



SwedenBIO

*Update on Clinical trials/ Regulatory – Hot topics for
Swedish companies (8th November 2006)*

Biosimilars – a new era in biotech
Company perspective

Andrew Fox
European Regulatory Affairs
Amgen

Agenda

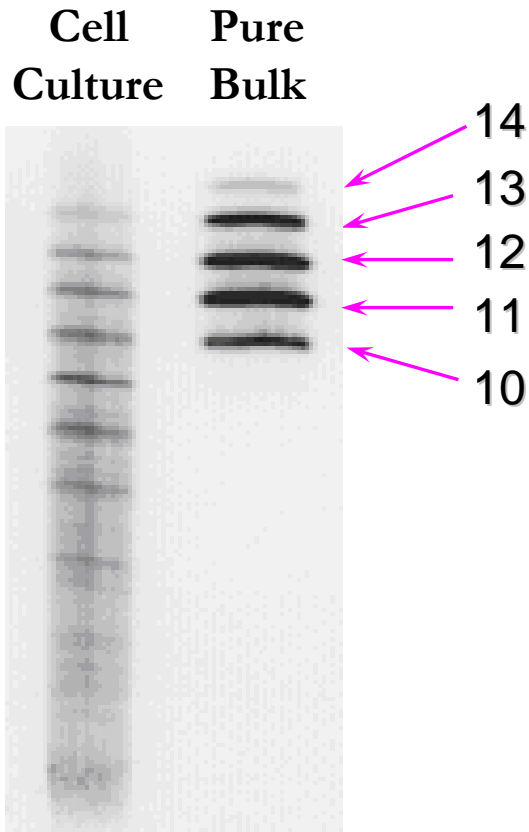
- Science
- EMEA guidelines
- Outstanding topics beyond the guidelines

What is a biosimilar?

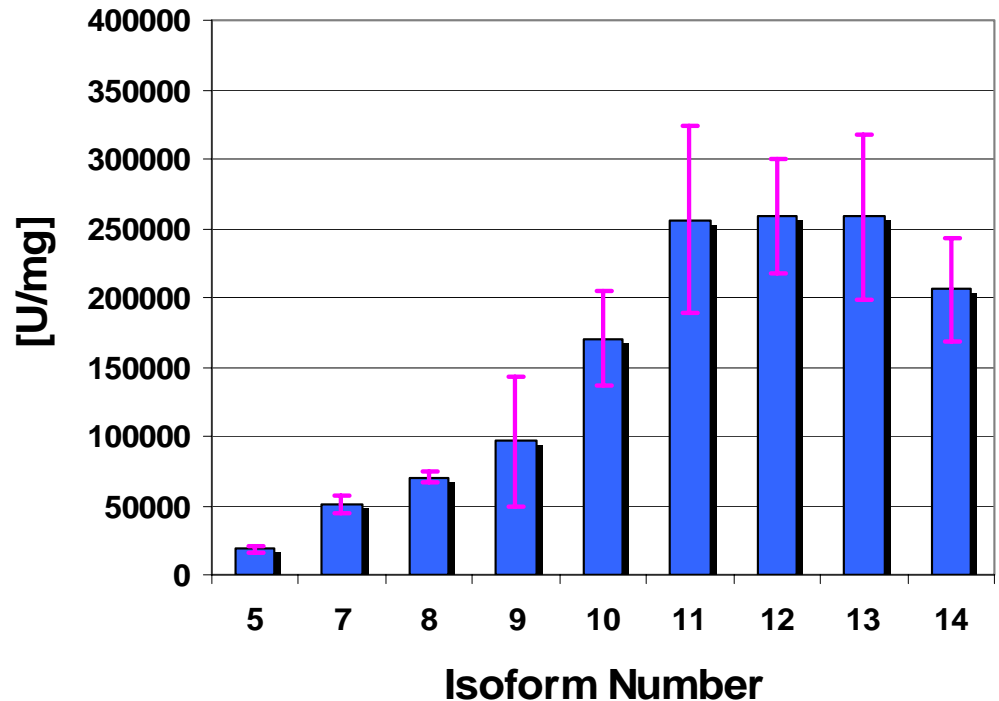
- Biosimilar, Follow-on Biologic, Follow-on Protein, Subsequent Entry Biologic
- Biological product that claims to be similar to an innovator biological product
- The innovator's product is off-patent and no regulatory data protection remains
 - Manufactured by a second manufacturer
 - New cell line, process, analytical methods
- Do they already exist?
 - Omnitrope[®] (somatropin) in Australia, EU and US
 - Valtropin[®] (somatropin) in EU
 - ... not the copies already existing in Asia and South America

