# Regulatory evaluation of therapeutic biological medicines

# Why and how should biosimilar medicines be regulated?

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Mexico, 15 August 2007

# Agenda

**Complexity of biologics**

**Safety as a priority**

**Worldwide regulatory situation**

**Guiding principles**

**Implementation considerations**

# Complexity of biological products

# Proteins are Different: Complexity and Molecular Size

The molecular weights (in Daltons) of some popular drug substances

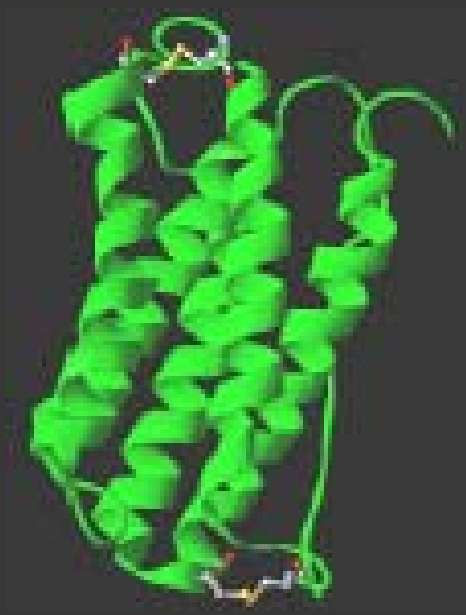
## Chemical Products

| | |
|---|---|
| Glucophage® | 166 |
| Vioxx® | 314 |
| Prozac® | 346 |
| Zantac® | 351 |
| Paxil® | 375 |
| Zocor® | 419 |
| Augmentin® | 420 |
| Crixivan® | 712 |
| Taxol® | 854 |

## Biotechnology Products

| | |
|---|---|
| Neupogen® | 18,800 |
| Roferon-A® | 19,625 |
| Humatrope® | 22,125 |
| Avonex® | 22,500 |
| NeoRecormon® | 30,400 |
| Pulmozyme® | 37,000 |
| Enbrel® | 75,000 |
| Zenapax® | 144,000 |
| Rituxan®/MabThera® | 145,000 |
| Factor VIII | 264,000 |

