Scientific Aspects for the Establishment of Biosimilar Guidelines

The Perspective of EBE/EFPIA

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on behalf of European Biopharmaceutical Enterprises , EBE a specialized group of EFPIA

Definitions

Generic	Biopharmaceutical	Biosimilar*
Chemical and therapeutic equivalent of original low molecular weight drug whose patent has expired	Biological medicinal products developed via biopharmaceutical techniques such as: • Recombinant DNA technology • Cell fusion	Biological product referring, but not identical, to an existing product, submitted for separate marketing approval following patent expiration

*also referred to as 'follow-on biologicals, FOBs' or "second entry biologicals, SEBs", term "Biosimilars" will be used in this presentation

Roger SD. *Nephrology* 2006;11:341–6;
Crommelin D et al. *European Journal of Hospital Pharmacy Science* 2005;1:11–7

Biosimilars are not Generics

- Article 10(4) introduced an abridged approval system for biosimilars – equivalent to the system for approval of small molecule generics in the EU
- BUT biosimilars are not generics
  - Generics are clinically identical to their reference products
  - ***Biosimilars can never be identical to their reference products***
- Due to the complexity & variability of a biological, the quality profile is determined by the manufacturing process
  - '***the product is the process***'
- Differences in process are inevitable between different manufacturers
  - ***minor process differences can lead to marked differences in clinical profile***

Characteristics of Biologics

Biosimilars can never be identical to a reference product:

- **The product is the process**
- **<u>Minor</u> process differences can lead to <u>marked</u> differences in clinical profile**

Why ?

- **Size**
- **Complexity** beyond size through the way of manufacturing and their molecular structure
- **Uncertainty** beyond complexity and size through the limitations of chemical analysis and preclinical studies

Size – Small Molecules & Proteins

	Small Molecule	Protein	Large Protein
Size	Aspirin 21 atoms	hGH ~ 3000 atoms	IgG Antibody ~ 25,000 atoms
Complexity	Bike ~ 20 lbs	Car ~ 3000 lbs	Business Jet ~ 30,000 lbs (without fuel)

Source: adapted from Genentech

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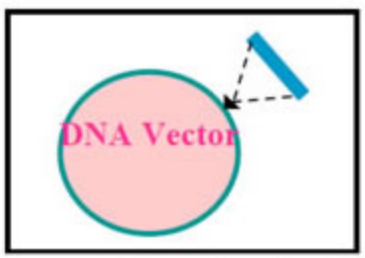
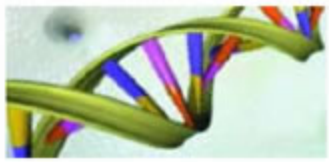
Manufacturing



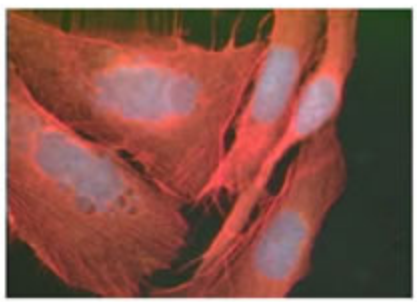


Cloning into DNA Vector

Transfer into Host Cell
Expression
Cell Development

Large-Scale Culture

Downstreaming



e.g., bacterial or mammalian cell

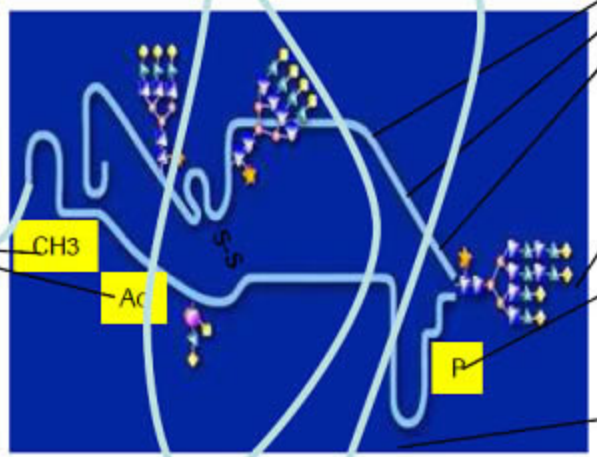
Formulation

Complexity of Proteins

Proteins will be modified both by the Manufacturing Cell itself and during the Production Process

artificial, desired modifications
(e.g. pegylation)

biologic, undesired modifications
(e.g., methylation, acylation, glycation, proteolysis/ truncation, splice variation)



process related, undesired modifications of amino acids
(e.g., oxidation, deamidation pyroglutamate formation)

