

BIOSIMILAR BASICS

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Domus medica, presentatie door Bio.be

AGENDA

■ Definitions

- Biosimilars vs. Generics
- Legal & Regulatory Framework
- Outstanding Issues
 - Pharmacovigilance
 - Substitution
 - Naming
 - Labeling

WHAT IS THE DIFFERENCE BETWEEN BIOTECH MEDICINES AND CHEMICAL MEDICINES?

- Biotech medicines are derived from living cells
 - Chemical medicines are derived from chemical processes
- Biotech medicines are complex in structure
 - Chemical medicines have a simple and well-defined structure
- Because of the way they are expressed by living cells, biotech medicines contain a mixture of related molecules and are difficult to characterise
 - Chemical medicines, on the other hand, are easy to characterise

There are more than 150 biotechnology medicines on the market

More than 325 million patients worldwide use biotech medicines

50% of medicines in clinical development are biotech medicines

WHAT ARE BIOSIMILARS?

- The expiry of patent protection and regulatory data protection for certain biotech medicines has led to the development of what are called biosimilars
- Biosimilars are products that claim to be a copy of the original, innovative biotech medicine
 - eg. epoetin, G-CSF, insulin, somatropin
- However, they are made with a different cell-line and a different manufacturing and purification process
- As they are made by a different manufacturing process
 - This will lead to biosimilars having similar, but not identical biophysical characteristics to the innovator biotech medicine

PATENT EXPIRATION OF BIOPHARMACEUTICALS

Pioneer company	Product	Indication(s)	EU patent/market exclusivity expires	USA patent/market exclusivity expires
NovoNordis	Norditropin® (somatropin)	Growth disorders	Expired	Expired
Eumedica	Actosolv® (urokinase) v	Ischaemic events	Expired	Expired
Eli Lilly	Humulin® (recombinant insulin) v	Diabetes	Expired	Expired
Genzyme	Cerezyme® (imiglucerase)	Gaucher disease	Expired	Expired
Aventis Beh	Streptase® (streptokinase) v	Ischaemic events	Expired	Expired
Schering-Plough	Introna® (IFN-alfa-2b) (v)	Hepatitis B v and C	Expired (France) 2007 (Italy)	Expired
Eli Lilly	Humatrope® (somatropin)	Growth disorders	NA	Expired
Janssen-Cilag	EPREX® (erythropoietin)	Anaemia	2004	2013
Roche	NeoRecormon® (erythropoietin)	Anaemia	2005	NA
Boehringer	Metalyse®(tenecteplase TNK-tPA)v	Acute myocardial infarction	2005	2005
Boehringer	Immukine® (IFN-gamma-Ib) v	Chronic granulomatous disease (CGD)	2004	2005, 2006, 2012
Novartis	Proleukin® (IL-2)	Renaal adenocarcinoom	2005	2006, 2012
Amgen	Neupogen® (filgrastim G-CSF)	Anaemia, leukaemia, neutropenia	2006	2015

DO BIOSIMILARS ALREADY EXIST?

- The first biosimilars in Europe were approved in 2006
 - Omnitrope (biosimilar to Genotropin)
 - Valtropin (biosimilar to Humatrope)
- Multiple biosimilar products are under development for the European market
 - by Novartis (Sandoz), Ratiopharm, Pliva etc.
- There are marketed biological products from companies outside US and Europe
 - eg. multiple epoetin alpha's in Asia and South America
 - but these are NOT biosimilars, as they do not meet the regulatory approval standards of Europe

SUMMARY - DEFINITIONS

- Biotech medicines are derived from living cells
- Biosimilars claim to be a copy of the original innovative biotech medicine, but they are not identical
- Biotech medicines cannot be copied exactly because they are derived from living cells and organisms