Biotech medicines are not a single active ingredient, they are a heterogeneous mix of similar isoforms

Isoelectric Focusing: epoetin alfa product is subfraction of cell culture isoforms



In-vivo Bioactivity



Epoetin alfa from other regions differ from Eprex[®]

Table 1. Epoetin alfa products

Sample	Concentration (IU/ml)	Country*
IA	2,000	Korea
IB	4,000	Korea
IIA	2,000	Korea
IIB	10,000	Korea
IIIA	2,000	Korea
IIIB	10,000	Korea
IV	2,000	Argentina
V	10,000	Argentina
VI	4,000	India
VII	10,000	China
VIII		China

*Location where the marketed samples were obtained.

Source: Schellekens H, EJHP, 3/2004, Scientific Section, pp 43-47.

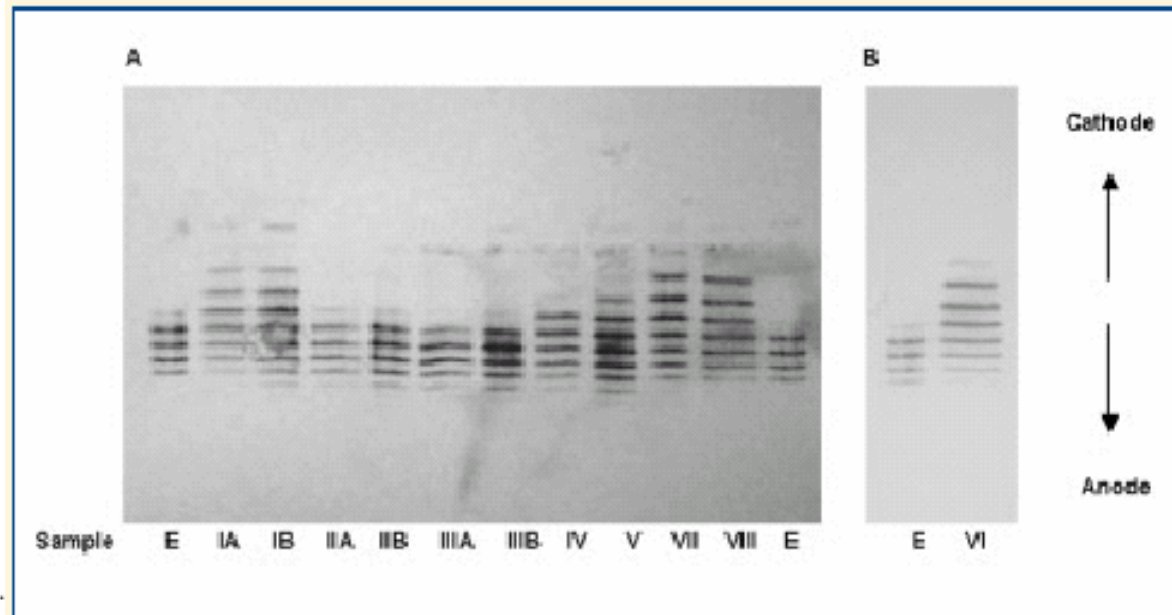


Figure 1

Isoelectric Focusing / Western Blot. Isoform distribution of each sample is shown. For comparison, the Eprex[®] (E) control is shown in the first and last lanes of Figure A and in the first lane of Figure B.

But, what looks the same may be different

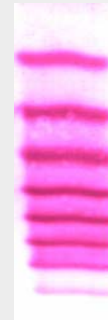
IEF pattern and sialic acid content of the two EPOs are very similar

