Biosimilars: What Can We Learn From the Past ?

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Biopharmaceuticals

- Introduced in the beginning of the 1980s
- More than 150 products marketed
- Over 370 products in development for a wide range of serious conditions

Biotechnology Industry Organization website (www.bio.org), 2004.

Patent Expiration of Biopharmaceuticals

Pioneer company	Product	Indication(s)	EU patent/market exclusivity expires	USA patent/market exclusivity expires
Genentech	Nutropin® (somatropin)	Growth disorders	Expired	Expired
Abbott	Abbokinase® (eudurase urokinase)	Ischaemic events	Expired	Expired
Eli Lilly	Humulin® (recombinant insulin)	Diabetes	Expired	Expired
Genzyme	Ceredase® (alglucerase); Cerezyme® (imiglucerase)	Gaucher disease	Expired	Expired
AstraZeneca	Streptase® (streptokinase)	Ischaemic events	Expired	Expired
Biogen / Roche	Intron A® (IFN-alfa-2b)	Hepatitis B and C	Expired (France) 2007 (Italy)	Expired
Serono	Serostim® (somatropin)	AIDS wasting	NA	Expired
Eli Lilly	Humatrope® (somatropin)	Growth disorders	NA	Expired
Amgen	Epogen®, Procrit®, EPREX® (erythropoietin)	Anaemia	Expired	2013
Roche	NeoRecormon® (erythropoietin)	Anaemia	2005	NA
Genentech	TNKase® (tenecteplase TNK-tPA)	Acute myocardial infarction	2005	2005
InterMune	Actimmune® (IFN-gamma-Ib)	Chronic granulomatous disease (CGD), malignant osteopetrosis	Expired	2005, 2006, 2012
Genentech	Activase®, Alteplase® (tPA)	Acute myocardial infarction	2005	2005, 2010
Chiron	Proleukin® (IL-2)	HIV	2005	2006, 2012
Amgen	Neupogen® (filgrastim G-CSF)	Anaemia, leukaemia, neutropenia	2006	2015

Adapted from Schellekens H. Trends Biotechnol 2004;22:406-10.

Definitions

Low molecular weight drug	**Classical medicinal pharmaceutical product**
Generic drug	**Chemical and therapeutic equivalent of low molecular weight drug whose patent has expired**
Biopharmaceutical	**'A medicinal product developed by means of one or more of the following biotechnology practices: rDNA, controlled gene expression, antibody methods'[1]**
Biosimilar, or similar biological medicinal product	**'A biological medicinal product referring to an existing one and submitted to regulatory authorities for marketing authorization by an independent applicant after the time of protection of the data has expired for the original product'[1]**

[1]EMEA definition

FDA definition: "Follow-on biologics"

Manufacture of Chemically-based Drugs vs Protein Product

Chemically-based drugs

- Made by adding and mixing known chemicals and reagents
- Using a series of controlled and predictable chemical reactions

Therapeutic proteins

- Made by harvesting the substances produced and secreted by constructed cells

FDA Guidance

- "Unlike small molecule drugs, whose structure can usually be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product."

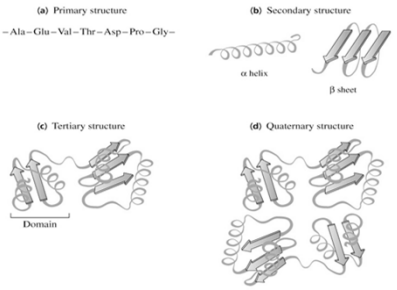
Why Biopharmaceuticals are Different

- High molecular weight
- Complex three-dimensional structure
- Produced by living organisms, therefore often heterogeneous
- Difficult to characterize completely by physico-chemical analytical methods or bioassays
- Prone to eliciting an immune response

Biosimilars are *not* generic biopharmaceuticals

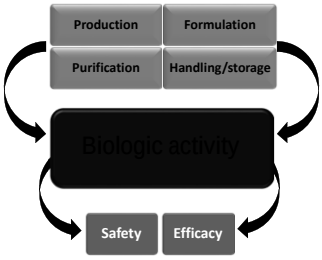
Crommelin DJA, et al. Int J Pharm 2003;266:3-16.