Biosimilars are similar – not identical



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FOUR THINGS TO CONSIDER ABOUT BIOSIMILARS



Molecular Properties



Manufacturing Process



Safety



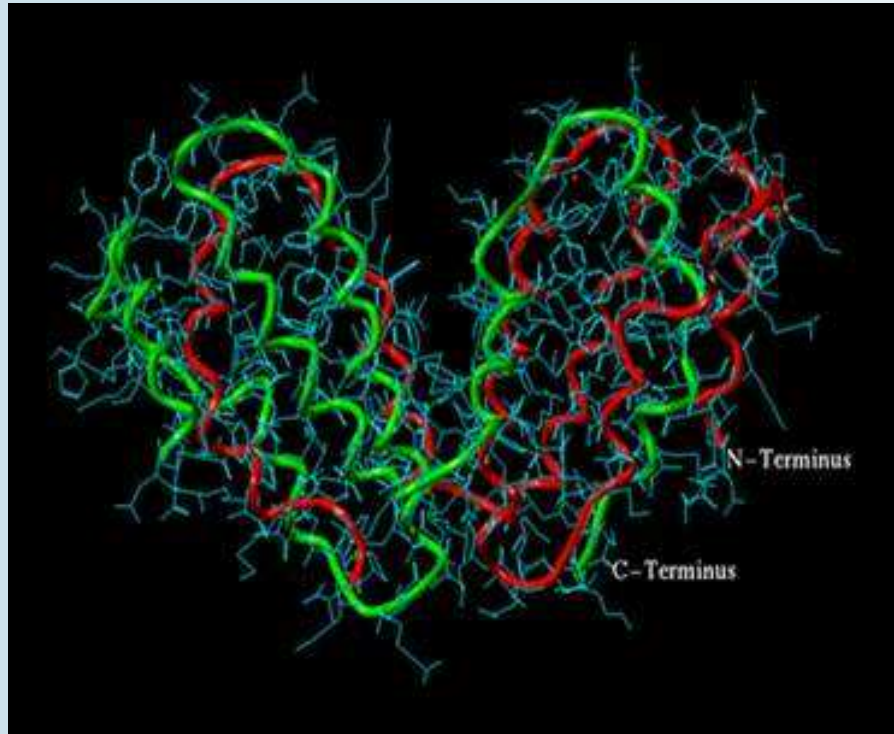
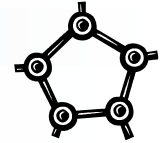
Efficacy



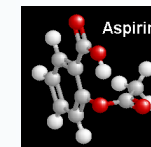
MOLECULAR PROPERTIES

- Biotech products are more complex than small molecules
 - Large molecules, typically 100 to 1000 times larger than a conventional small molecule drug
 - Posses a fragile 3-dimensional structure
 - Not 'pure' homogeneous molecules.

EXAMPLE: INTERFERON BETA VS. ASPIRIN

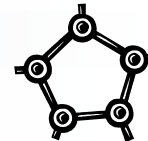


Interferon Beta
MW 19'000D



Aspirin:
MW 180D

Source: Fraunhofer IGB (Interferon Beta)

