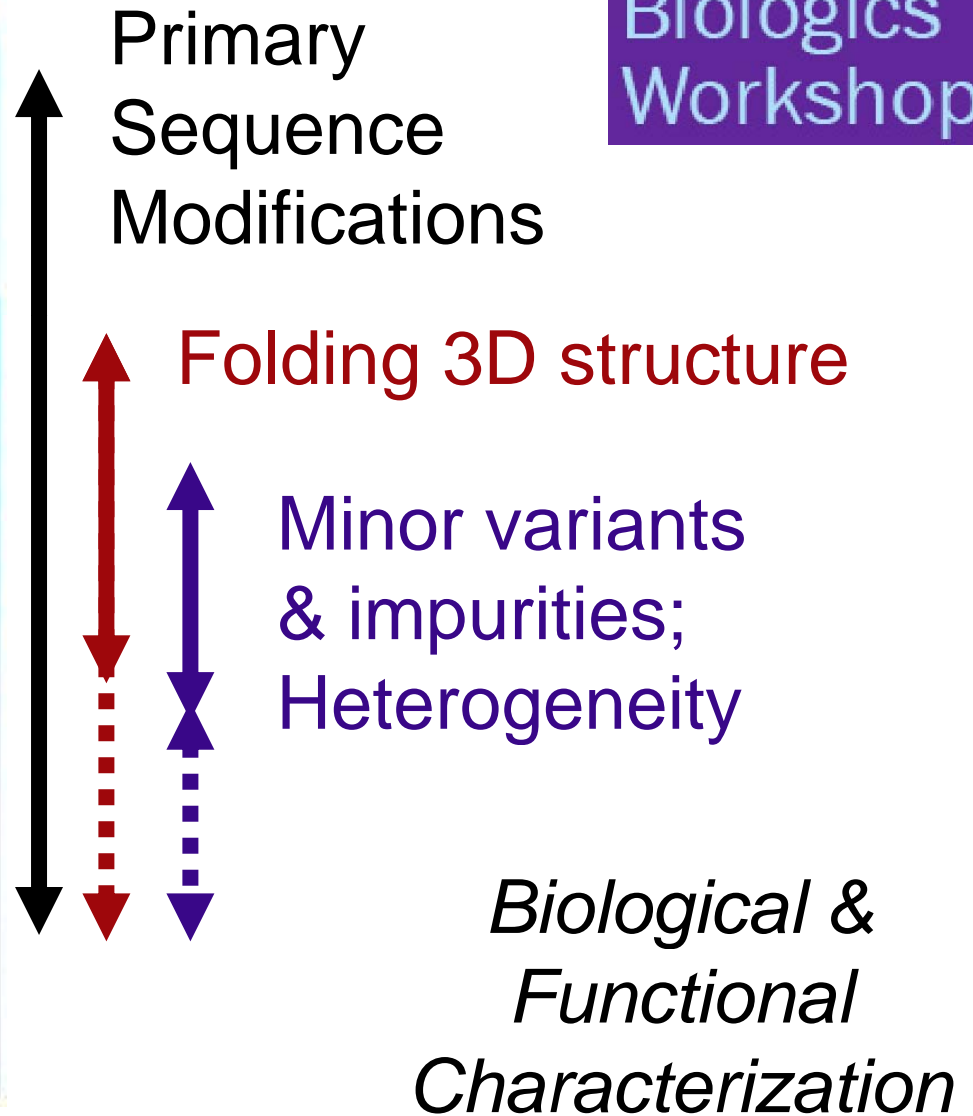
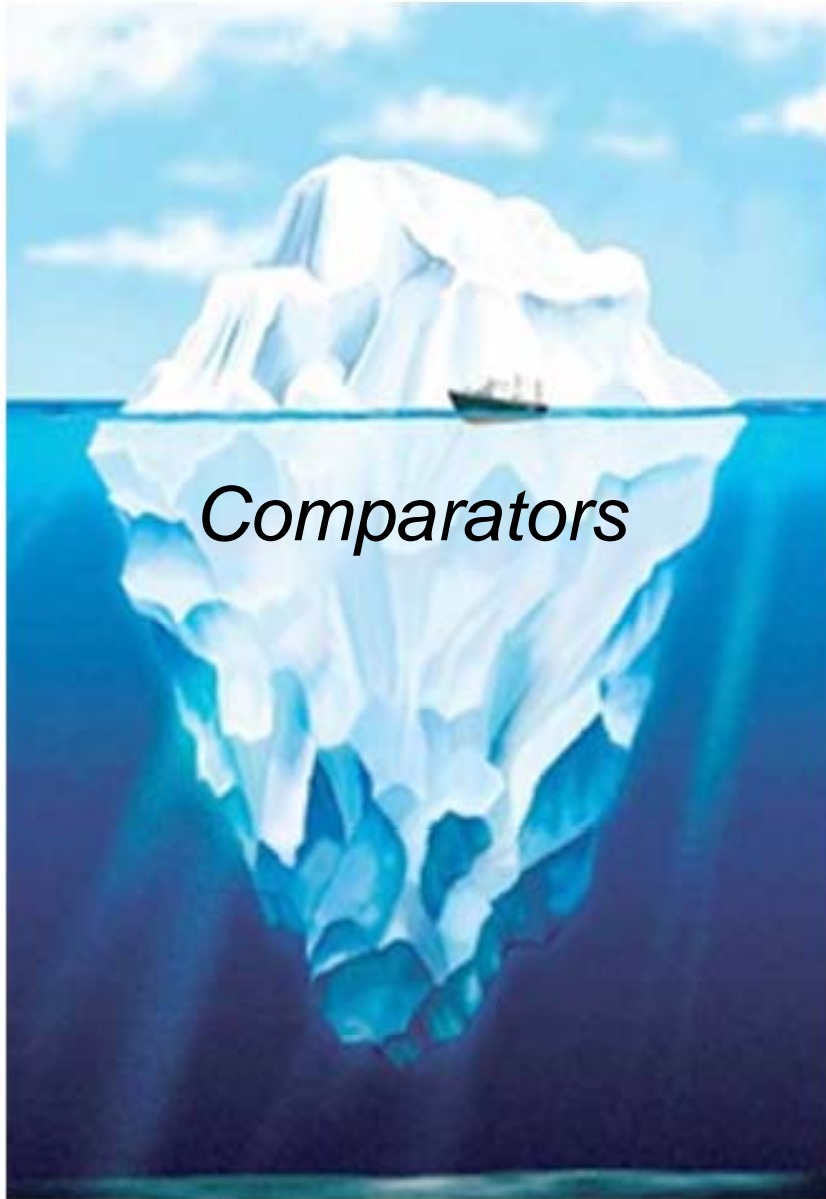
- Because of the variability and complexity of protein molecules...it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product.
- Therefore, the section 505 (j) generic drug approval pathway, which is predicated on a finding of the same active ingredient, will not ordinarily be available for protein products.

