eurahp
European Academy of Hospital Pharmacy

# Biosimilars

Don’t push the river, it flows by itself

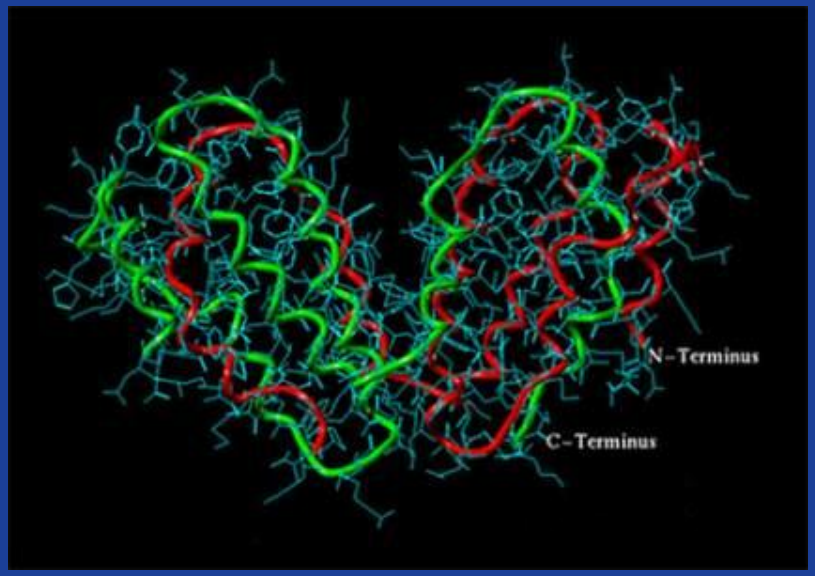
European Association
of Hospital Pharmacists

# The problem

| Pioneer Company | Product | Indication(s) | US Patent / Market Exclusivity Expires | EU 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 | 2002 | 2003 (France) 2007 (Italy) |
| Serono | Serostim™ (somatropin) | AIDS wasting | 2003 | NA |
| Eli Lilly | Humatrope™ (somatropin) | Growth disorders | ODE*** 2003 | NA |
| Amgen | Epogen™, Procrit™, Eprex™ (erythropoietin) | Anaemia | 2013 | 2004 |
| Roche | NeoRecormon™ (erythropoietin) | Anaemia | NA | 2005 |
| Genentech | TNKase™ (tenecteplase TNK-tPA) | Acute myocardial infarction | 2005 | 2005 |
| InterMune | Actimmune™ (IFN-gamma-Ib) | Chronic granulomatous disease (CGD), malignant osteopetrosis | 2005, 2006, 2012 | 2002, 2004 |
| Genentech | Activase™, Alteplase™ (tPA) | Acute myocardial infarction | 2005, 2010 | 2005 |
| Chiron | Proleukin™ (IL-2) | HIV | 2006, 2012 | 2005 |
| Amgen | Neupogen™ (filgrastim G-CSF) | Anaemia, leukaemia, neutropenia | 2015 | 2006 |