... but the biological activity is very different

The carbohydrate structures of the two EPO isoforms are different

huEPO - 1

huEPO - 2



isoform 2

isoform 2

Sialic acid

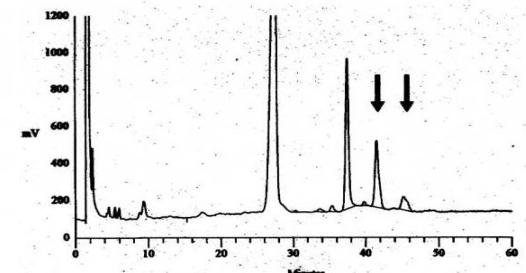
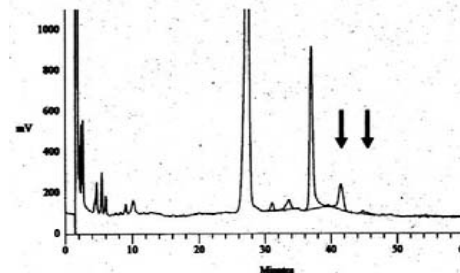
14.0

In-vivo activity
(U/mg)

226,000

14.2

400,000



Adapted from Kresse
(Burg, J. et al. 1998 PCT/EP/98/07876)

Biosimilars will be similar, not identical, to the product they seek to copy

EMA Guidelines

- “It is not expected that the quality attributes ... will be identical”
- “Minor differences in the active substance, such as variability in post-translational modifications may be acceptable, however, must be justified”
- “there may be subtle differences between biosimilars”



