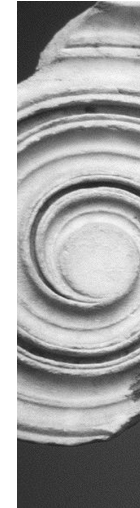


## Biosimilars Status Update:

### Current Regulatory Landscape, Legislative Proposals, and European Experience

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## Introduction - Linda Horton

- Counsels clients in the pharmaceuticals, medical devices, animal health industries and food sectors on regulatory requirements of the European Union, the U.S. FDA and regulatory counterparts elsewhere
  - Strategies, regulatory pathways, clinical trials
  - Marketing practices and relations with health professionals, in Europe and globally
  - Transatlantic cutting edge issues, e.g., drug safety, biosimilars, combination products
- Helps other countries develop laws and regulations
- *PLC Which Lawyer?*, EU - Life Sciences: Regulatory, Recommended, 2007 - 2009
- Served FDA for 30+ years as Director, International Policy; Deputy Chief Counsel; Device/Drug Counselor; Trial Attorney; Legislative Director
- Former adjunct professor, FDA administrative law, George Washington Law School; international food, drug and medical device law, Georgetown Law School



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## What I will discuss

- Current regulatory and legislative issues and actions
- Lessons learned from the European experience

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## EU / U.S. Laws



### ***Biosimilars: “similar biological medicinal products”***

- One set of laws for all “medicinal products” without a separate biologics law
- Since 2004/05, a regulatory pathway for biosimilars
- General exclusivity period of 8+2+1 years



### ***Follow-on biologics (or follow-on proteins)***

- Two laws for pharmaceutical approvals
- Public Health Service Act: No biosimilar pathway
- Federal Food, Drug and Cosmetic Act, 505(b)(2): FDA believes it has authority to approve follow-on versions of those therapeutic proteins handled as new drugs under the FDCA, e.g., Omnitrope somatropin (recombinant human growth hormone); Hatch-Waxman periods apply

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## FDA views

- FDA has been considering for some years the circumstances in which review and approval of follow-on protein products may be appropriate.
- FDA uses the term *follow-on protein products* generally to refer to proteins and peptides that are intended to be sufficiently similar to a product already approved under the Federal Food, Drug, and Cosmetic Act or licensed under the Public Health Service Act to permit the applicant to rely on certain existing scientific knowledge about the safety and effectiveness of the approved protein product.
- FDA notes that follow-on protein products may be produced through biotechnology or derived from natural sources.
- Focus has been on scientific issues, including product 'characterization,' data standards for approval, issue of interchangeability, and product names.
- Agency is willing to cut data requirements if the agency believes that there is a scientific basis for doing so without compromising patient safety.
- FDA is cautious, even skeptical, about interchangeability.
- FDA wants Congress to sort out exclusivity period.



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## Biosimilars: Battle Lines Are Set

- Obama administration budget outline supportive
  - \$9 billion over 10 years (assuming 7 years exclusivity)
- Health care reform effort likely to include biosimilars as budgetary offset
- Senate's Kennedy/Enzi bill from last Congress
  - "Hard" 12 years of exclusivity
  - Tussle over "evergreening" issue
- Chairman Waxman now in driver's seat
  - Long-standing and aggressive proponent of generics
  - Strong influence over process in the House

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## Follow-on Biologics

- Significant differences among the bills
  - HR 1427 (Waxman)
  - HR 1548 (Eshoo)
  - S 726 (Schumer; companion to Waxman)
  - S \_\_\_\_ (Kennedy/Enzi; not yet introduced)

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## Follow-on biologics

- Waxman/ Schumer Bill
  - 5 years of exclusivity
  - Additional 3 years of exclusivity for drug improvements if “significant therapeutic advance”
  - 6-month extension available for supplemental BLA
- Eshoo/Inlee/Barton Bill
  - 12 year exclusivity
  - Additional 2 years exclusivity for medically significant new indications
  - Another 6 months for pediatric studies
  - Safety standards for interchangeability