# Biologicals are large, complex molecules

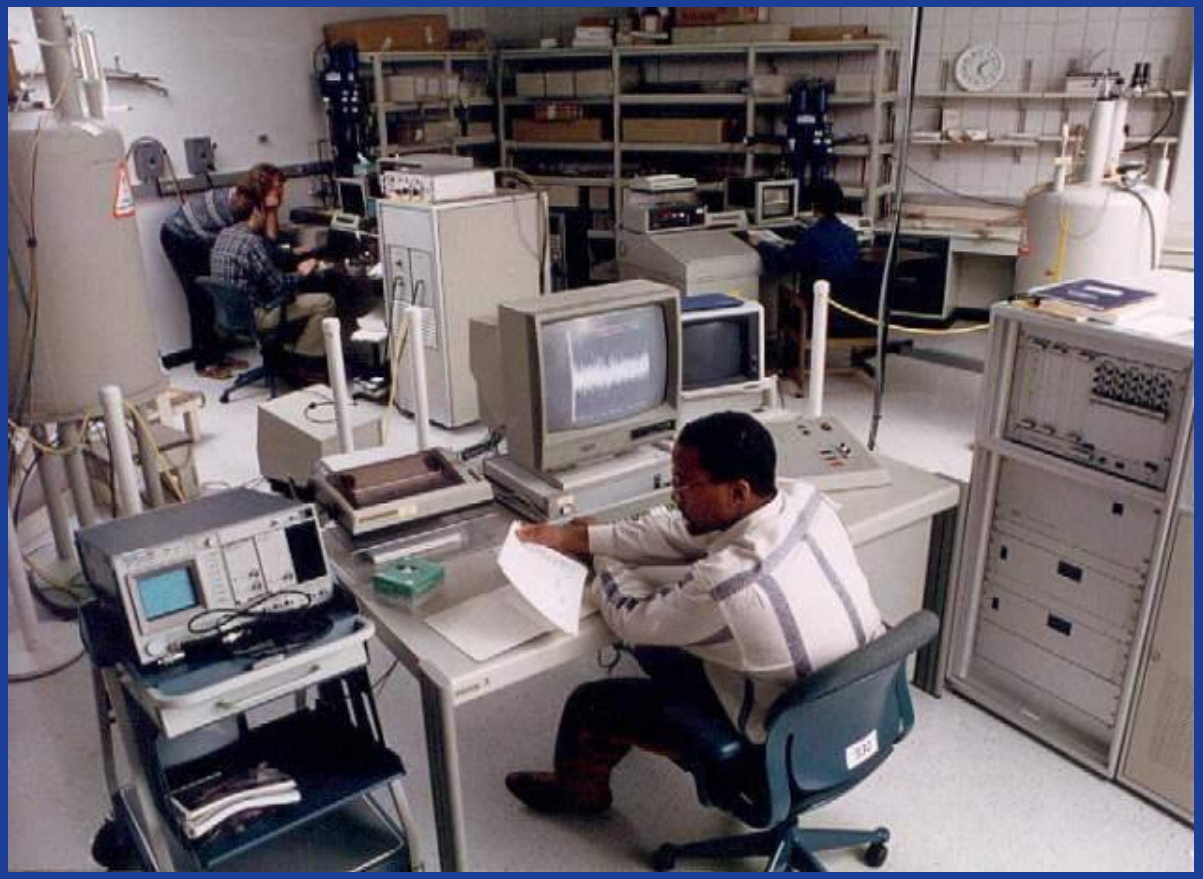
- Biologicals are much larger with more complicated structures than classical drugs




Interferon beta
Molecular weight 19,000


Aspirin
Molecular weight 180

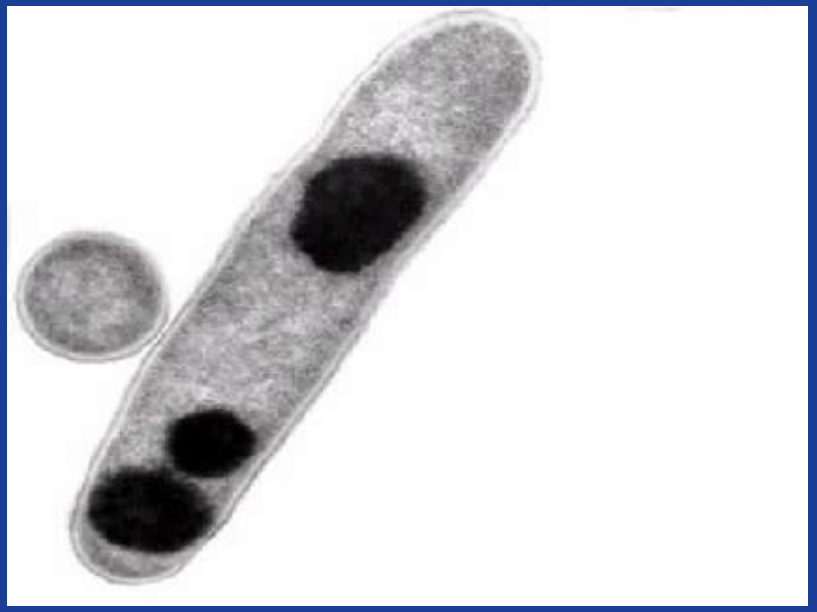
# The Biological and Clinical Properties of Biologics cannot be predicted from physical chemical analyses



The analytical tools for biologics are 10-100 times less sensitive than for classical drugs

# Biopharmaceutical manufacturing is complex and variable (1)

- Biologicals are produced under controlled conditions
- Newly generated proteins undergo complex post-translational modifications:
  - Very sensitive to production conditions
  - Minor changes can have major impacts on biological activity