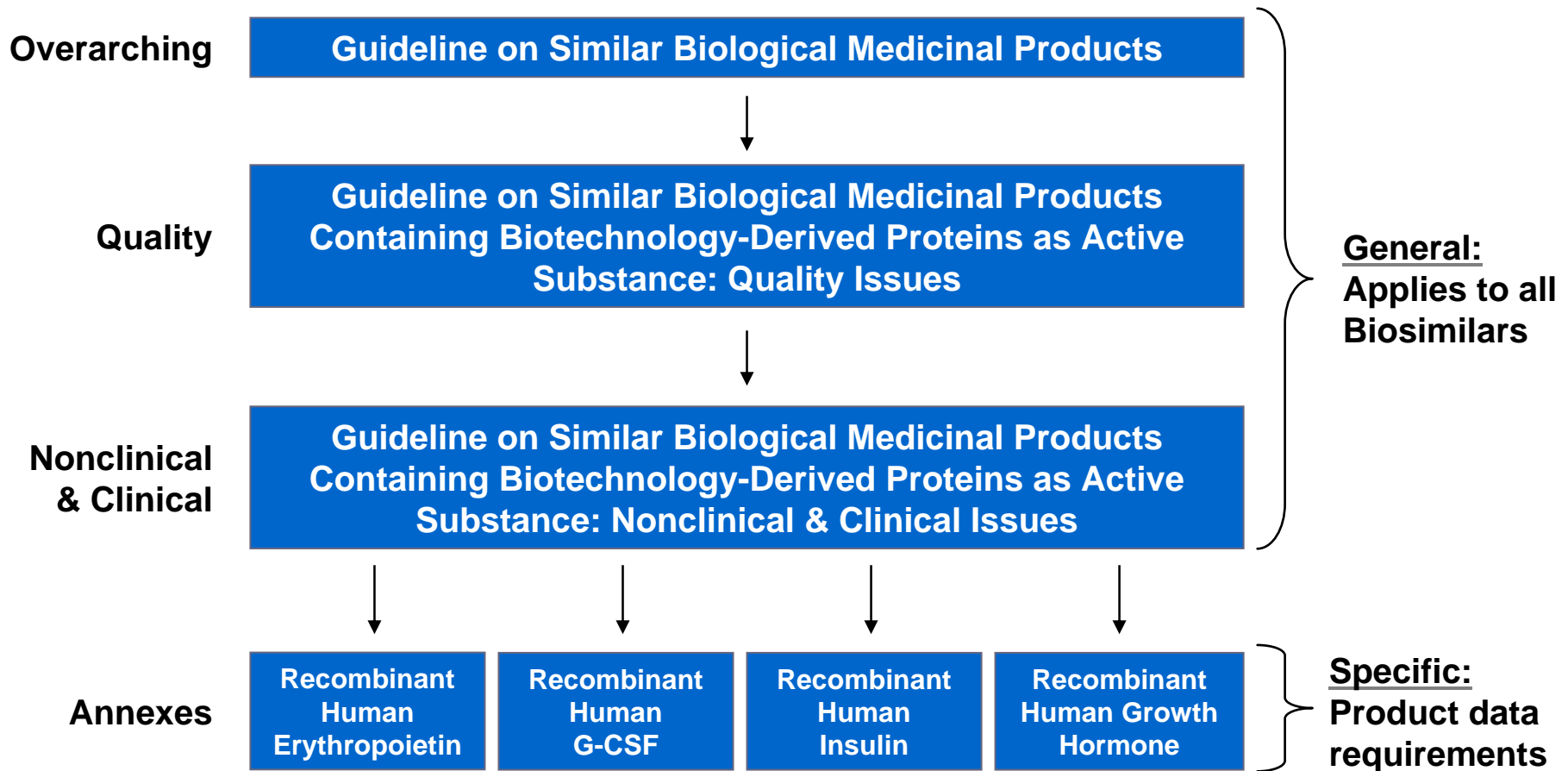
EMEA Guidelines

Legal & regulatory status in Europe

- European Commission have decided on a new legal pathway to bring Biosimilars to market
 - ie. not the generic pathway
- The EMEA has finalised guidelines on the scientific and clinical requirements for Biosimilars
 - ie. not generic requirements
- This means that biosimilar products are not generic products, either legally or scientifically



Overview of EMEA guidelines



Normal MAA *vs.* biosimilar MAA

CMC

- Drug substance
 - Manufacture
 - Characterisation
 - Control
 - Reference standard
 - Container
 - Stability
- Drug product
 - Description
 - Development
 - Manufacture
 - Control
 - Reference standard
 - Container
 - Stability

- + Comparability data
 - + Analytical comparison with reference product

Nonclinical

- Pharmacology
 - Primary pharm.
 - Secondary pharm.
 - Safety pharm.
 - Interactions
- Pharmacokinetics
 - ADME
 - Interactions
- Toxicology
 - Single dose
 - Repeat dose
 - Genotoxicity
 - Carcinogenicity
 - Reproduction
 - Local tolerance

Clinical

- Pharmacology
- Pharmacokinetics
 - Single dose
 - Repeat dose
 - Special populations
- Efficacy and safety
 - Dose finding
 - Schedule finding
 - Pivotal
 - Indication 1
 - Indication 2
 - Indication 3
 - Indication 4
- Risk management plan

Characteristics of G-CSF guideline

Preclinical studies	Comparative non-clinical studies 28-day toxicology
Human PK & PD studies	Single dose in healthy volunteers using SC and IV ANC and CD34+ in healthy volunteers
Efficacy studies	2-arm (vs. reference product) <u>OR</u> 3-arm (vs. reference product + placebo) equivalence trial in CIN <u>OR</u> PD study in healthy volunteers (if justified)
Extrapolation	Yes – Equivalence in CIN will allow extrapolation to other indications, if mechanism of action is the same
Safety	Evaluate AE's and immunogenicity in CIN study 6-month follow-up
Post-Approval Commitments	Specific monitoring for LOE in extrapolated indications

Characteristics of EPO guideline

Preclinical studies	Comparative non-clinical studies 28-day toxicology
Human PK & PD studies	Single dose in healthy volunteers using SC and IV Include PD evaluation (reticulocytes) in PK studies
Efficacy studies	2 randomised, double blind studies in nephrology (6-month) SC and IV Dose and Hb as primary endpoints
Extrapolation	Yes – equivalence in renal anaemia may allow extension to other indications, if justified by applicant
Safety	Safety from efficacy studies is adequate for approval 12-month, comparative immunogenicity data
Post-Approval Commitments	Pure red cell aplasia to be addressed Safety in cohort of patients from all indications (ie. including extrapolated indications)



Outstanding Topics

Pharmacovigilance systems should cope with biosimilar introduction

**This is not an issue unique to biosimilars
existing issue that is highlighted and exaggerated by their arrival**

Eporex® → Biosimilar EPO α (1) → Biosimilar EPO α (2) → *Adverse Event*

Ensure traceability

Company and Regulatory Agency AE reporting systems should distinguish one manufacturer's product from another

- Complex, if biosimilars have the same INN as the innovator
- AE reports are often incomplete eg. lot number