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## Follow-on Biologics: Major Issues

- Demonstrating biosimilarity
  - Waxman does not require clinical trials
  - Eshoo would require showing of biosimilarity for each indication
- Standards for interchangeability
  - Demonstrating sameness will be difficult, as a matter of science
  - Intersection with state substitution laws

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## Follow-on Biologics: Major Issues

- Periods of marketing exclusivity
  - Waxman: 5 years
  - Eshoo: 12 years
- Exclusivity for product innovations
- Established name
  - Waxman would require same name for biosimilars
- Resolving patent issues

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## Trade association views

- BIO President and CEO Jim Greenwood stated that BIO supported a 14-year exclusivity period, noting that while "[l]ots of folks in the generic industry think it should be less," BIO was concerned that "if the industry does not have enough time to recover its investments, those investments will never be made." He called the debate over the exclusivity period "a huge issue" for BIO's membership.
- January 2009
- ... "we support a pathway to approve follow-on biologics but any such pathway must place ensuring patient safety – not potential cost savings – as the central concern."



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## BIO Principles on Follow-On Biologics

- **As Congress explores the creation of any regulatory pathway for follow-on biologics, it is essential that Congress recognize and adopt the following key principles:**
- Ensure Patient Safety.
- Recognize Scientific Differences Between Drugs and Biologics.
- Maintain the Physician-Patient Relationship.
- Preserve Incentives for Innovation.
- Ensure Transparent Statutory and Regulatory Processes.
- Continue to Prioritize FDA Review and Approval of New Therapies.
- March 26, 2007 ([www.bio.org](http://www.bio.org))

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## EU Experience

### Biosimilars



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## EU: not the same as the U.S.

- Each of the 27 EU Member States has its own healthcare system and makes its own decisions about reimbursement, pricing etc., and medicine substitutability
- In the EU, national differences persist in the patent system.
- No linkage, no Orange Book, no Paragraph IV, no 180-day generic exclusivity in the EU: EU pharma regulators rarely consider patents and patent litigation
- Origin of EU 10-year exclusivity was 1987 “EU Hatch Waxman” law; biosimilar approval pathway came separately and much later (2004). In the U.S. we have the benefit of studies that might more accurately predict timelines/cost for biologic

## Biosimilar medicinal products: EU

### EU REGULATORY PATHWAY:

- Article 10(4), Community Code on Medicinal Products (Directive 2001/83/EC):
  - *“Where a biological medicinal product which is similar to a reference biological product **does not meet the conditions in the definition of generic medicinal products**, owing to, in particular, **differences** relating to raw **materials** or differences in **manufacturing processes** of the biological medicinal product and the reference biological medicinal product, **the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided**. The type and quantity of supplementary data to be provided **must comply** with the relevant criteria stated in the **Annex and the related detailed guidelines**. **The results of other tests and trials from the reference medicinal product’s dossier shall not be provided.**”*
- The Annex mentioned to is the EU version of the International Conference on Harmonization’s Common Technical Document (CTD). It specifies data requirements for biologicals & “similar biological medical products.”
- Under EU law there could, in theory, be a “biogeneric” if the sameness and bioequivalence requirements in Article 10.1 were met. This is not viewed as possible today, unless the innovator/marketing authorization holder seeks approval under the generic pathway of a product completely identical to its own, directly or through a licensee.