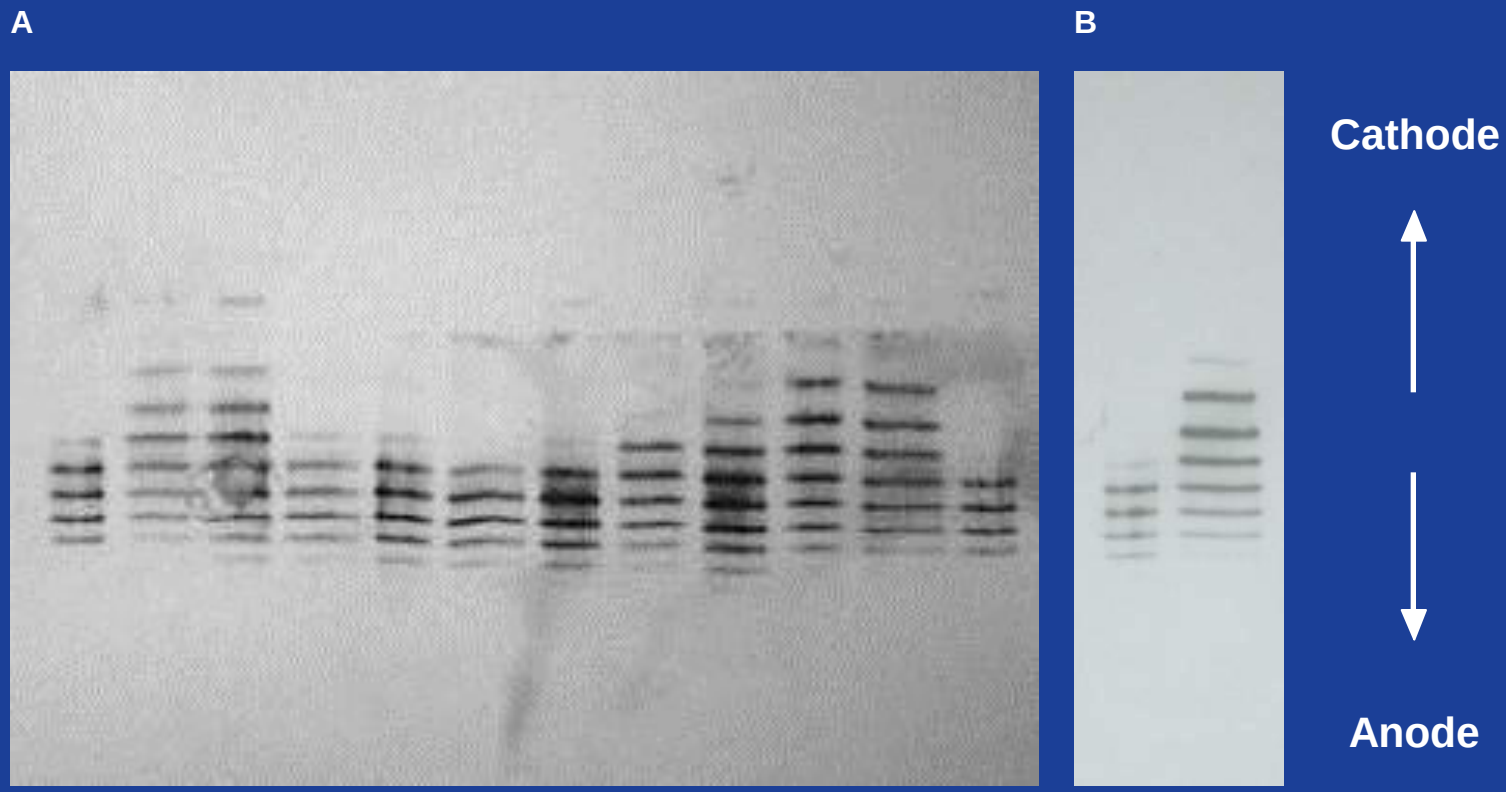


*E. coli bacterium producing interferon gamma*

Roger SD. *Nephrology* 2006;11:341–6;
Dews I. *Clinical Research Focus* 2006;17:5–10;
Schellekens H. *Nephrol Dial Transaplant* 2005;20(Suppl4):iv31–6

# Biologics are heterogeneous

**Different epoetins from around the world – Isoelectric focusing**




Schellekens H and Combe C et al. Poster ERA-EDTA Congress 2004

# Biopharmaceutical manufacturing is complex and variable (2)

- Production and purification of biologics is a complicated process
  - Fewer than 100 product quality tests are typically required for a small molecule pharmaceutical
  - Typically more than 2000 tests are required in the process of manufacturing a biopharmaceutical