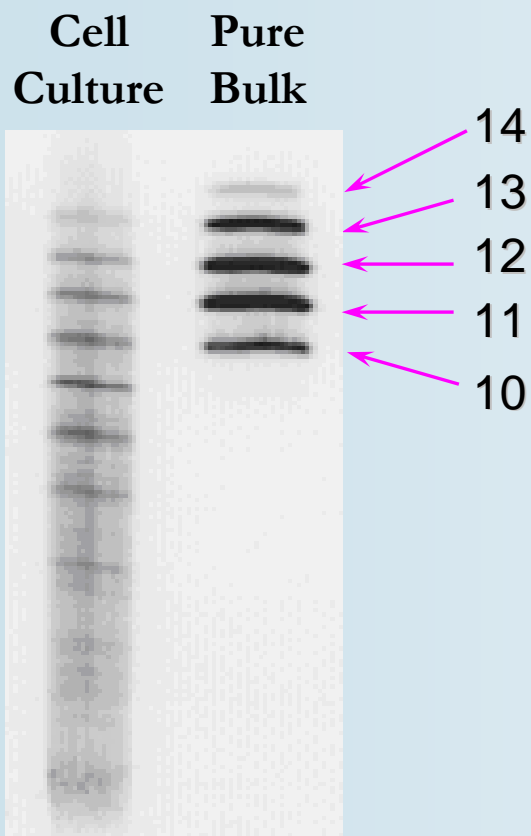


BIOTECH MEDICINES DO NOT CONTAIN A SINGLE ACTIVE INGREDIENT, THEY ARE A HETEROGENEOUS MIX OF SIMILAR ISOFORMS*

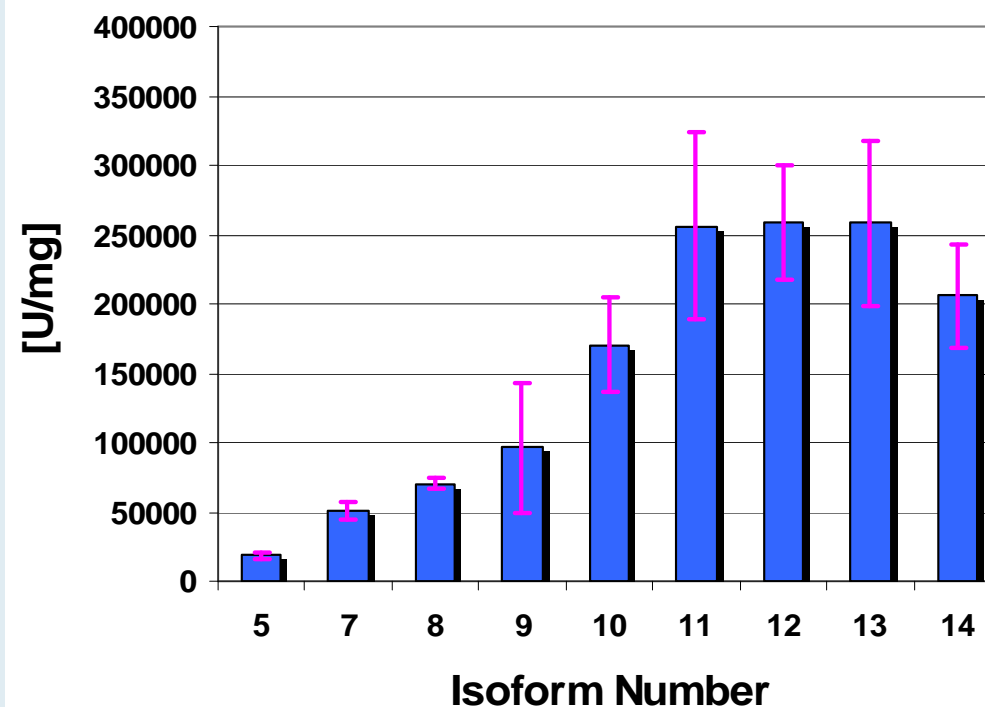
(DIFFERENT ISOFORMS IF SUGAR

MOLECULES ARE ATTACHED TO OTHER BINDINGSITES)

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



In-vivo Bioactivity



EPOETIN ALFA FROM OTHER REGIONS ARE NOT IDENTICAL TO EPREX® (IMPACT ON PK, EFFICACY-SAFETY)

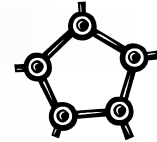


Table 1. Epoetin alfa products

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.