EMA Guideline on Similar Biological Medicinal Products

Effective October 2005

- Due to complexity of biological/biotechnology products the generic approach is scientifically not appropriate.
- Biosimilar approach
 - more likely highly purified products
 - more difficult...products...difficult to characterize
- Subtle differences
 - to support pharmacovigilance...specific product... clearly identified

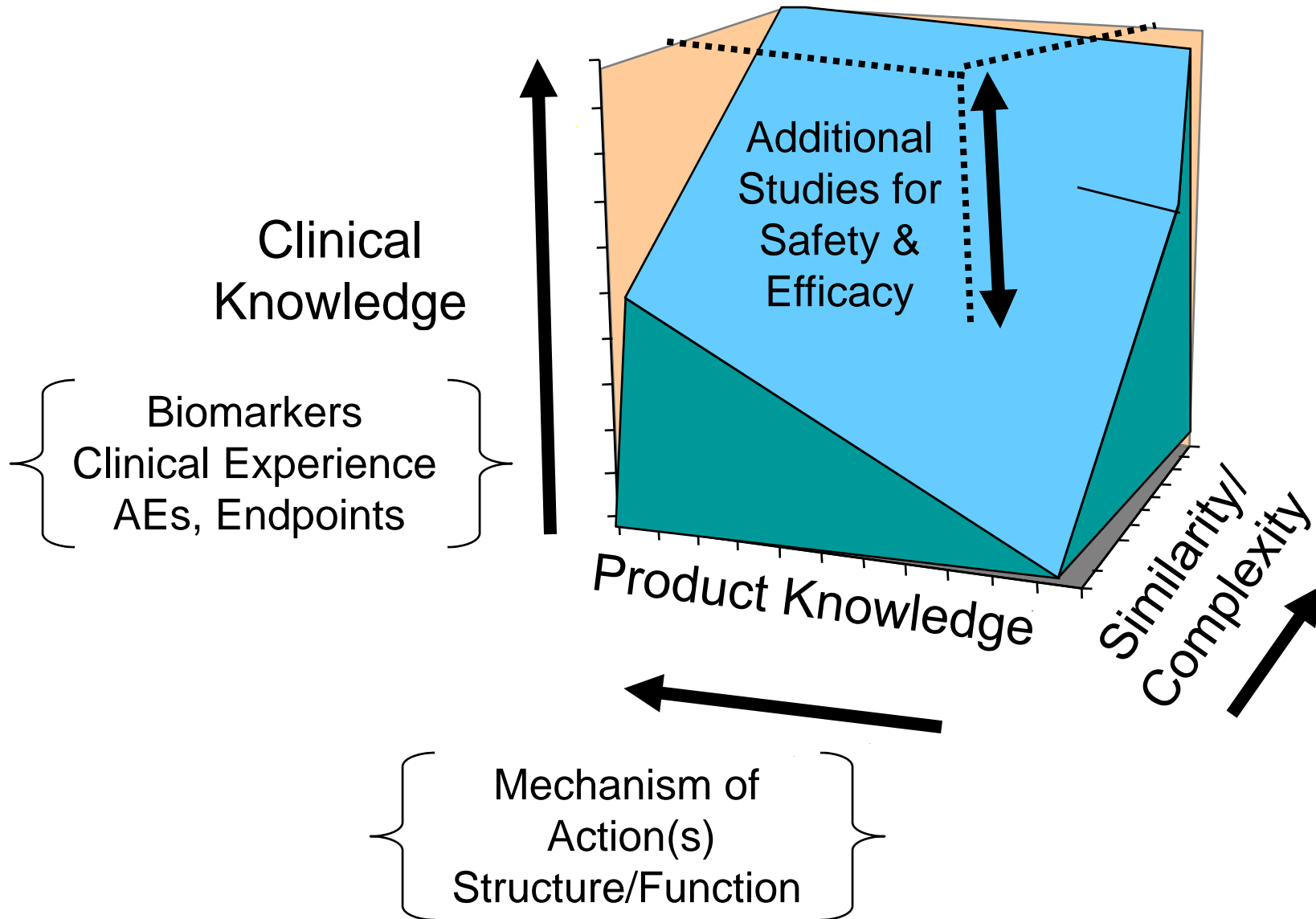
Protein Characterization



Overview

- Regulatory Statutes
- Challenges & Analysis of Similarity
- **Non-clinical & Clinical Studies**
- Examples

Additional Studies



Many Possible Outcomes

- Modified efficacy
 - Alternative endpoints
 - Surrogates
 - Biomarkers
 - Smaller numbers
- Modified safety
 - Targeted for expected AEs
 - Smaller numbers
 - Limited toxicology
- Indication(s)
 - Mechanism(s)
- PK/PD Studies
 - Bioequivalence
 - Clearance

Immunogenicity

JW congressional testimony FOPPs

- An immune response to a therapeutic protein can range from... not clinically significant antibodies, to an... impact on safety or effectiveness [PK].
 - "Neutralizing antibody" responses can decrease the clinical effect...
 - Adverse safety events from an immune response could include
 - hypersensitivity reactions...
 - cross-reaction with an endogenous... protein
- The ability to predict immunogenicity of a protein product... is extremely limited.
- ...some degree of clinical assessment of a new product's immunogenic potential will ordinarily be needed.
- ... a determination that the follow-on protein product would be substitutable
 - ... repeated switches from the follow-on product to the referenced product (and vice versa) would have no negative effect

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- **Examples**

Examples

JW congressional testimony FOPPs

- ...the interest in development of follow-on protein products pertains to versions of follow-on products manufactured using biotechnology. [FD&C Act or PHS Act]
- ...FDA has considerable experience with reviewing some protein products