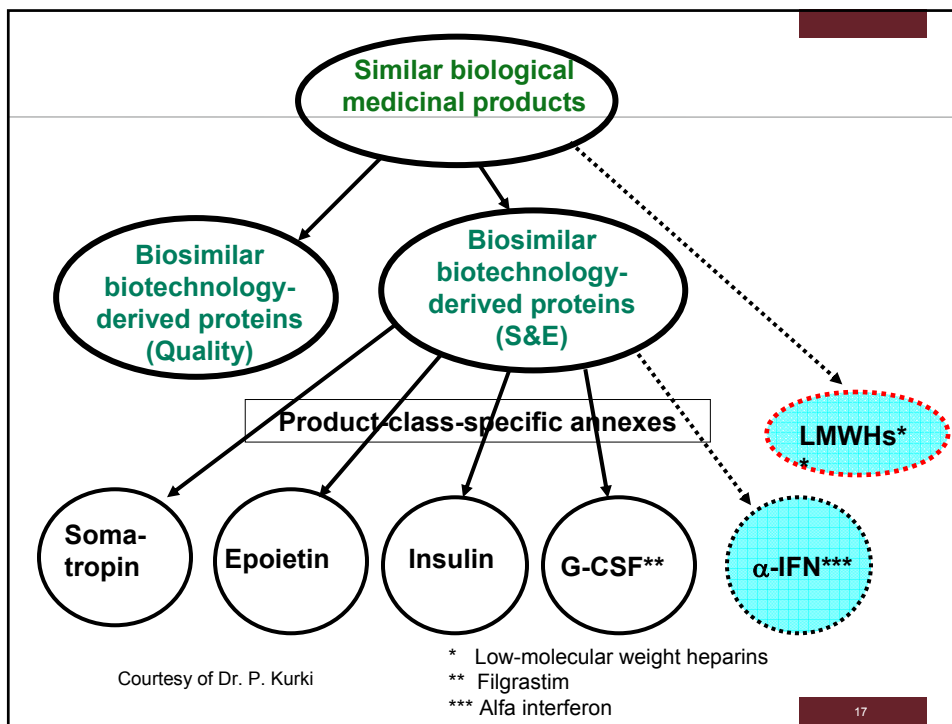
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## Overview of Regulatory System

### Biosimilars are authorized:

- by the European Commission
- through the centralized authorization procedure; EMEA’s Committee on Medicinal Products for Human Use (CHMP) assesses the application
- the Reference Product must have been authorized in the EU
- Comparability studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product.
- Whether a medicinal product would be approvable using the “similar biological medicinal product” approach depends on the state of development of analytical procedures, the manufacturing processes employed, and clinical and regulatory experiences.
- The EMEA emphasizes a “case by case” approach.

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### Overview of 5 EU Biosimilar Products: 2 HGHS (from 2 mfrs), 5 EPOs (from 2 mfrs), 4 filgrastims (from 1 mfr)

#### Authorized biosimilars:

- Omnitrope® (somatropin) (Sandoz): Recombinant human growth hormone - Reference product Pfizer's Genotropin®.
- Valtropin® (somatropin) (BioPartners): Recombinant human growth hormone - Reference product Lilly's Humatrope
- Binocrit® (epoetin alfa) (Sandoz)-Reference product J&J's Eprex for all authorizations
- Epoetin alfa Hexal® (epoetin alfa) (Hexal Biotech Forschungs)
- Abseamed® (epoetin alfa) (Medice Arzneimittel Pütter)
- Silapo® (epoetin zeta) (Stada Arzneimittel AG)
- Retacrit® (epoetin zeta) (Hospira Enterprises B.V.)
- Ratiograstim (filgrastim) (ratiopharm GmbH)-Reference product Amgen's Neupogen for all
- Biograstim (filgrastim) (CT Arzneimittel GmbH)
- Tevagrastim (filgrastim) (Teva Generics GmbH)
- Filgrastim ratiopharm (filgrastim) (ratiopharm GmbH)

**Rejected as biosimilar; negative opinion:** Alpheon® (BioPartners): Recombinant interferon alpha - Reference product Roche's Roferon-A®

**Withdrawn by applicant:** 3 biosimilar versions of insulin from Marvel LifeSciences (of MJ Group, Mumbai) when EMEA committee would not extend time for answering questions after previous extension: intended reference product—reference product Lilly's Humulin

## EU's emerging norm: "8+2+1"

- 8 years data exclusivity dating from the European Commission authorization decision: before that, no generic applications are fileable
- +2 years marketing protection: no generic applications approvable
- + 1 year: new indication(s) if it constitutes a significant clinical benefit
- For all products, regardless of centralized or Member State agency approval procedure
- Not retroactive; does not affect exclusivity periods for products for which applications were submitted before effective date (late 2005)