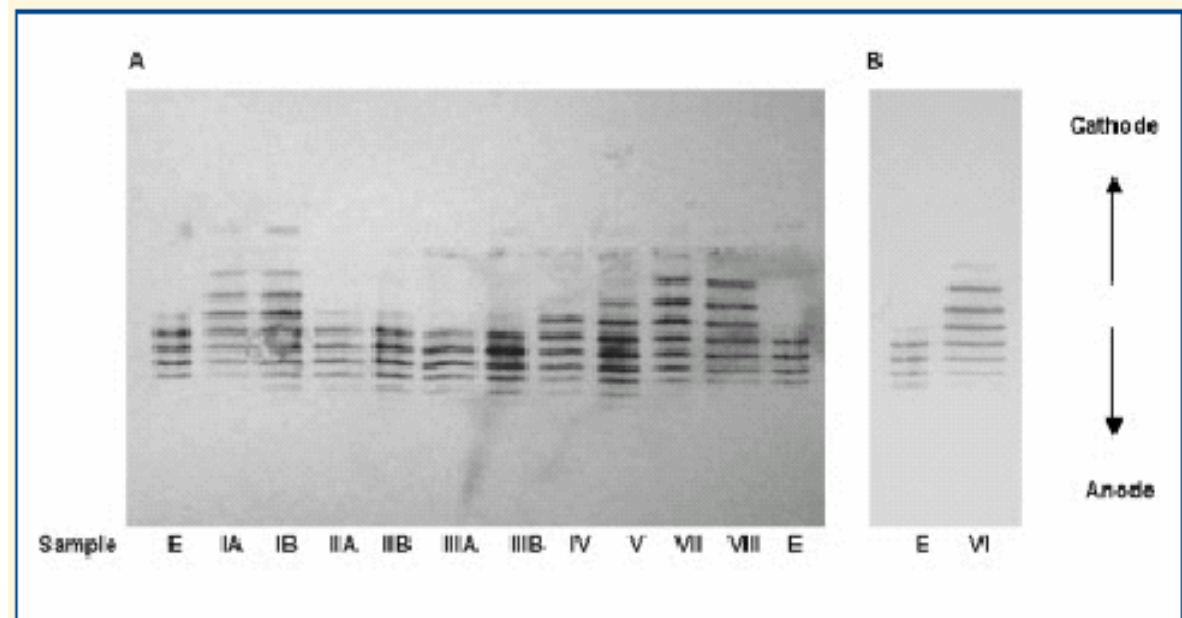
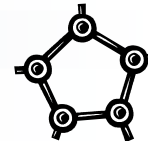


Figure 1

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.

Isoform patterns: deviations displayed by 9 of the 11 samples (including additional basic and acidic isoforms, and increased bar intensity) compared with the EU standard (E) (if less active isoforms: potency decreases)



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



8
7
6
5
4
3
2
1

isoform 2

Sialic acid 14.0
In-vivo activity (U/mg) 226,000

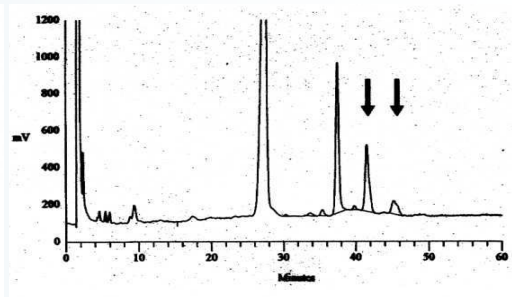
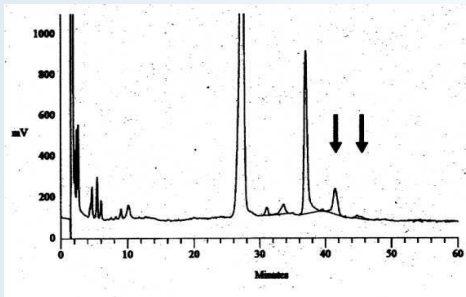
huEPO - 2



8
7
6
5
4
3
2
1

isoform 2

Sialic acid 14.2
In-vivo activity (U/mg) 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

European Medicines Agency Guidelines for Biosimilars

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



MANUFACTURING

- The quality and consistency of the product are highly dependant on the manufacturing process
 - The process defines the product

- Minor differences in the biophysical characteristics of a biotech medicine can have clinical consequences (critical effect on clinical efficacy and safety)

HOW ARE BIOPHARMACEUTICALS



MADE?

- **Develop host cell**
DNA sequence for protein, select vector to carry the gene, insert this in genome of a host (E. coli or yeast)
- **Establish a cell bank** (cell screening and yielding)
- **Protein production** (in spinners and bioreactors)
- **Purification** (remove endotoxines, viruses, other proteins)
- **Analysis** (3D structure, aggregation, isoform profile: the way glycosylation is performed, heterogeneity, potency) : cannot be fully characterised (not able to detect all characteristics that may affect clinical efficacy and safety)
- **Formulation** (eg. add stabilizer, HSA or polysorbate)
- **Storage and handling** (eg do not shake, cold chain)

⇒ Each of these stages can have a major influence on the characteristics of the end product



MANUFACTURING

- The average time from first cell culture to finished biological product is time-consuming:
8-9 months
- The manufacturing process is far more complex than for low molecular weight drugs (and generics)