Complexity of Protein Structure



Taken from Horton HR, et al. Principles of Biochemistry. 3rd ed. 2002.

Proprietary Cell Lines



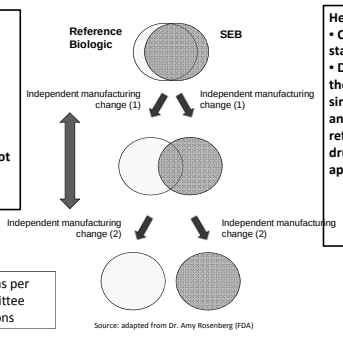
Production cell lines
- Proprietary
- Not available to the producers of SEBs

Manufacturing process
- Changes in the active pharmaceutical ingredient can affect downstream safety and efficacy

Kuhlmann & Covic. Nephrol Dial Transplant. 2006;21[suppl 5]:v4–v8.
Chow et al. Statist Med 2013; 32:370–81.

Manufacturing Drift

Health Canada
- **Evaluates comparability before and after process changes**
- **Helps ensure that patient outcomes will not be affected.[1]**



Health Canada
- **Considers an SEB a standalone product**
- **Does not require the assessment of similarity between an SEB and reference biologic drug after approval[2]**

Change image as per Steering Committee recommendations

Source: adapted from Dr. Amy Rosenberg (FDA)

Current Market Approval of Generic Low Molecular Weight Drugs

Demonstration of 'essential similarity':

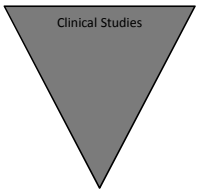
- Same qualitative and quantitative composition in terms of the active substance
- Same physico-chemical form
- Bioequivalence in healthy volunteers

Can this established concept also be applied to biosimilars?

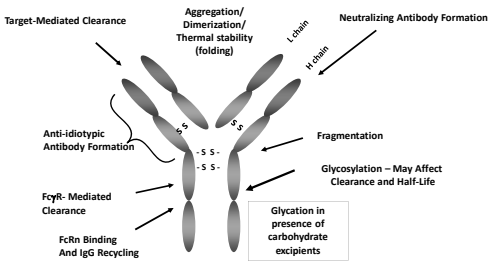
Chen ML., et al. Pharm Res 2001;18:1645-50.

Clinical Evidence of Safety and Efficacy: Innovator Biologics vs SEBs

- Subsequent Entry Biologic
- Innovator biologic



Pharmacokinetics and Immunogenicity



All of these factors directly or indirectly contribute to or are influenced by protein heterogeneities and can impact PK and/or immunogenicity

Immunogenicity: The Issues

- It is impossible to predict all biological or clinical properties of biopharmaceuticals by physical chemical characterization
- The human immune system is highly efficient in detecting differences between biopharmaceuticals and endogenous proteins
- In vitro detection is assay dependent

VI-2
Schellekens H. Nat Rev Drug Discov 2002;1:457-62.

Factors Influencing Immunogenicity

- Product-related factors
  - Sequence variation
  - Glycosylation
  - Host cells
  - Contaminants and process-related impurities
  - Formulation
  - Handling and storage

Changes in the manufacturing process, and inadequate handling and storage of a drug, may alter its immunogenicity

VI-5 Schellekens H. Nat Rev Drug Discov 2002;1:457-62.

Factors Influencing Immunogenicity (cont.)

- Patient factors
  - Route of administration: SC > IM > IV
  - Dose and treatment duration
  - Concomitant diseases and/or medication
  - Genetic factors
- Unknown factors

Although important factors have been identified, there are still several unknowns

VI-6 Schellekens H. Nat Rev Drug Discov 2002;1:457-62.