# Biopharmaceuticals differ from conventional drugs

| Generic | Biosimilar* |
| --- | --- |
| Chemical and therapeutic equivalent of original low molecular weight drug whose patent has expired | Biological product referring, but not identical, to an existing product, submitted for separate marketing approval following patent expiration |

# The arguements

- The process is the product
- Examples of problems

# Safety: Critical Considerations

**Tryptophan-Eosinophila Myalgia Syndrome (EMS)**

Production strain changed-purification modified

Unrecognised impurity caused EMS

(>1300 cases, 38 deaths)

**ADR-Tick Bone Encephalitis Vaccine**

Thiomersal removed from formulation: ↗AEs

Albumin removed from formulation: ↗AEs

**Thrombopoietin Immunogenicity**

Pegylated rHuMGDF: highly immunogenic

persistent thrombocytopaenia

=> development programme stopped

**Immunogenicity of GM-CSF**

Non-immunogenic: immunosuppressed patients

ABs in non-immunosuppressed patients

**1998: Increased incidence of PRCA with EPREX SC**

Related to formulation change (change HSA to Twin 80)

Appearance of neutralising ABs to EPO

Leachates from uncoated stoppers reacting with Twin 80

SC route was withdrawn in most countries

AE, adverse event; SC, subcutaneous; AB, antibody; PRCA, pure red cell aplasia; ADR,

Source: Dr Chris Holloway, PRA

# The regulations

# Definitions

**IDENTICAL**

- The product attributes are the same as those of the comparator drug (difficult for complex products)

**SIMILAR**

- The product attributes are similar enough to establish the same safety and efficacy as the comparator drug

S. Koszlowski FDA/DIA Scientific Workshop on Follow-on Protein Pharmaceuticals, 2005

The European Agency for the Evaluation of Medicinal Products
*Pre-Authorisation Evaluation of Medicines for Human Use*

Annex I was published on 25 June 2003

London, 26 June 2003
CPMP/3184/03

# COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS SUMMARY OF OPINION for OMNITROP

International Non-proprietary Name (INN): Somatropin

On 26 June 2003, the Committee for Proprietary Medicinal Products (CPMP) adopted a positive opinion, recommending to grant a marketing authorisation for the medicinal product OMNITROP 3.3 mg/ml solution for injection, intended for the treatment of growth disturbance in children (over three years of age) and adolescents due to insufficient secretion of growth hormone and growth disturbance associated with Turner syndrome or chronic renal insufficiency and as replacement therapy in adults with pronounced growth hormone deficiency. The applicant for this medicinal product is Sandoz GmbH.

The active substance of OMNITROP, somatropin, is manufactured by recombinant DNA technology. Somatropin is an anterior pituitary lobe hormone, ATC code H01AC01, which stimulates linear growth and increases the growth rate in children. In adults as well as in children, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilisation of body fat.

The benefits of OMNITROP have been demonstrated by the efficacy results obtained with the liquid formulation, supportive clinical studies performed with a lyophilised formulation, and the results mentioned in literature for other, well-known, growth hormone containing products. It is concluded that the efficacy of OMNITROP parallels that of other growth hormone containing products. The overall design of the comparability programme has taken into account the nature of the molecule, the knowledge of the mode of action of the molecule and the experience with growth hormone in clinical use. The most common side effects are the development of antibodies to the protein without any growth-inhibiting effects, hypothyroidism, disturbances in fluid balance (oedema), arthralgia, myalgia, stiffness in the extremities, paraesthesia and transient local injection site reactions.

# Action brought on 14 January 2004 by Sandoz GmbH against the Commission of the European Communities

**(Case T-15/04)**

(2004/C 71/63)

*(Language of the case: English)*

An action against the Commission of the European Communities was brought before the Court of First Instance of the European Communities on 14 January 2004 by Sandoz GmbH, Kundl, (Austria), represented by C. Thomas and N. Dagg, Solicitors, and B. Oosting, lawyer.

The applicant claims that the Court should:

— annul the Commission decision, notified to the applicant by letter dated 14 November 2003, not to proceed with the decision for a marketing authorisation of Omnitrop under Article 10(1)(a)(ii) of Directive 2001/83 and to send the CPMP opinion of 26 June 2003 back to the EMEA;

— order the Commission to pay the applicants costs.