IMMUNOGENICITY: IMPACT ON EFFICACY AND SAFETY

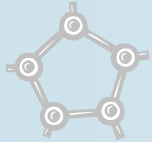
- If a Biological product is injected which is not the natural protein → immune system starts working to attack the foreign protein. This immune response can vary from no perceptible effect to significant clinical effects:
 - Generalized immune effects (allergy, anaphylaxis)
 - Neutralization of exogenous protein (loss or enhancement of drug efficacy)
 - Neutralization of the endogenous protein (serious adverse event)
- Factors influencing immunogenicity:
 - Amino acid sequence, glycosylation, host cell, impurities, formulation, handling/storage (aggregate formation)
 - Route of administration SC>IM>IV, concomitant disease, genetic factors



IMMUNOGENICITY: IMPACT ON EFFICACY AND SAFETY

- Biosimilars cannot be assumed to have the same immunogenicity profile as the original product
- Because immunogenicity is largely unpredictable, the assessment of a biosimilar must be based on:
 - a thorough risk-benefit analysis
 - robust post-marketing risk management programmes
- Physicians and hospital pharmacists should remain alert to unexplained changes in drug efficacy or side-effects

SUMMARY



Molecular Properties

- Are more complex than chemical medicines



Manufacturing process is crucial to the product

- Extremely sensitive to changes in manufacturing and production
- Minor variations could produce vastly different products



Safety

- The long term safety profile of biosimilars needs to be established
- Prescribers and patients should be aware of this to ensure appropriate introduction into clinical practice



Efficacy

- Can differ significantly with small changes in protein biophysical characteristics or in formulation of the drug product

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LEGAL & REGULATORY STATUS IN THE EU

The European Community has decided on a new legal pathway to bring Biosimilars to market



- i.e. NOT the generic pathway

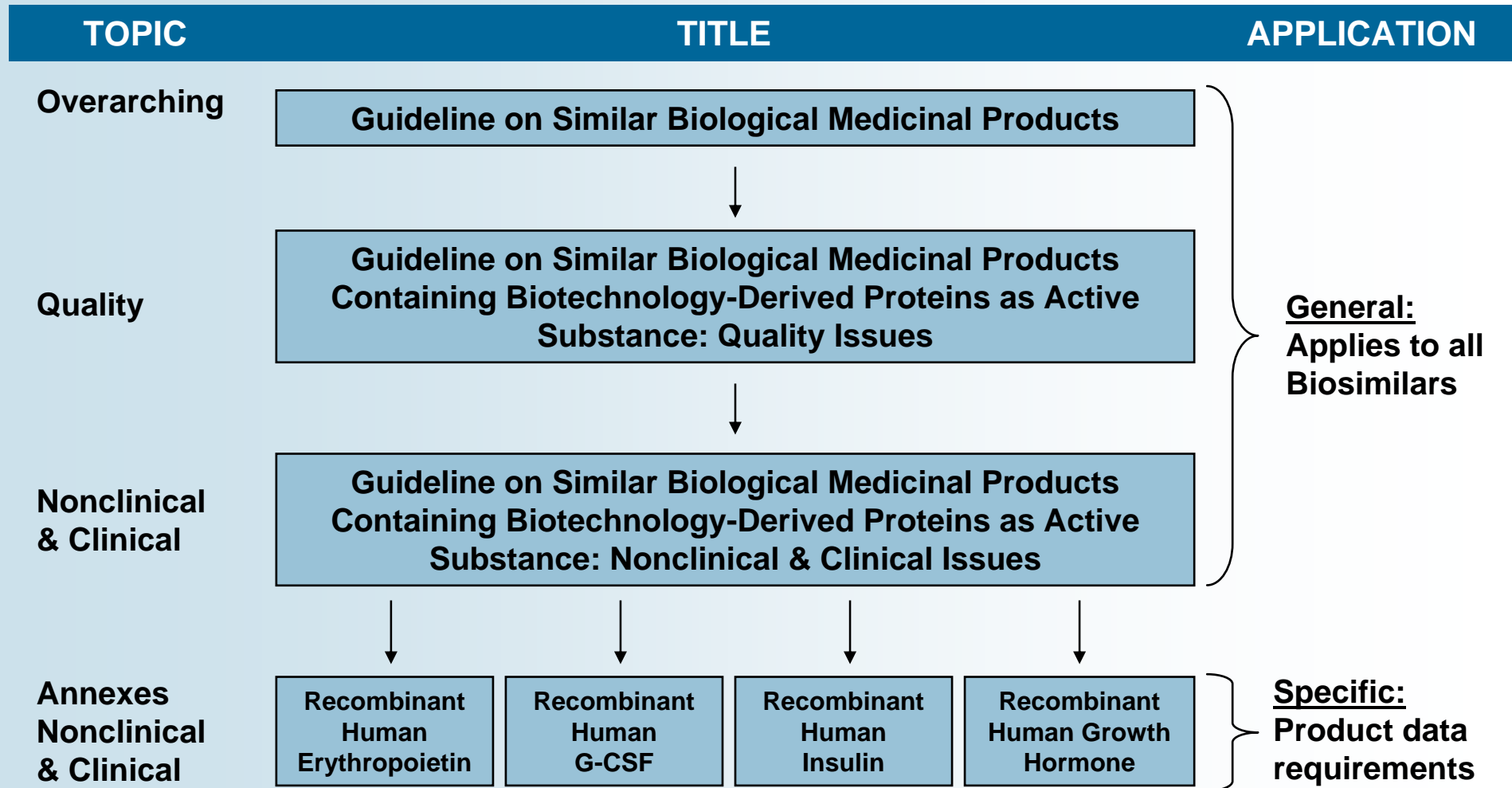
The EMEA has finalized guidelines on the scientific and clinical requirements for Biosimilars