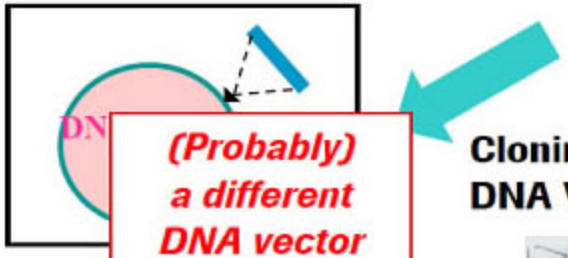
biologic, desired modifications
(e.g., glycosylation, phosphorylation, sulfatation, acylation)

process related, undesired modifications of the tertiary and quaternary structure
(e.g., partial denaturation, aggregation)

Even highly purified proteins will always be a family of closely related molecules

Manufacturing

A second manufacturer uses...

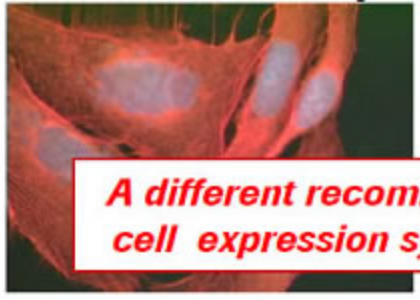


(Probably) a different DNA vector

Maybe the same genetic sequence

Cloning into DNA Vector

Transfer into Host Cell
Expression
Cell Development

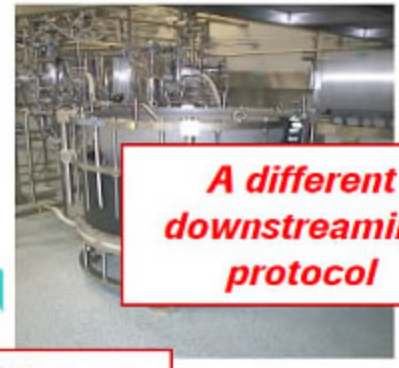


A different recombinant cell expression system

e.g., bacterial or mammalian cell