European Medicines Agency
*Press office*

**Annex I was published on 25 June 2003** →

London, 27 January 2006
Doc. Ref. EMEA/31797/2006

# Press release
# European Medicines Agency adopts first positive opinion for a similar biological medicinal product

The European Medicines Agency has adopted the first positive opinion for a similar biological medicinal product. The product, Omnitrope, is manufactured by Sandoz GmbH and contains somatropin, a recombinant-DNA growth hormone. It is intended for the treatment of growth disturbance and growth hormone deficiency in children and adults.

The Agency's scientific committee, the Committee for Medicinal Products for Human Use (CHMP) adopted the opinion at its meeting of 23-26 January 2006. The Committee considered that, in accordance with European Union requirements, Omnitrope has been shown by studies demonstrating comparable quality, safety and efficacy to be similar to a reference medicinal product already authorised in the EU, namely Genotropin.

The European Commission and European Medicines Agency have worked actively over a number of years to put in place a legal and regulatory framework for similar biological medicinal products. The first guidelines on quality, non-clinical and clinical issues were adopted by the CHMP in December 2003. A general regulatory guideline on similar biological medicinal products was adopted in September 2005.

Further guidelines, including guidance on specific classes of products, are planned for adoption during the first quarter of 2006. A conference was held in Paris in December 2005 as part of the public consultation process.

# Human code

Article 10, paragraph 4

*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 Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided*

# Annex I (1)

- Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.
- Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.
- The general principles to be applied are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency. In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.

European Medicines Agency
*Press Office*

London, 8 March 2006
Doc. Ref. EMEA/84561/2006

# Press release
# European Medicines Agency finalises set of guidelines on similar biological medicines and publishes two more new concept papers

The European Medicines Agency today published a set of five final guidelines on similar biological medicinal products. They are intended to give guidance to industry in the development of this new type of applications for marketing authorisation.

A general regulatory guideline on similar biological medicinal products was finalised in September 2005. The guidelines published today give guidance on quality, non-clinical and clinical issues. The product class specific annexes to the guideline on non-clinical and clinical issues give guidance for certain classes of medicines: those containing insulin, containing somatropin and those containing recombinant granulocyte-colony stimulating factor. The guidelines come into effect from 1 June 2006. In addition, a further class specific annex for medicines containing epoetin will also be available shortly.

The finalisation of the guidelines follows an extensive public consultation exercise, including a workshop held in Paris in December 2005, which generated feedback from regulators, industry, academia, healthcare professionals and patient groups. In accordance with the Agency's commitment to transparency, an overview of comments received will be published shortly.

# Biosimilars: EU regulatory framework

- General guidance documents supplemented by individual quality and non clinical & clinical guidelines with separate annexes, for: G-CSF, erythropoietin, insulin and GH
- Guidance document on interferon and immunogenicity currently being drafted

G-CSF, Granulocyte colony-stimulating factor; GH, growth hormone

# Similar biological medicinal product (SBMP)

Overarching guideline "Guideline on Similar Biological Medicinal Products" (CHMP/437/04) covering biotechnology-derived "Biosimilar" proteins

# The reality

# The situation in the EU in 2007


- EU: the only region with a comprehensive regulatory framework for Biosimilars
- Biosimilars evaluated by the EMEA (4 drugs in 2006, 11 planned for 2007)

- Two GHs approved (Omnitrope®,Valtropin®) - launched in Germany, Austria
- One Interferon rejected (Alpheon)
- First Erythropoietin approved (Sandoz et al)

# EMEA news

- EMEA has rejected BioPartners' Alpheon (interferon alpha) on the grounds of characterisation, manufacturing, and quality control concerns

European Medicines Agency

London, 28 June 2006
Doc. Ref. EMEA/190896/2006

# QUESTIONS AND ANSWERS ON RECOMMENDATION FOR REFUSAL OF MARKETING APPLICATION for ALPHEON

International Non-proprietary Name (INN): ***interferon alfa-2a***

On 28 June 2006 the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Alpheon 6 million IU/ml solution for injection intended for the treatment of hepatitis C. The company that applied for authorisation is BioPartners GmbH. They may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

**What documentation has been presented by the company to support the application to the CHMP?**

The company that makes Alpheon presented information showing that Alpheon had been compared to Roferon-A (structure of the active substance, composition and purity of the medicine, the way it works, safety and effectiveness in hepatitis C). The study in patients with hepatitis C compared the efficacy of Alpheon with that of the reference medicine in 455 patients. The study measured how many patients responded (no sign of virus in their blood) after 12 out of the 48 weeks of treatment and 6 months after stopping treatment.