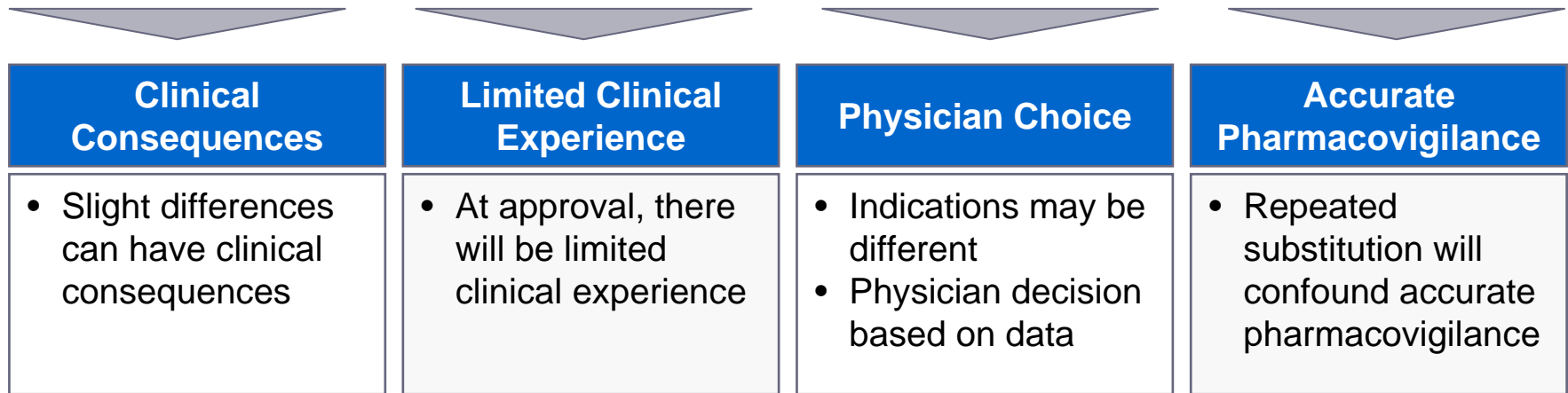
Prevent repeated, uncontrolled substitution

Repeated, uncontrolled substitution will confound accurate pharmacovigilance

- Occasional changes are inevitable or necessary in chronic therapy

Should automatic substitution rules apply to biotechnology products?

Biosimilars are similar, but not identical to the reference product



United States (U.S. FDA Considerations on Possible INN Policies for Biosimilars)

- “U.S. FDA believes that the only way to establish pharmacologic interchangeability is through scientific data”

Europe (Thomas Lonngren media interview)

- “It is not possible we would guarantee a biosimilar is interchangeable (with its originator) ... the decision is based on clinical experience that you could switch ...”

Labelling

Summary of product characteristics - different to reference product

Summary of Product Characteristics

1	Name of the medicinal product	Different
2	Qualitative and quantitative composition	Potentially different
3	Pharmaceutical form	Potentially different
4.1	Therapeutic indications	Potentially different
4.2	Posology and method of administration	Similar
4.3	Contraindications	Potentially different
4.4	Special warnings and precautions	Different
4.5	Interactions	Similar
4.6	Pregnancy and Lactation	Similar
4.7	Ability to drive/use machines	Similar
4.8	Undesirable effects	Different
4.9	Overdose	Similar
5	Pharmacological properties	Different
6	Pharmaceutical particulars	Different

4.4 Special warnings and precautions

Advice to healthcare providers on substitution:

- “Changes from {Brand X} to another {common name} preparation should be done under medical supervision”

4.8 Undesirable effects

- Unique data from biosimilar product could be included
 - Number of patients, indications & data
- Cross-reference to reference product

5.1 Pharmacological properties

- Define basis for approval as a biosimilar & identify the reference product
- Define which indications are based on data and those that are extrapolated

AMGEN

Naming

Same or similar International Nonproprietary Name (INN)

New products = New name

- New chemical or biological entities

For example:

- Filgrastim, lenograstim & nartograstim
- Atorvastatin, simvastatin

Identical = Identical name

- Small-molecule generics

For example:

- Atorvastatin, simvastatin

Similar = Similar name?

- *Biosimilars*

- *No provision under World Health Organisation (WHO) criteria*

WHO Open Meeting with Pharmaceutical Manufacturers on Nomenclature for Biological and Biotechnological Substances, including Biosimilars

Geneva, 13 November 2006

“The aim of the INN system ... is important for the clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists worldwide.”

Conclusions

- Biosimilars are a new class of medicinal product
 - Not generics in the small-molecule sense
- EMEA have established a good standard for approval
 - Outstanding questions can be addressed post-approval
- There are still outstanding topics relating to their introduction into clinical practice
 - Pharmacovigilance
 - Application of automatic substitution rules
 - Labelling
 - Naming