A different cell culture process

Large-Scale Culture



A different downstreaming protocol

streaming

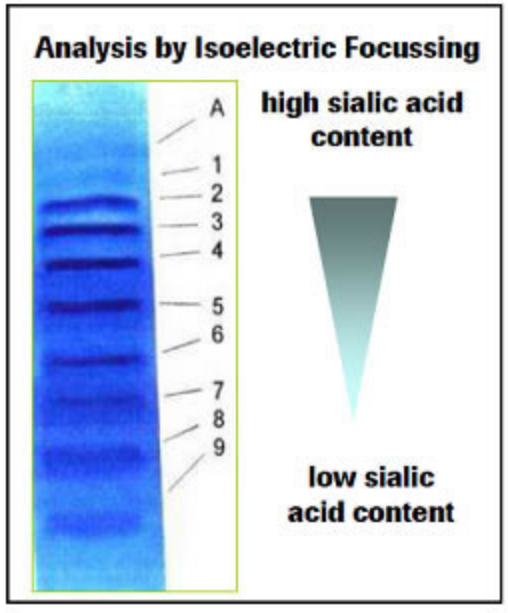
Different in-process controls

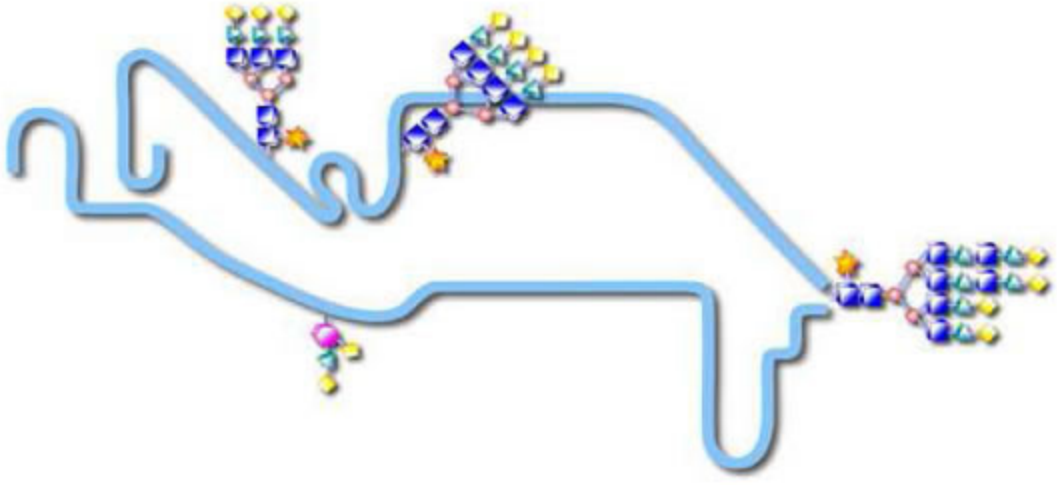
Maybe different formulation

Formulation

Different Process → different product – challenging to demonstrate similarity

Complexity of EPO





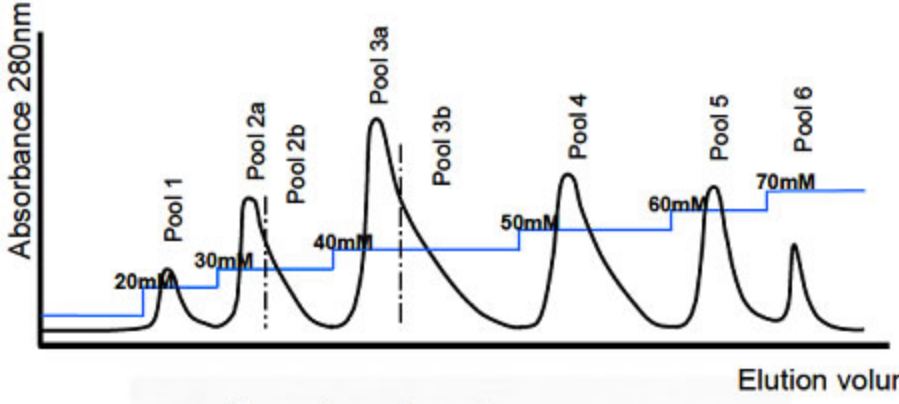
Differences in glycosylation lead to

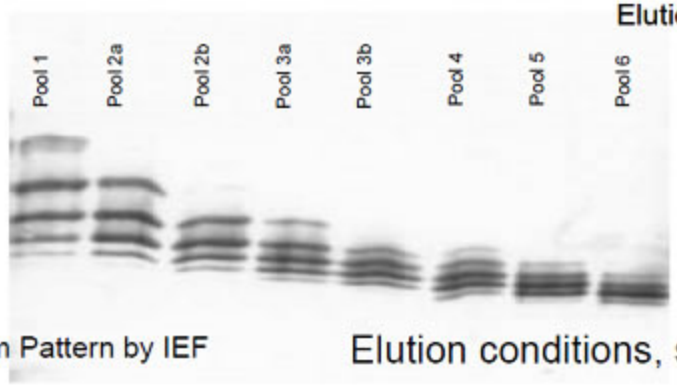
- difference in stablility

- difference in serum half life

→ difference in bioactivity

Heterogeneity of EPO Products





Isoform Pattern by IEF

- Process conditions and in-process controls will determine the product composition