**What were the major concerns which led the CHMP to recommend the refusal of the marketing authorisation?**

The CHMP had major concerns regarding the comparability of Alpheon and Roferon-A, because of differences identified between the two medicines (such as impurities). They also had concerns that there was not enough data on the stability of the active substance and of the medicine that was going to be marketed. Also, the process used for making the finished medicine had not been adequately validated.

The number of patients with hepatitis C responding to treatment with Alpheon and Roferon-A was similar in the clinical study. However, some differences were seen between the two medicines: more patients experienced a return of the disease after treatment with Alpheon was stopped than with the reference medicine, and there were more side effects with Alpheon. In addition, the test used in the study to investigate the potential for the medicine to trigger an immunological response (when the body makes special proteins, called antibodies, against the medicine) had not been sufficiently validated.

At this point in time, the CHMP was of the opinion that Alpheon could not be considered as a biosimilar medicine of Roferon-A, the reference medicinal product. Hence, the CHMP recommended that Alpheon be refused marketing authorisation.

# The key case

The first biosimilar epo

# June 2007 CHMP Meeting

**3 biosimilar EPOs with positive opinions**

- **Binocrit** (Epoetin alfa), Sandoz GmbH
- **Epoetin alfa Hexal** (Epoetin alfa), Hexal Biotech Forschungs GmbH
- **Abseamed** (Epoetin alfa), Medice Arzneimittel Pütter GmbH & Co

- Demonstration of similarity to the reference product Erypo/Eprex
- Received Community Marketing Authorisation from EU Commission in August

EPO, Erythropoietin

# Novartis to launch generic biological drug

BY ANDREW JACK IN LONDON

PUBLISHED: Financial times

SEPTEMBER 10 2007 23:45 | LAST UPDATED: SEPTEMBER 10 2007 23:45

*NOVARTIS IS TO SHAKE UP THE MARKET FOR AMGEN'S BLOCKBUSTER EPO DRUG FOR KIDNEY PATIENTS BY LAUNCHING A CUT-PRICE GENERIC EQUIVALENT IN EUROPE AS SOON AS NEXT MONTH, A SENIOR COMPANY EXECUTIVE SAID ON MONDAY*

*ANDREAS RUMMELT, HEAD OF SANDOZ, NOVARTIS'S GENERICS ARM, SAID THE SWISS GROUP'S VERSION OF EPO ALFA WOULD BE PUT ON SALE IN THE UK AND GERMANY IN THE COMING WEEKS, AND WAS LIKELY TO BE PRICED ABOUT 25–30 PER CENT CHEAPER THAN THE ORIGINAL MEDICINE*

# The outstanding issues

- How similar is similar?
- Naming
- Labeling
- Substitution/Exchange
- Post marketing surveillance
  - Background data?
  - Lack of standardization

# French parliament adopts new law

- 6 Feb 2007: French parliament adopted a new law on “human medicinal products”
- This law recognises the unique nature of Biosimilars and **does not allow automatic substitution of biological medicines at the pharmacy level without the consent of the treating physician**
- Physicians must be able to monitor their patients for adverse reactions, therefore it is essential that they retain control over the treatment

# The FDA?

# The situation in the rest of the world

- WHO guideline in preparation
- Switzerland: EU model?
- Australia: Omnitrope® approved in 2004, case-by-case approach
- Canada: Same legislation as for originator products?
- China: Regulation requiring a clinical development programme
- Japan: No regulatory provision yet
- India, South Korea, Latin America: ???

WHO, World Health Organisation

# The FDA regulatory situation

- US: FDA still in the process of defining regulations
- Submission of a 'New Drug Application' (NDA) for well-characterised molecules is possible – e.g. Insulin, GH

- Omnitrope® approval in 2006: not through established procedure 'not a biosimilar but sufficiently similar - follow-on protein'
- FDA commented that Omnitrope® was not interchangeable and emphasised that this approval did not create an automatic approval mechanism for biosimilars in the US

# The US situation: Waxman-Schumer Bill

- Introduced 14 February 2007 by senators Waxman, Schumer and co-sponsored by Clinton
- Proposing that abbreviated applications currently used for generics be applied to Biosimilars
- The abbreviated application must show the Biosimilar's
  - Comparability to the reference product
  - Highly similar molecular structure to reference product
  - Mechanism of action (MoA) same as the reference product
  - Product label carrying at least 1 of reference product's approved indications
  - Route of administration, dosage form and strength same as reference product

# Discussion