FDA Regulation of Biosimilars

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The Past

- **Biologics approved under Public Health Services Act – until 2010, no abbreviated pathway**
  - Precursor? -- Comparability Guidance, April 1996
- **NDAs -- for few biologics (e.g., HGH, insulin) – were approved**
  - No set criteria on appropriate data set to support approval
  - Evaluated on a case-by-case basis
- **Therapeutic Biologics – transferred from CBER to CDER –** June 2003

Bioequivalence

- **Lynchpin to traditional Waxman-Hatch generic approval process – depends on:**
  - Pharmaceutical "equivalents" – active ingredient, dosage form, strength, etc., must be SAME
  - Highly unlikely with Biosimilars –
    - ***Characterization*** – still a challenge even for the innovators – clinical trials may be needed to show comparability after process changes
      - Chances of "equivalence" conclusions faint as even a single amino acid can throw off conclusion (e.g., HGH)
      - Lovenox – only 70% characterized (but, is under an NDA and approved under an ANDA in summer 2010)

Bioequivalence …

- **Janet Woodcock, Director, Center for Drugs (before Congress, March 2007):**
  - "there is general recognition that the idea of *sameness,* as the term is used in the generic drug approval process under the Federal Food, Drug, and Cosmetic (FD&C) Act and applied to small molecules, will not usually be appropriate for more structurally complex molecules of the type generally licensed as biological products under the Public Health Service Act."

Substitutability …

- **Substitution -- core of classic Generic Industry Business Model**
  - Depends on therapeutic equivalence
  - Allows for minimal sales forces
  - Drives pricing down -- multiple generics common – the generic becomes a ***commodity***
- **Biosimilar world –**
  - Substitution – aka "interchangeability" -- may evolve, but on a very, very limited basis
    - ***Woodcock*** – must be able to handle repeated brand/follow-in switching without adverse events
    - Thus, business model will ***not*** be multiple generics & ***not*** a commodity
  - Without interchangeability, the Biosimilar ***IS*** a branded drug

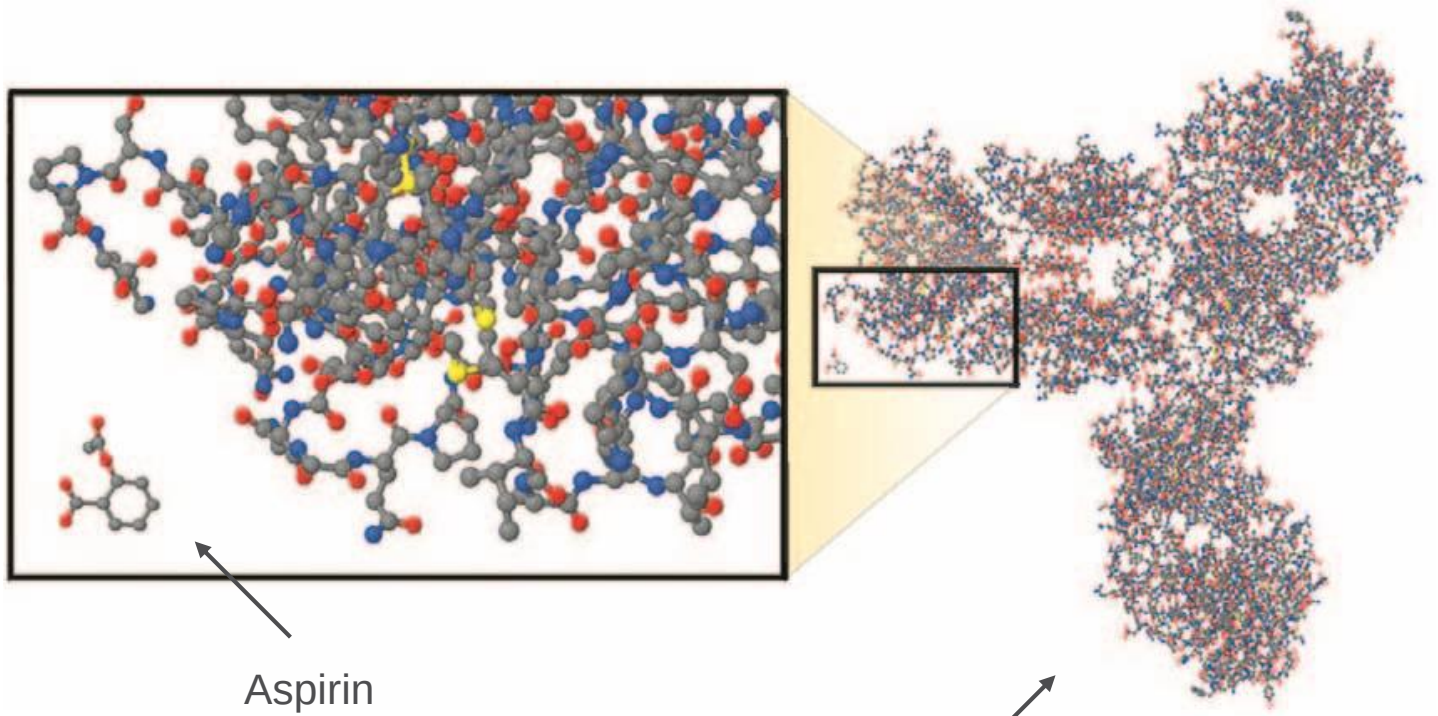
2006 – FDA Approves Omnitrope®

- **A Biosimilar?**
  - approved as a 505(b)(2) NDA
  - no interchangeability
  - extensive data requirements – rumored to cost well into eight figures, if not nine
- **No floodgates because the NDA pathway was limited to a handful of products**