Elution conditions, separation and IEF analysis of EPO fractions

Heterogeneity of EPO Products

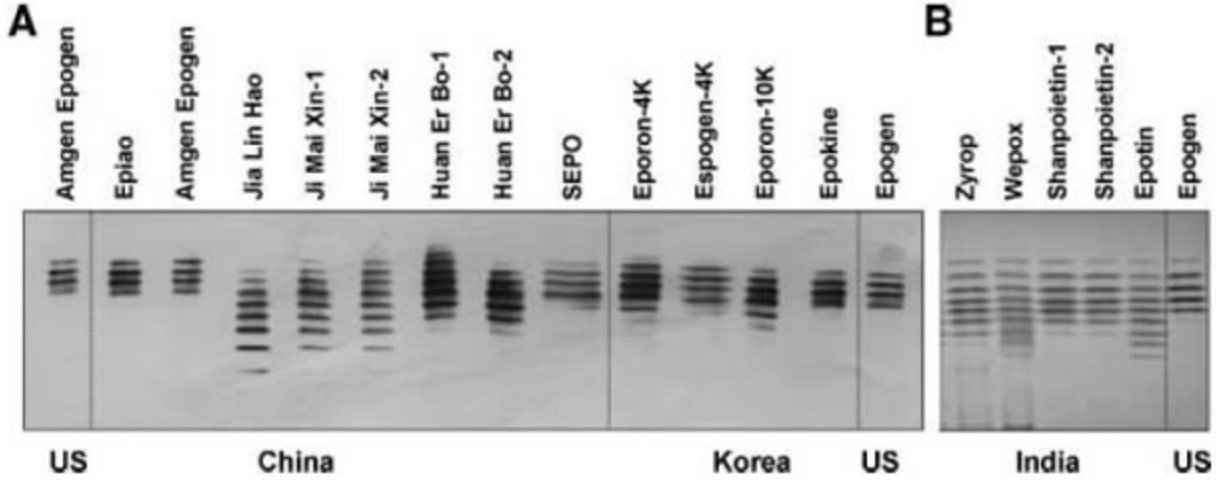
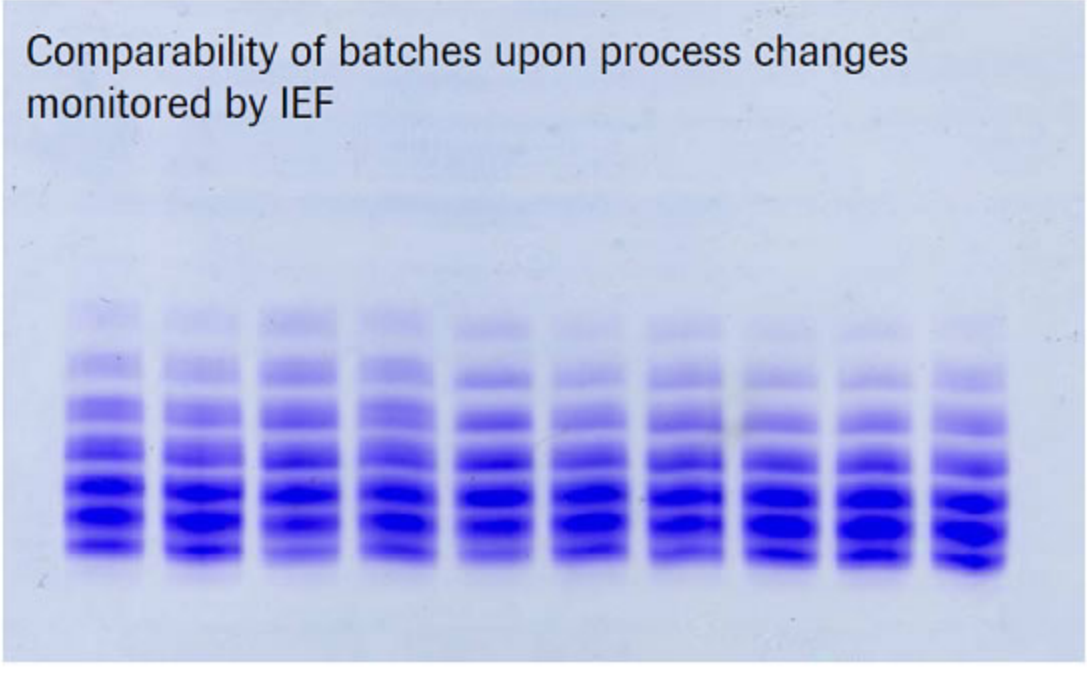


Figure 1. Iso-electro-focus (IEF) Gel with Western blots for isoform detection: (A) samples from China (lanes 2–9) and Korea (lanes 10–13) and (B) samples from India (lanes 1–5).

Park et al., J Pharm Sci Sep 2008, http://dx.doi.org/10.1002/jps.21546

Comparability of EPO Batches

from an established process



G025-G029: 5 fermentation runs (basic process)

G030: reference standard

G039: variation, optimized RP-HPLC

G044: variation, sterile filtration

G061: variation, fermentation media constituent

G003: variation, produced in new building

Source: H: Haug, V. Pfeifer, Roche Penzberg

Comparability vs. Biosimilarity

Comparability and Similarity are two distinct concepts:

- **Comparability** is "a conclusion that products are highly similar before and after manufacturing process changes and that no adverse impact on the quality, safety or efficacy of the drug product occurred" (ICH Q5E).
- **Similarity** applies to the evaluation of an independently manufactured subsequent-entry product claiming to be similar to a reference innovator product

Comparability testing according to ICH Q5E cannot be applied to compare products from different manufacturing process,

- where product manufacturing-, quality-, non-clinical- and clinical history does not exist,

- where a new cell line is used and multiple differences exist as compared to the innovator's process.

Characteristics of Biologics

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Why ?