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## Other Exclusivity or Related Provisions

- **New combinations of old medicinal products** are treated as new products eligible for 8+2+1 years exclusivity (Art. 10b Community Code; Notice to Applicants Volume 2A Procedures for Marketing Authorization, Section 5.5)
- 1 year data exclusivity for a **new indication for a well-established substance**
- 1 year data exclusivity for **change of the classification** from Rx to OTC or vice versa
- **Orphan** drugs 10 years market exclusivity remains unchanged. Product may have 10 years market exclusivity for orphan indications and 8+2+1 for others.
- New **pediatric** regulation: marketing authorization holder can extend supplementary protection certificate from 5 years to 5.5 years
  - OR use the +1 extension of exclusivity (not both)
  - OR add +2 years to orphan drug market exclusivity for total of 12 years
- Also new **Pediatric Use Marketing Authorization (PUMA)** for off-patent products offers 8+2 exclusivity period
- Since 1992, there has been the possibility of a 5-year **Supplementary Protection Certificate** for a patent in force, covering an authorized pharmaceutical (somewhat analogous to U.S. patent term restoration). This potential 20+5 patent/SPC period runs separately from regulatory exclusivity.

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### **For centrally authorized products assessed by EMEA**

- Art. 14.11 of the EMEA Regulation:
- Without prejudice to intellectual property law, medicines authorized under the EMEA Regulation shall benefit from an 8 year period of data protection and a 10 year period of marketing protection.
- The latter period shall be extended to a maximum of 11 years if, during the first 8 of the 10 years, the marketing authorization holder obtains an authorization of one or more new therapeutic indications which are held to bring a significant clinical benefit in comparison with existing therapies.
- All biotech biosimilars are assessed by EMEA.

This provision applies to all applications submitted to the EMEA after November 20, 2005.

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### **For generic products (not biosimilars) authorized by Member State agencies**

- Art. 10(1), Community Code on Medicinal Products: Without prejudice to intellectual property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the product is a generic of a reference medicinal product which is or has been authorized for not less than 8 years in a Member State or in the Community.
- A generic authorized under this provision shall not be placed on the market until 10 years have elapsed from the initial authorization of the reference product.
- As with centrally authorized products assessed by the EMEA, an 11<sup>th</sup> year is available, governed by the same criteria.
- Note: this provision governs approvals by national Member State agencies and by its terms relates to generics, not to biosimilars. It might apply where a national agency approves a non-biotech biologic whose reference product was not one assessed by the EMEA.
- This provision should apply to all applications submitted to Member State agencies after October 30, 2005 [European Commission guidance says after Member State implementation of Directive.]

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## Interchangeability and substitutibility

- Interchangeability:
  - Scientific issue
  - In the U.S., handled at national (FDA) level
  - FDA issues findings that become legal “standard of care”
- Substitutibility
  - Legal issue: may a pharmacist prescribe a product different from what the doctor prescribed?
  - In the U.S., handled mostly at State level *but* most pharmacists are believed to follow FDA advice

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## Interchangeability: FDA View

- “Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, 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.” (Statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, FDA, before the US House Committee on Oversight and Government reform, “Follow-on Protein Products,” March 26, 2007) (“Woodcock Testimony”) (emphasis added).

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## FDA views, continued

- Science will govern:
  - “As a science-based agency, the FDA will continue to integrate scientific advances and public health needs into its review of protein products.” Woodcock, et al. *The FDA’s assessment of follow-on protein products: a historical perspective*, in *Nature* (June 2007) at 442.
  - Woodcock Testimony:
    - Although current technology, like peptide mapping, can determine amino acid sequence of a recombinant protein, more complex aspects of a protein’s structure govern function, such as:
    - Folding of the protein’s amino acid chain into highly organized structures;
    - Association of multiple protein molecules into aggregates; and
    - Modification of proteins through biochemical additions, such as glycosylation, acetylation, and phosphorylation