Biosimilars

Basic FDA Provisions Of The Biologics Price Competition & Innovation Act Of 2009 (BPCIA)

Small Molecule v. Biologic



Source: Woodcock et al., *Developing the Nation's Biosimilars Program* (N Engl J Med 365(5) pp. 385-88)

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What Hath Health Care Reform Spawned?

- **Biologics Price Competition & Innovation Act of 2009 (BPCIA)**
  - Creates an abbreviated pathway for "biosimilar" versions of biologics, but gives FDA great flexibility/discretion in how it implements statute
- **Key features**
  - Abbreviated pathway created under the Public Health Service Act (PHSA) by adding Subsection (k) to Section 351 of the PHSA
  - Exclusivity – 12 years for new biologics
  - Complex handling of patents
  - FDA – flexibility granted in how it regulates biosimilars

What's Required for a Biosimilar Application?

- **Must be biosimilar to Reference Product, by including:**
  - Analytical studies to show your product is ***Highly similar*** to the Reference Product (RP) – i.e., the Biosimilar has no clinically meaningful differences from the RP in terms of safety, purity and potency, notwithstanding minor differences in clinically inactive components; ***and***
  - Animal Studies – including toxicity studies; ***and***
  - "A clinical study or studies" -- including assessment of immunogenicity and pharmacokinetics or pharmacodynamics
    - to show safe, pure and potent
    - in 1 (one) or more appropriate conditions of use for which the RP is licensed and intended to be used
- **FDA – can decide any of the above are unnecessary**

Required for a Biosimilar Application …

- **Must use same mechanism(s) of action –** if the MOA is known for the RP
- **Conditions of use in labeling --** have to be previously approved for the RP
- **Must match RP as to:**
  - Route of administration
  - Dosage form
  - Strength
- **Facility in which manufactured, processed, packed or held –** must meet standards designed to assure the biosimilar continues to be: Safe. Pure. Potent.

Interchangeability

- **Not required – 351(k)(2)(B)**
- **To prove interchangeability – 351(k)(4)**
  - Drug must be biosimilar to RP
  - BP "can be expected to produce the same clinical result" as the RP "in any given patient"
  - If BP is administered more than once to patient, the risk in terms of safety or diminished efficacy of switching between the BP and the RP is "not greater than the risk of using the RP" without switching
    - How to study – multiple switch study

Miscellaneous Rules

- **Only One RP per BP application –** 351(k)(5)(A)
- **Reviewing division –** same as handled the RP – 351(k)(5)(B)
- **REMS authority under FDAAA --** applies to Biosimilars – 351(k)(5)(C)
- **Biologics approved under Section 505 of Federal Food, Drug, and Cosmetic Act as New Drug Applications (NDAs)**
  - Can still be filed as NDAs (indeed, must be until an "innovator" BLA is approved)
  - However, if there is a BLA-licensed biologic that you want to use as the RP, the biosimilar application must be filed as a BLA
  - Ten years after enactment – all NDAs for biologics are deemed approved under Section 351 of PHSA

Questions?

- ***Call, e-mail or fax:***

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About Your Speaker

***Michael A. Swit, Esq.*, has been addressing critical FDA legal and regulatory issues since 1984. Before joining Illumina as a Senior Director, Legal, in December 2014, Swit was a special counsel at the global law firm of Duane Morris LLP in its San Diego office. Before joining Duane Morris in March 2012, Swit served for seven years as a vice president at The Weinberg Group Inc., a preeminent scientific and regulatory consulting firm in the Life Sciences. His expertise includes product development, compliance and enforcement, recalls and crisis management, submissions and related traditional FDA regulatory activities, labeling and advertising, and clinical research efforts for all types of life sciences companies, with a particular emphasis on drugs, biologics and therapeutic biotech products. Mr. Swit has been addressing vital FDA legal and regulatory issues since 1984, both in private practice with McKenna & Cuneo and Heller Ehrman, and as vice president, general counsel and secretary of Par Pharmaceutical, a top public generic and specialty drug firm. He also was, from 1994 to 1998, CEO of *FDANews.com,* a premier publisher of regulatory newsletters and other specialty information products for FDA-regulated firms. He has taught and written on many topics relating to FDA regulation and associated commercial activities and is a past member of the *Food & Drug Law Journal* Editorial Board. He earned his A.B., *magna cum laude*, with high honors in history, at Bowdoin College, and his law degree at Emory University.**