- **Size**
- **Complexity** beyond size through the way of manufacturing and their molecular structure
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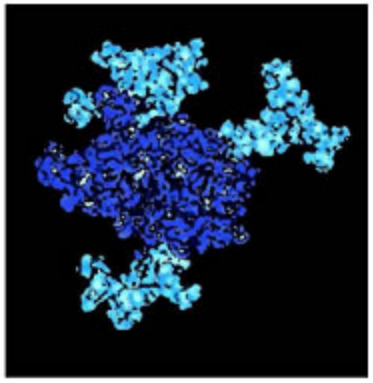
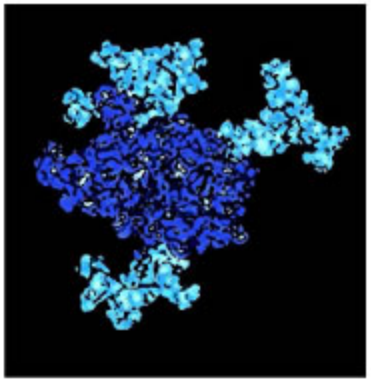
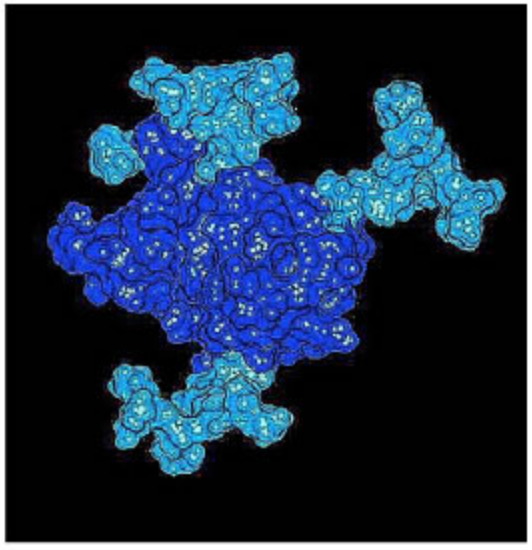
The dilemma of improving analytics of complex molecules



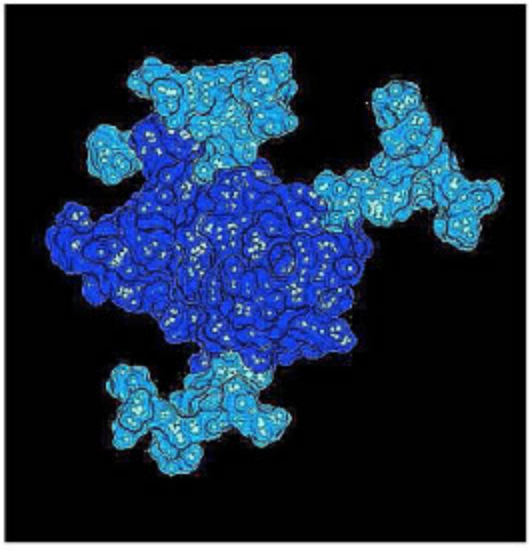
Things that look alike at low resolution...





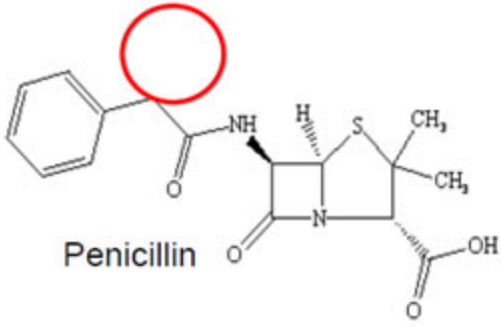
... may become less similar on increased analytical sensitivity

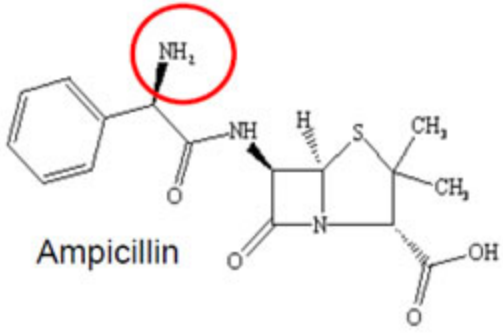
The closer you look, the more you will see