- i.e. NOT generic requirements

Therefore: Biosimilar products are not generic products, either legally or scientifically

OVERVIEW OF EMEA GUIDELINES



EMA REGULATORY APPROVALS PROCESS (1)

- **Guideline on Similar Biological Medicinal Product**
 - The EMA set an overarching ‘umbrella’ guideline on the approach to bringing biosimilar products to market

- **Quality Guidelines**
 - This guideline indicates that biosimilar manufacturers need to identify a single reference product and conduct tests to demonstrate biophysical similarity
 - The EMA accepts that “It is not expected that the quality attributes ... will be identical” to the reference product

- **Non-Clinical & Clinical**
 - There is a requirement to provide non-clinical and clinical data to demonstrate clinical similarity to the reference product

EMEA REGULATORY APPROVALS PROCESS (2)

- Surrogate endpoints may be used to show similar clinical characteristics
 - Only if the endpoint is appropriately validated
 - Otherwise an efficacy study in an appropriate indication is required
- If the reference product has multiple indications
 - Biosimilar manufacturer may extrapolate to other indications if the mechanism of action is the same and if appropriately justified.
- The guidance requires immunogenicity data to be provided before approval
- Product specific annexes provide details for
 - EPO, G-CSF, Insulin and HGH



SUMMARY – REGULATORY FRAMEWORK

- 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 (Summary of Product Characteristics)
 - Naming (International Non-proprietary Names)

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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

Eprex[®] → 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

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PRINCIPLE OF GENERIC SUBSTITUTION DOES NOT APPLY TO BIOSIMILARS

Medicines are the same = therefore can be safely substituted



Generics / chemical drugs

Substances are identical = therefore can be substituted



Biosimilars/Biotech medicines are not identical

Can generic substitution rules be applied?

Therefore, with biotech medicines and biosimilars, the generic substitution rules do not apply



SUMMARY - SUBSTITUTION

- Biosimilars are not identical to originator, therefore automatic/generic substitution rules should not apply
- Any decision to substitute one biotechnology medicine with another should be made with the knowledge and explicit prior consent of the physician

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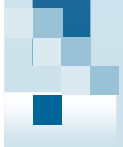
Naming

- Labeling

WHAT IS 'NAMING'?

“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.”

- The WHO International Non-proprietary Name (INN) system aims at identifying every medicinal product
- The INN is the ‘technical’ name for medicinal products
- The generic version of chemical medicines are assigned the exact same name, as they are identical copies of the reference product
- The WHO is currently deciding whether biosimilars should be assigned a different INN to that of the original biotechnology medicine



ERROR: syntaxerror
OFFENDING COMMAND: %ztokenexec_continue

STACK:

-filestream-
true
true