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## EMA views: CHMP Guideline

- *“It should be recognised that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established.”*

EMA Committee on Medicinal Products for Human Use (CHMP)  
Guideline on Similar Biological Medicinal Products, CHMP/437/04, 30 Oct.  
2005, p. 4

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## Interchangeability - EMEA View

- *“It is not possible we would guarantee a biosimilar is interchangeable (with its originator). Substitution is a national competency and needs to be discussed at the national level”*

EMEA Executive Director Thomas Lönngren, 21 July 2006

- EMEA/74562/2006, 19 April 2007

*“Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional.”*

- European Commission, Pharma Package, December 2008:
- Proposal on Pharmacovigilance: proposed to require that records on adverse events involving biologicals identify the precise product

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## New EU pharmacovigilance guideline advises inclusion of brand-specific information in adverse event reports

September 2008, Volume 9A Rules for Medicinal Products on Pharmacovigilance, at 57, 114.:

- “For adverse reactions relating to biological products, the definite identification of the product with regard to its manufacturing is of particular importance. Therefore, Competent Authorities [1] should give advice to reporters[2] to provide the name[3] of the medicinal product and the batch number and should follow-up the reports when this information is missing.”
- This advice contemplates that the doctor has prescribed by brand name and there is no possible substitution by pharmacist OR, if substitution is allowed, someone is prepared to go back and check dispensing records in the pharmacy or hospital and find an accurate record of what was actually dispensed to the patient.
- This is just one part of substantial post-marketing pharmacovigilance responsibilities.

[1] i.e., national drug regulatory agencies.

[2] those who report adverse reactions, generally the market authorization holder or health care professionals.

[3] “The name, which may be either an invented name [“brand name”] not liable to confusion with the common name [INN or “generic name”], or a common or scientific name accompanied by a trade mark or the name of the marketing authorization holder.” Art 1(20), Community Code

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## EU countries forbidding substitution-1

- **Austria:** Physicians are obliged to prescribe by brand name
- **Czech Republic:** Physicians are obliged to prescribe by brand name
- **Denmark:** Official guidelines against substitution.
- **Finland:** By law, no injectable drug may be automatically substituted.
- **France:** law prohibits the automatic substitution of one biological medicine for another, without the consent of the treating physician (reason given: innovator biotech products and follow-on medicines are not identical).
- **Germany:** Since biosimilars are not generics, they are not automatically substitutable.
- **Greece:** Physicians are obliged to prescribe by brand name.
- **Hungary:** Since biosimilars are not generics they are not automatically substitutable.
- **Italy:** The Italian Medicines Agency (AIFA) recommends, for clinical reasons, that no substitution of these products take place

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## EU countries forbidding substitution

- **The Netherlands:** The Royal Society of Pharmacists has issued guidance against automatic substitution of biologics.
- **Norway:** The Medicines Agency has stated that “biosimilars” are complex products and should not be substituted.
- **Slovakia:** An official list sets forth products which cannot be substituted; list includes many biotech medicines (e.g. epoetins, Factor VII, GCSF, HGH, insulin).
- **Slovenia:** A law has been adopted that prohibits substitution of biologics.
- **Spain:** A recent amendment to the law includes all biotech medicines on a list of products that cannot be automatically substituted.
- **Sweden:** Regulatory authorities have informed the pharmaceutical industry in writing that biologics are not to be substituted automatically.
- **UK:** The UK Medicines and Healthcare products Regulatory Agency (MHRA) has stated that biologics should be prescribed by brand name to ensure that automatic substitution of a biosimilar does not occur when the medicine is dispensed by the pharmacist.

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## Looking to the future...

- Biosimilars are not an easy way to make money.
- Despite the size of the biosimilar business opportunity, it is recognized that regulatory demands far exceed requirements for chemical generics.
- The interchangeability debate underlines the question of acceptance in the marketplace: will doctors and patients feel comfortable with biosimilars?
- Will authorities mandate, or doctors write on Rx's, "No substitution"?

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