

## Update of Complex Biologics and Follow-On Biologics: Regulatory and Legislative Background

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### Disclosures:

- Dr. Carter is an Employee of Pharmaceutical Strategic Initiatives, LLC., which from time to time may receive consideration from pharmaceutical companies in its normal course of business.
- Dr. Carter does not receive direct consideration from any current pharmaceutical client company, nor is there any commercial interest between any pharmaceutical company.

## Powering the Biosimilar Debates

- Health care reform
- Potential cost savings
- Patent cliff for biologics
- Technological advancements
- Innovator and generic company interest
- Growing global precedents

**Debates on Biosimilars and Generic Biologics are Global in Scope and Impact**

## Biosimilar

“Product is defined as ‘biosimilar’ if no clinically meaningful differences between the biological product and the original product are *expected* in terms of safety, purity, and potency (safety and effectiveness) of the product”

## Food and Drug Administration Mission

- FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, cosmetics, products that emit radiation and food supply.
- 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.
- The FDA shares with the public accurate, science-based information they need to use medicines and foods to maintain and improve health.

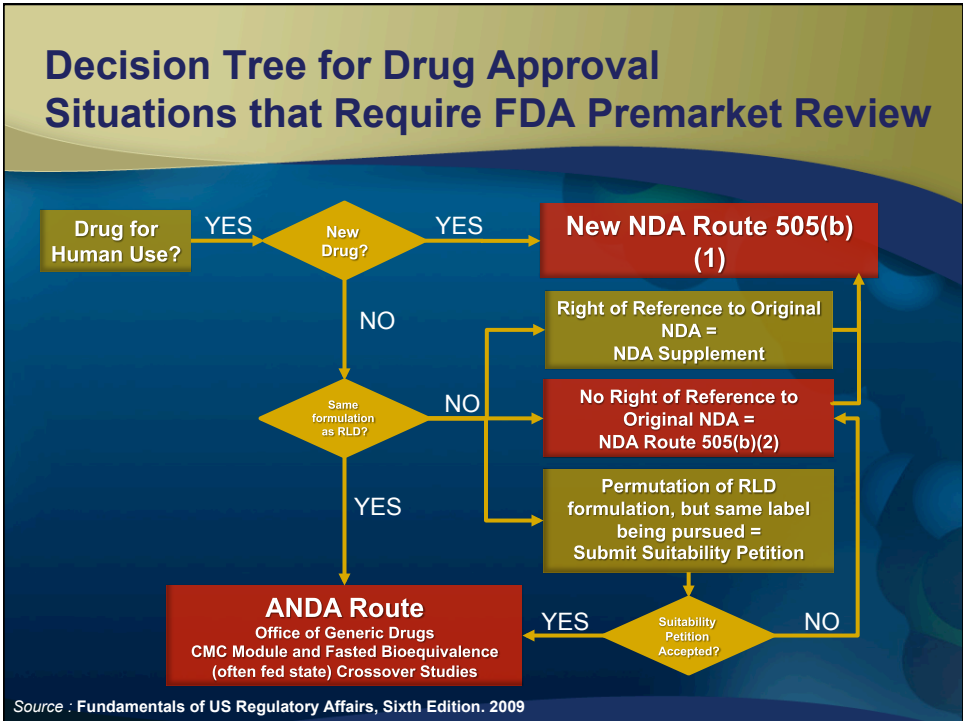
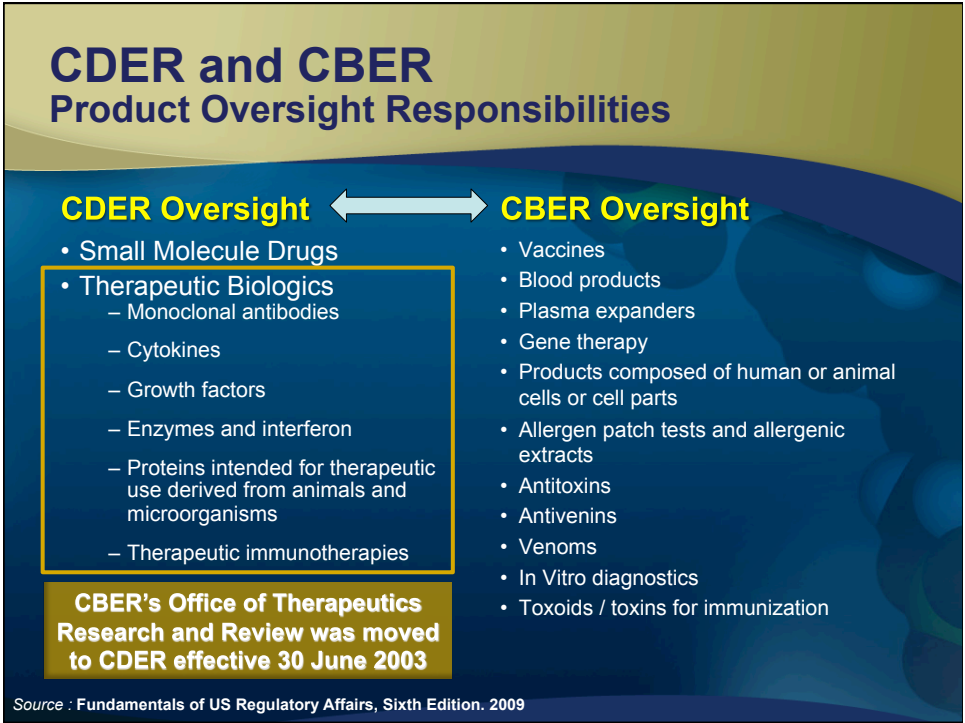
Source : Fundamentals of US Regulatory Affairs, Sixth Edition. 2009