Immunogenicity: Effects

- Immune responses to biopharmaceuticals can vary from no perceptible effect to significant clinical effects:
  - Generalized immune effects (allergy, anaphylaxis)
  - Neutralization of exogenous protein (loss or enhancement of drug efficacy)
  - Neutralization of the endogenous protein (serious adverse event)

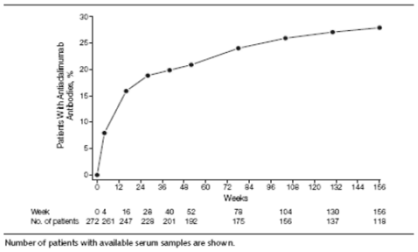
VI-3 Schellekens H. Nat Rev Drug Discov 2002;1:457-62.

Significant Clinical Effects of Antibody Formation

Consequence of antibody	Biopharmaceutical
Loss of efficacy	Insulin Streptokinase Staphylokinase Adenosine deaminase Salmon calcitonin Factor VIII Interferon-α2 Interferon-β Interleukin-2 Gonadotropin-releasing hormone Denileukin diftitox Human chorionic gonadotropin Granulocyte-macrophage colony-stimulating factor
Neutralization of native protein	Megakaryocyte-derived growth factor Erythropoietin

VI-4 Reproduced with permission from Nature Reviews Drug Discovery (2002;1:457-62)

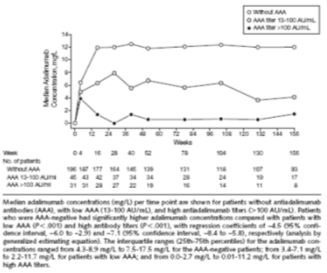
Percentage of ADAs to Adalimumab Over Time



Number of patients with available serum samples are shown.

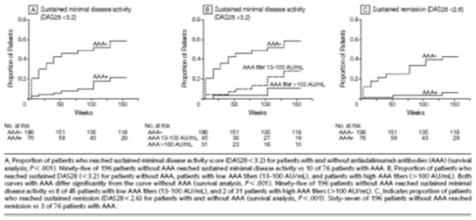
Bartelds GM, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA. 2011 Apr 13;305(14):1460-8.

Median Adalimumab Concentration Over Time



Bartelds GM, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA. 2011 Apr 13;305(14):1460-8.

Sustained Disease Activity and Remission in Patients with and without Anti-adalimumab Antibodies



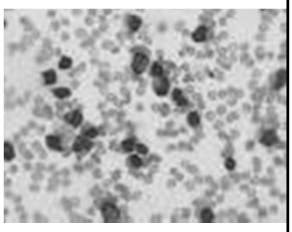
Bartelds GM, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA. 2011 Apr 13;305(14):1460-8.

An Example from Nephrology: Complexity of the Biopharmaceutical Epoetin-Alfa

- Natural human erythropoietin is a glycoprotein hormone with large carbohydrate side-chains
- Recombinant human erythropoietin (e.g. epoetin alfa) is heterogeneous, consisting of several different isoforms
- Different epoetin alfa isoforms have different biological properties

Pure Red Cell Aplasia (Diamond-Blackfan Syndrome)

- Uncommon immune disorder
- Antibody response to erythroblasts in the bone marrow
- Absence of precursors leads to anemia
- Associated with immune disorders, drug therapy, malignancy, parvovirus infection
- Recombinant EPO



ESAs and Pure Red Cell Aplasia

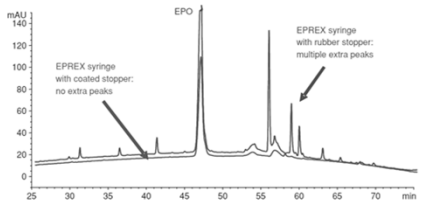
- First reported 1998
- "Epidemic" by 2002 ~ 200 cases
- Associated with s.c. administration
- Severe concern in nephrology community
- What is the cause?
- Withdrawal?