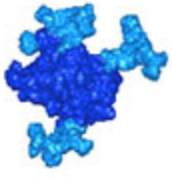
Protein Complexity

Structure-Function Relationship

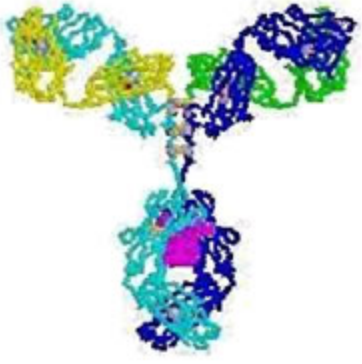




In **small molecules**, every atom is critical for the biological function of the molecule



Erythropoietin
> 4000 atoms



Monoclonal Antibody
> 25 000 atoms

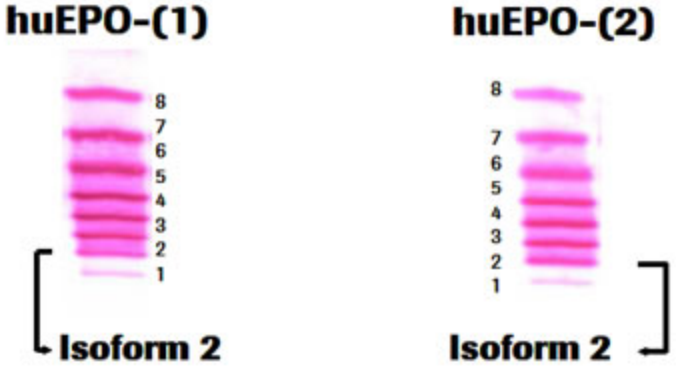
In **proteins**, each atom may, or may not, affect clinically relevant properties such as half-life, safety, efficacy, or immunogenicity of the molecule

Therefore, the **impact** of differences on clinical **efficacy and safety** usually cannot be predicted

Heterogeneity of EPO Products

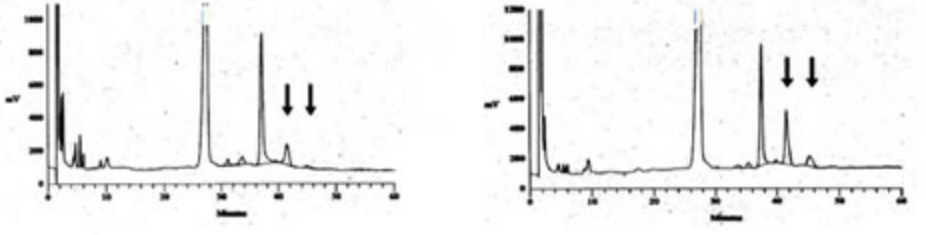
IEF pattern and sialic acid content of the two EPO isoform preps are very similar

Source data: Burg, J. et al. 1998 PCT/EP/98/07876



	14.0	Sialic acid	14.2	(mol/mol)
But bioactivity is different	226,000	in vivo activity	400,000	(U/mg)

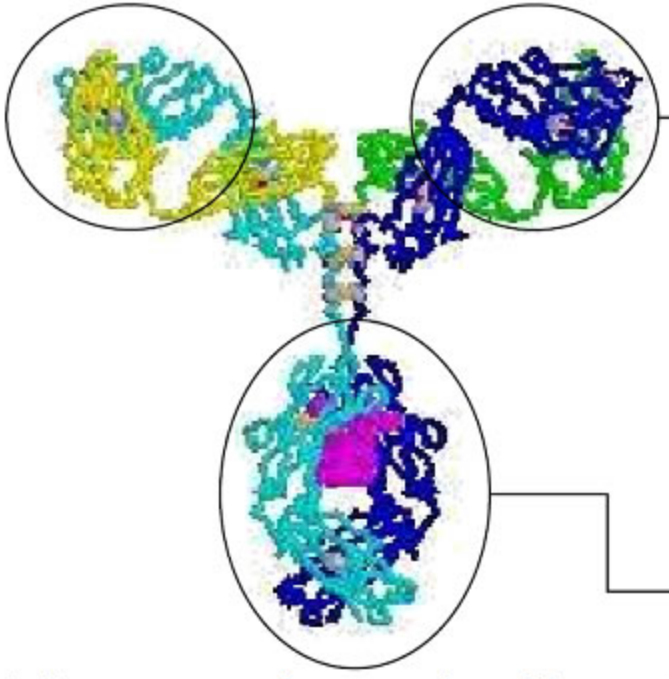
The carbohydrate structures of the two EPO isoforms differ



The absence of detectable difference is no evidence for identity

Monoclonal Antibodies

. . . are multi-functional molecules . . .