*The FDA's assessment of follow-on protein products:
a historical perspective*

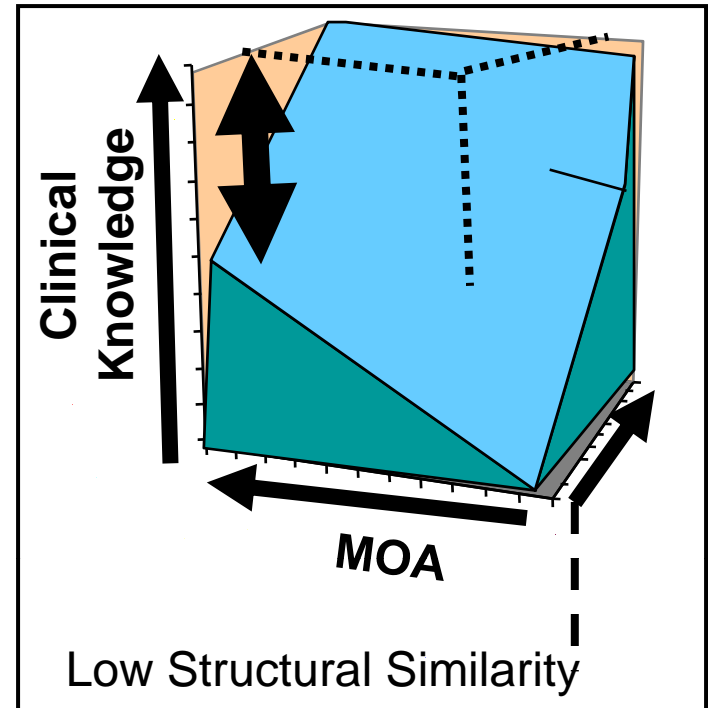
Janet Woodcock et al. 2007

Nature Review Drug Discovery

Structural Differences

(within manufacturer)

- Recombivax HB
 - Structure:
 - recombinant versus natural source
 - differences in
 - lipid incorporation
 - glycosylation
 - and disulfide bonds
 - MOA:
 - antibody to HBsAg correlates with protection
 - Clinical Knowledge:
 - experience with 2 large clinical trials showing protection at defined antibody titers
 - Gaps Addressed:
 - Large trial for antibody titer
 - Smaller trial showing prevention in maternal-fetal transmission



Comparability

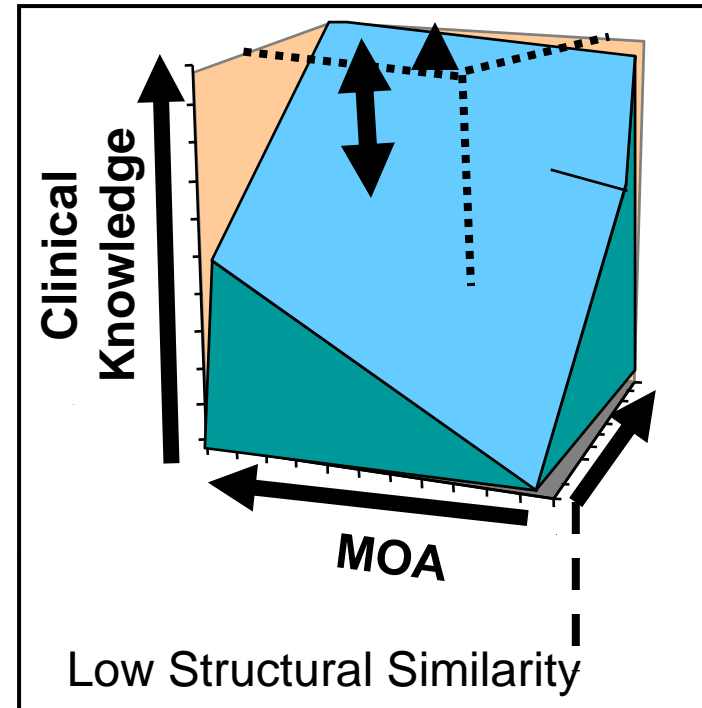
(within manufacturer)

- Many changes do not require clinical studies

- Some do require studies

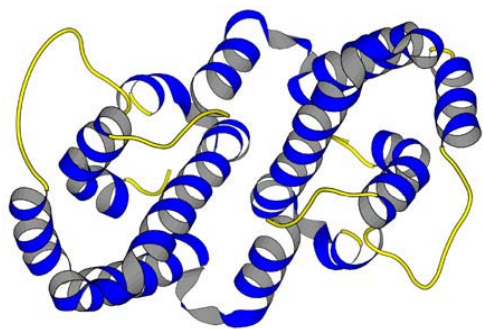
- Cases of at least some access to manufacturer data

- Eprex/Epogen
 - Immunogenicity based AE
 - PRCA
- Bioferon/Avonex
 - Decreased immunogenicity



Biotechnology Follow On

- Omnitrope (Somatropin) 505(b)(2) 2006
 - 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
 - Not substitutable