## Food and Drug Administration Organization

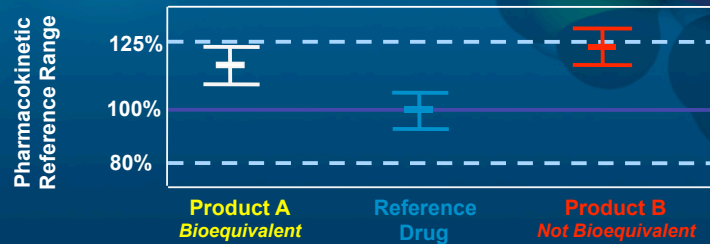
### Department of Health and Human Services Nine Centers / Offices

- Office of the Commissioner (OC)
- Center for Food Safety and Applied Nutrition (CFSAN)
- Center for Veterinary Medicine (CVN)
- Center for Biologics Evaluation and Research (CBER)
- National Center for Toxicological Research (NCTR)
- Center for Devices and Radiological Health (CDRH)
- Office of Chief Counsel (OCC)
- Center for Drug Evaluation and Research (CDER)
- Office of Regulatory Affairs (ORA)

Source : Fundamentals of US Regulatory Affairs, Sixth Edition. 2009.



## Bioequivalence Determination



- **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

Source : *Approved Drug Products With Therapeutic Equivalence Evaluations*, 27th ed. 2006. FDA/CDER Web site. Available at: [http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Therapeutic Equivalence-Related Terms](http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Therapeutic%20Equivalence-Related%20Terms).

## 505(b)(2) New Drug Application

- FDA position that a 505(b)(2) application can rely on safety and effectiveness “finding” with respect to the reference innovator NDA

## Biologics Regulated Under the Public Health Service (PHS) Act

- What Does PHS Act currently require for a “biosimilar” version of a biologic?
- **Prior to March 21, 2010**
  - Required full clinical studies to demonstrate the biologics were safe, pure, and potent
  - No counterpart to the ANDA or 505(b)(2) NDA process

11

## SEC. 7002: Approval Pathway for Biosimilar Biological Products

Overview

## Biosimilarity

### SEC. 7002: Approval Pathway for Biosimilar Biological Products

- The biological product **is biosimilar** to a reference product based upon data derived from:
  - Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
  - Animal studies (including the assessment of toxicity); and
  - A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.

**FDA may determine that one or more of these requirements are unnecessary**

## Guidance Documents

### SEC. 7002: Approval Pathway for Biosimilar Biological Products

- FDA may issue general or specific guidance, after opportunity for public comment
- The issuance or non-issuance of such guidance does not preclude approval of a biosimilar
- FDA must establish a process through which the public can provide FDA with input regarding priorities for issuing guidance

## Approach to Biosimilars USA versus EU

### US Approach

- Legislative proposal defined biosimilars
- Two sets of law governing pharmaceutical approvals (FD&C and PHS Acts)
- Patent linkage
- Exclusivity rights granted to first follow-on product to encourage development of biosimilar

15

## Approach to Biosimilars USA versus EU

### EU approach [1/2]

- EU law does not define a similar biological product; rather what a biosimilar is not
- One set of laws governing pharmaceutical approvals but biological products are recognized as distinguishable from conventional pharmaceutical products
- Guideline driven approach
- Authority given to EMEA to determine “biosimilarity”: case-by-case approach

16

## Approach to Biosimilars USA versus EU

### EU approach [2/2]

- No patent linkage
- No exclusivity granted to the first generic or biosimilar product
- Single non-renewable exclusivity period: before and after the new law
- Centralized approval does not affect product substitution/interchangeability status at Member State level

17

## EU Product Class Specific Guidelines

- Recombinant Erythropoietins
- Granulocyte-Colony Stimulating Factor
- Somatropin
- Recombinant human insulin
- **Low-molecular-weight heparins**
- Interferons
- Monoclonal antibodies (in discussion)

18

## Approval Status in the EU

- **rh-GH (somatropin)**
  - Omnitrope (Genotropin)
  - Valtropin (Humatrope)
- **rh-erythropoietins (epoetin) (Eprex)**
  - Binocrit; Epoetin alfa Hexal; Abseamed (D)
  - Silapo (epoetin zeta)
  - Retacrit (epoetin zeta)
- **rh-GCSF (filgrastim) (Neupogen)**
  - Ratiograstim
  - Biograstim
  - Tevagrastim
  - Filgrastim Ratiopharm

19

## Remaining Key Questions

- How much pre-clinical and clinical data are required?
- Safety arising from immunogenicity ?
- Clinical endpoints and data extrapolation?
- Harmonization?
- Substitution versus interchangeability?
- Complex biologics?

20

## Summary

- Biosimilar debates will continue
- Guidance documents and rulemaking will emerge
- Biosimilars of complex biologics, such as complex sugars (LMWH), are a challenge
- Differentiation between generic biologics and biosimilars is critical
- Patient focus: safety and efficacy