CDRs (complementarity determining regions)

- selected for optimum target mediated effects (light chain and heavy chain variable binding domains)

Fc part:

- different isotypes with different effector functions
- contains 2 glycosylation sites (1 in each of the 2 chains)

.. and all parts contribute to the efficacy and safety in a cooperative way

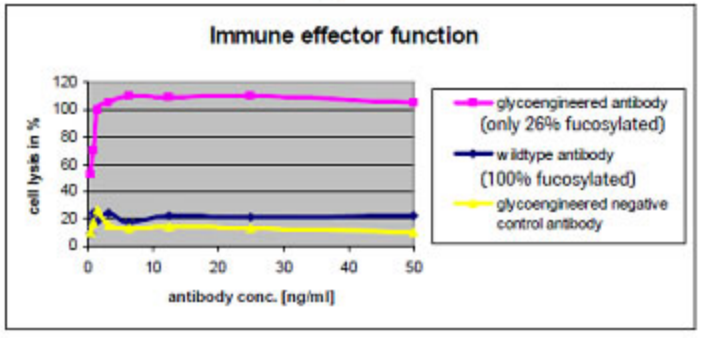
Monoclonal Antibodies

a small change can make a big difference

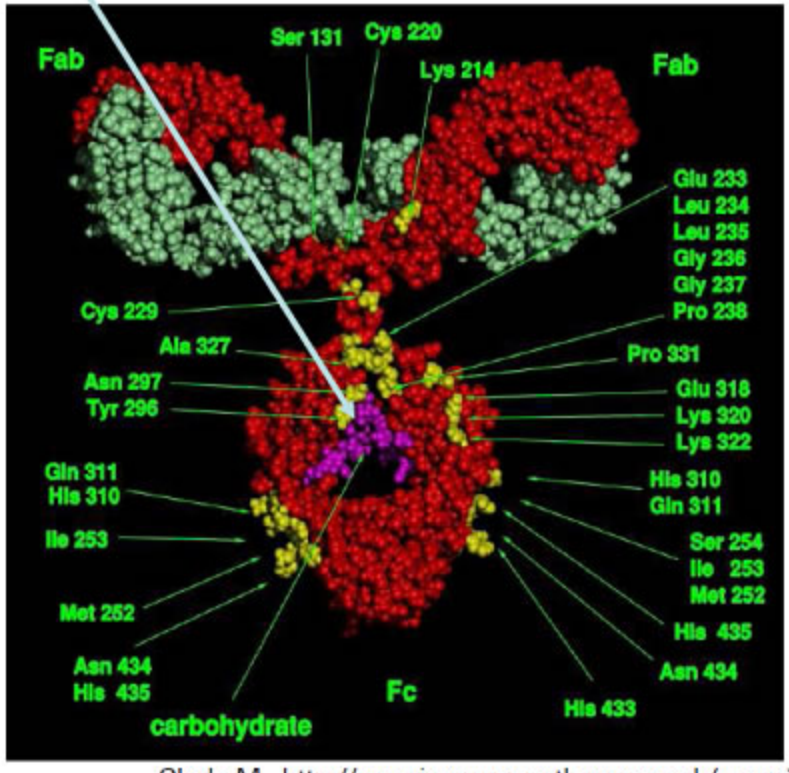
Presence or absence of **one sugar residue** (fucose) can affect the biological activity (killing of target cells).

Changes in immune effector function may influence **potency**, but also **safety** of the drug.

This finding was unexpected. Similar, still unknown effects may exist.