Differing Omnitrope Perspectives

**EU
Approves
Epo
Biosimilar**

EMA Approval

NATURE REVIEWS | DRUG DISCOVERY

First generic biologics finally approved

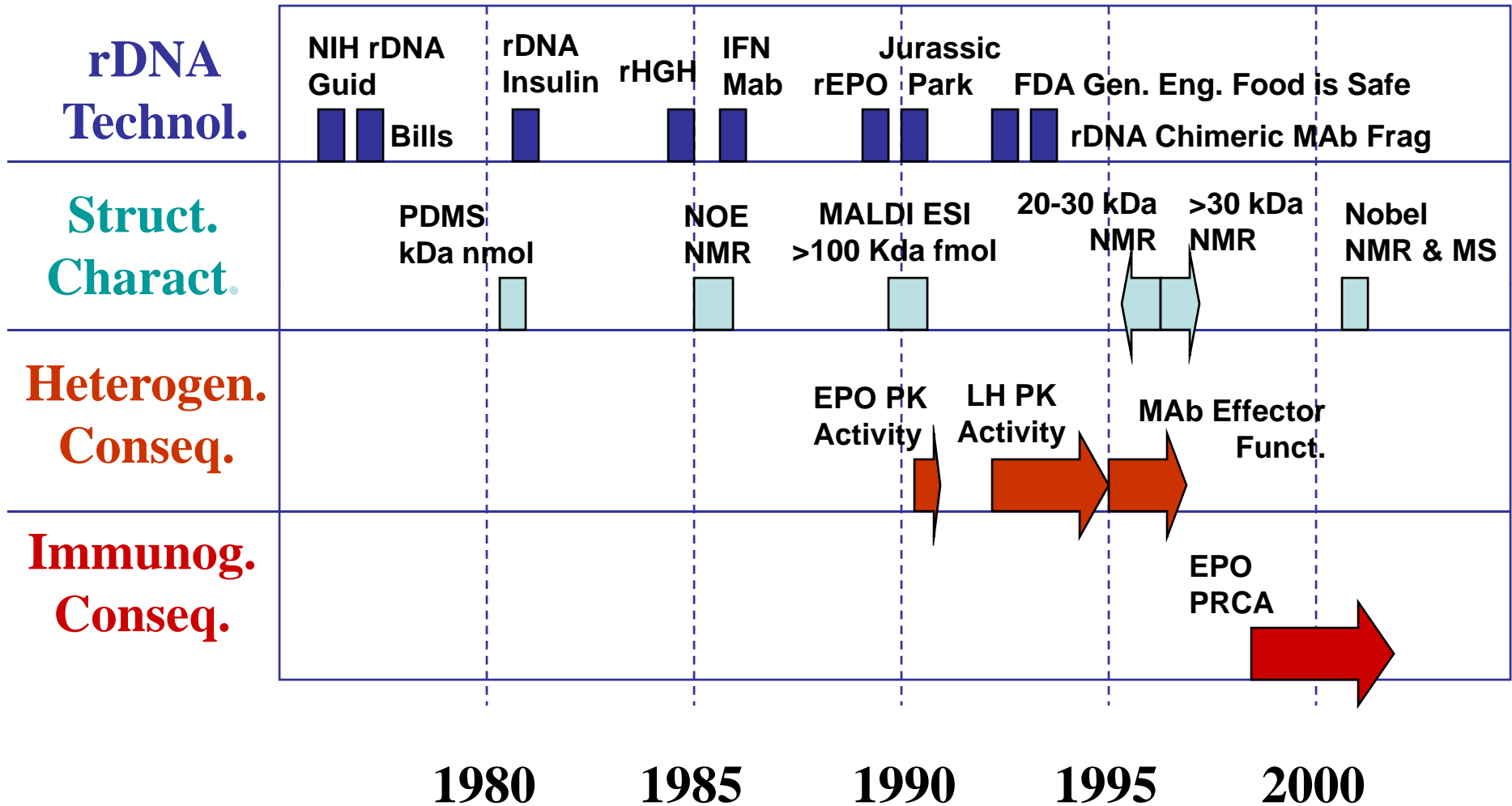
Decision ends years of fierce debate on follow-on protein products,
but won't lead to an opening of the approval floodgates

FDA Approval

in-Pharma
Technologist.com

Sandoz approval could open the floodgates for biosimilars in US

Historical Context



Credits

- Emily Shacter
- Barry Cherney
- Keith Webber
- Chris Joneckis
- Elizabeth Shores
- Frank Holcomb
- Patrick Swann
- Amy Rosenberg
- Kathleen Clouse
- Dena Hixon
- Ajaz Hussain
- Helen Winkle
- Paul Rudolf
- Janet Woodcock
- Etc.