The New England Journal of Medicine

PURE RED-CELL APLASIA AND ANTIERYTHROPOIETIN ANTIBODIES IN PATIENTS TREATED WITH RECOMBINANT ERYTHROPOIETIN

Casadevall N et al. N Eng J Med. 2002;346(7):469-75

ESAs and Pure Red Cell Aplasia



- Cause identified 2004
- Change in plasticizer in stoppers – resulted in adjuvant activity – formation of anti EPO antibodies
- Illustrates need for supply chain controls and pharmacovigilance systems post-market

Boven K et al. Kidney Int. 2005;67(6):2346-53

Biosimilars ESAs and PRCA

- Multiple cases of PRCA reported from Thailand
- Related to biosimilar ESAs
- Cause? – Manufacturing vs. others


commentary

see original article on page 88

Erythropoiesis-stimulating agents and pure red-cell aplasia: you can't fool Mother Nature

Jay B. Wish[1]

Subtle alterations in the properties of biopharmaceutical agents may increase their immunogenicity and lead to the production of autoantibodies. Biosimilar agents may not undergo the same quality control in their production, packaging, storage, and distribution as their patented competitors. The extensive use of biosimilar erythropoiesis-stimulating agents led to an epidemic of pure red-cell aplasia in Thailand. The response of Thai regulators may be a model for other countries as the use of biosimilar agents expands.

Wish J. et al. Kidney Int. 2011;80:11-13

Data Extrapolation

The use of efficacy/safety data as a surrogate for efficacy/safety in a population/regimen that has not been studied

Expert Opinion on Extrapolation

Summit on Regulatory and Clinical Topics Related to SEBs

- The mechanisms of action of the TNFa antagonists are not completely understood, and that subtle molecular differences in a biologic drug may alter binding to targets in the body and lead to different clinical effects
- It may not be possible to extrapolate clinical data for a monoclonal antibody in one indication to other rheumatologic indications because of differences in:
  - dose
  - duration of therapy
  - efficacy of monotherapy vs. combination therapy
  - stated claims of efficacy for those indications

Kay et al. 2012; Biologicals 40:517-27.

Interchangeability

Health Authority	Canada (Health Canada)	Europe (European Medicines Agency)	USA (FDA)
Position	**Outside of mandate (provincial authority)** **HC does not support automatic substitution**	Outside of mandate 2007 - decision on using biosimilar should be made by qualified HCP[3] • 2012 - Biosimilars are not the same as generics, which have simpler chemical structures and are considered to be identical to their reference medicines[4]	Biosimilar authorization framework allows for possibility of interchangeable designation[6]
Naming	**Health Canada[2] prefers unique brand name** **Position on INN remains to be determined**	European Commission Directive Dec 2012[5] *Brand* name should be used for biologic Rx	No official position No biosimilars approved to date

Health Canada Guidance on SEBs

- Authorization of an SEB is not a declaration of pharmaceutical or therapeutic equivalence to an innovator. SEBs are not "generic" biologics
- Health Canada does not support "automatic substitution", but does not have jurisdiction on interchangeability of SEBs and innovators.

http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/fs-fi_seb-pbu_07-2006-eng.php

Expert Opinion on SEBs
A Viewpoint from Canadian Researchers

- SEBs must have an acceptable safety and efficacy profile
- **SEBs are not interchangeable with each other nor with brand name biologics**
- Each biologic product must have a unique product name…Given the fact that SEB products are not identical to innovator products and could have significantly different clinical outcomes…
- Cost must not override safety and efficacy
- Strict post-marketing surveillance must be followed

Conclusions

- Biosimilars cannot be considered generic biologics
- Because immunogenicity is largely unpredictable, the assessment of a biosimilar must be based on:
  - a thorough risk-benefit analysis
  - robust post-marketing risk- management programs
- Physicians\ pharmacists should remain alert to unexplained changes in efficacy or side-effects
- Extrapolation and Interchangeability are important issues for patients and physicians that will bear careful monitoring