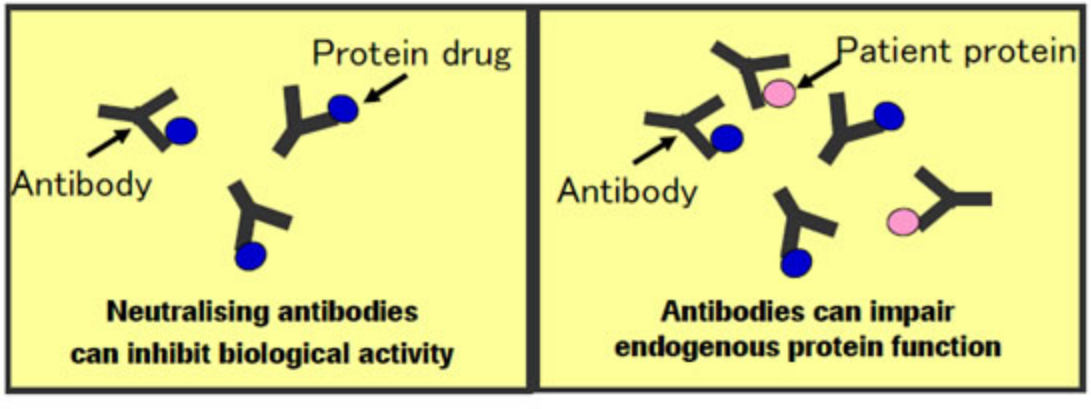
Fucosylation



Clark, M., http://wwwimmuno.path.cam.ac.uk/~mrc7/

Immunogenicity: a Key Safety Issue

- Most biopharmaceuticals (including recombinant human proteins) induce antibodies
- Immunogenicity can be due to the **presence of "foreign" epitopes/sequences**, or to **breaking B-cell tolerance** against the body's own set of proteins
- Immunogenicity depends on **patient- and disease-specific factors**, as well as on the **quality** of the drug product (e.g., content of protein aggregates or impurities)
- Immunogenicity can only be revealed through **human clinical trials** - in-vitro assays and animal models are **not predictive** for the situation in human patients
- The **consequences** of immunogenicity may be **benign** and manageable (e.g. loss or enhancement of efficacy, general immune effects), but can be **severe** (e.g., neutralization of endogenous protein, serious clinical adverse events)



Impact of small differences among biotech products on efficacy and safety is unpredictable

- Safety and efficacy can differ significantly with small changes in
  - protein biophysical characteristics or
  - formulation of the drug product
- Long term safety profile of biosimilars has yet to be established
- Prescribers and patients should be aware of this to ensure appropriate introduction into clinical practice

Need to recognize safety and efficacy issue in both approval process and introduction into clinical practice of biosimilars

Biosimilars are a Reality in the European market …

EU have established a pathway for biosimilars approval …	…which should open the way for biosimilars entering the market
• EU has recognized that biosimilars are different from "generics" - Not identical to original product - Need to undergo evaluation trials prior to approval • and has developed product specific regulatory approval guidelines for Erythropoietin, G-CSF, Somatropin and Insulin	• Approval of several biosimilars for each of the original products in next years, e.g. - G-CSF - Erythropoietin - Somatropin - Insulin

Expect to see more biosimilars on the market in 5-years

… however the market entry of Biosimilars poses some unique challenges

Biosimilars will be similar but not identical to the reference products

Automatic/Generic Substitution Rules	Clear Identification for Healthcare Providers	Accurate Pharmacovigilance
• Should rules designed for small molecules apply to biotech/biosimilar products?	• How will physicians and pharmacists distinguish one biotech product from another? • How will they be provided with the approval data and post-approval data?	• Will existing Pharmacovigilance systems cope? • Are any changes needed?

Need to address open issues to ensure patient safety in clinical practice

No automatic substitution	Physician should always be involved in decision to dispense ▪ Generic substitution rules should not apply to biotech medicines, including biosimilars ▪ Explicit prior consent of the physician to substitute ▪ Impact on pharmacovigilance
Transparent Product Info	Biosimilar product labelling should provide clear and transparent information ▪ Advice on interchangeability (ie. under strict medical supervision) ▪ Unique clinical data (safety and efficacy) ▪ Identify reference product
Distinct naming (INN)	All biotech/derived therapeutic proteins should have distinct INNs ▪ If no distinct INN for biotech products, different identification and subscription rules need to be designed
Ensure accurate pharmacovigilance	Pharmacovigilance systems should cope with biosimilar introduction ▪ Traceability should be ensured ▪ Repeated, uncontrolled switching should be prevented

Basic Guidelines for Biosimilars

- A biosimilar should meet the same quality standards as required by the National Regulatory Agency for innovator biological medicines.
- Biosimilars should undergo appropriate non-clinical testing sufficient to justify the conduct of clinical studies in healthy volunteers or patients.
- The base expectation for a biosimilar is that it will have equivalent clinical characteristics to the reference product.
- Clinical comparability assessment without analytical similarity (quality comparison with the reference product) is not recommended
- Post-market surveillance systems should be established or in place to enable continued evaluation of benefit/risk and characterisation of less frequent adverse events that could not be adequately studied before approval.
- Biosimilars should not, simply by virtue of their approval by the National Regulatory Agency, be considered as subject to automatic substitution provisions that may be applied to some small-molecule generics.
- The labelling of biosimilars should provide transparent information to healthcare professionals and patients on issues that are relevant to the safe and effective use of the medicinal product.
- All biotech medicines should have distinct INN and brand names