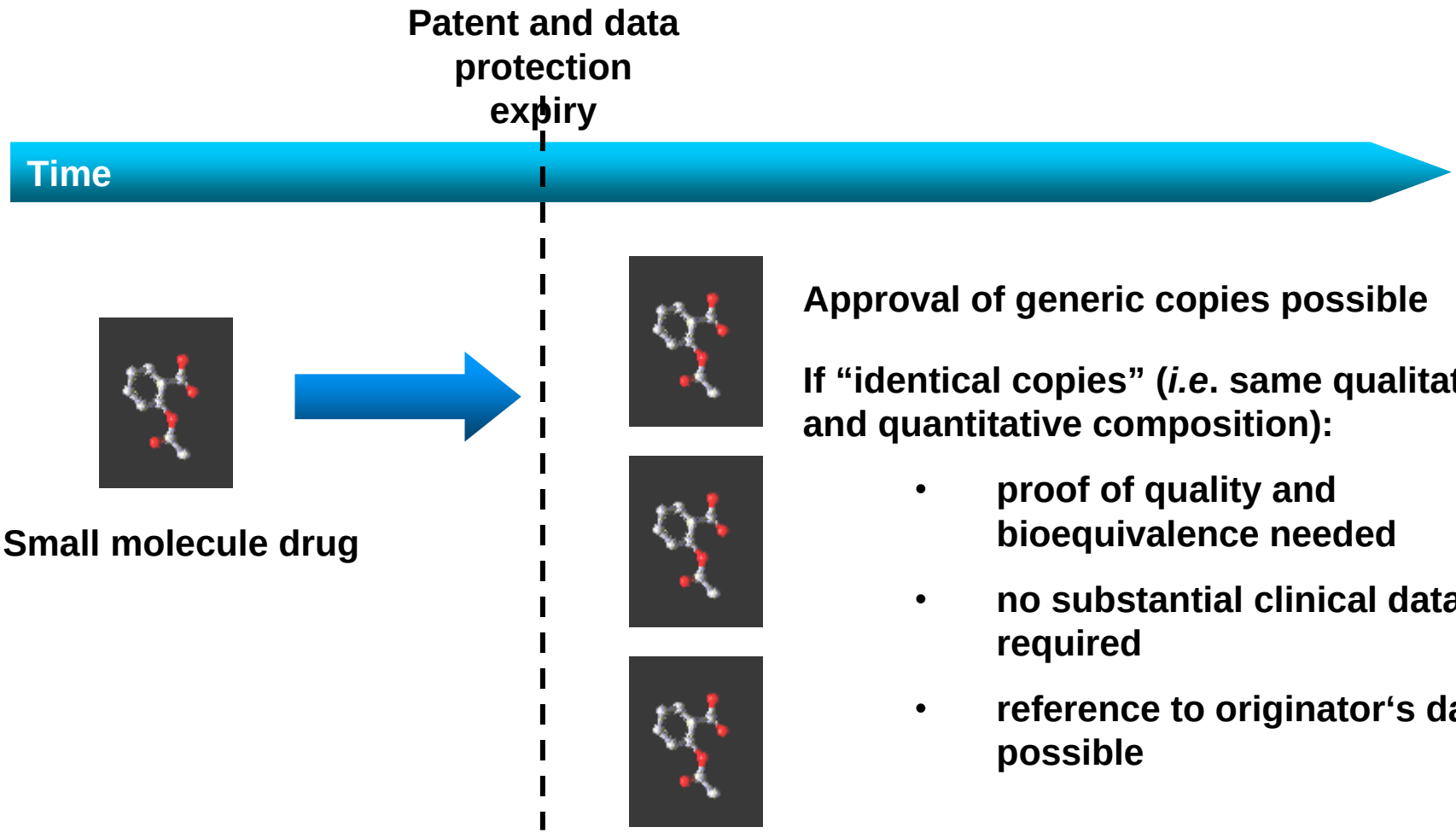
*Source:* EUROPABIO



Q + Bioequivalence -------> Data? -------> Q + Safety + Efficacy

Level of Complexity

# Generics




**Approval of generic copies possible**

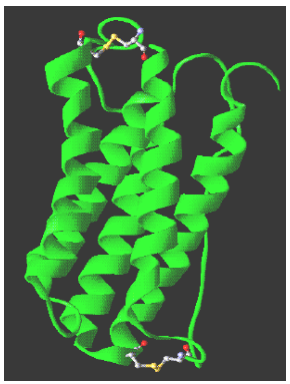
**If “identical copies” (*i.e.* same qualitative and quantitative composition):**

- **proof of quality and bioequivalence needed**
- **no substantial clinical data required**
- **reference to originator‘s data possible**

# Generics vs. Biosimilars

Patent and data protection expiry

Time



Protein drug

## Biosimilars (EU)

**Approval of follow-on products possible**

**NO identical copies – just similar**

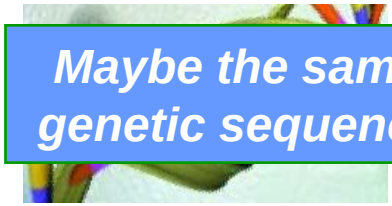
**➔ full quality dossier plus appropriate preclinical or clinical data necessary, both in comparison with a reference product**

**➔ only limited reference to originator‘s data possible => also abbreviated pre-clinical development**

**Alternative: “stand-alone” application**

**normal development with full clinical dossier; no comparison to reference product necessary**

# Biosimilars Manufacturers: Different Process→Different Product



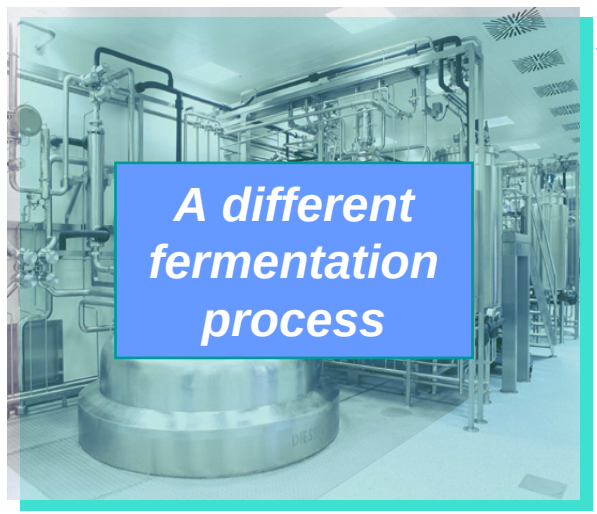
*Maybe the same genetic sequence*

*(Probably) a different DNA vector*

**Cloning into DNA Vector**

*A different downstreaming protocol*

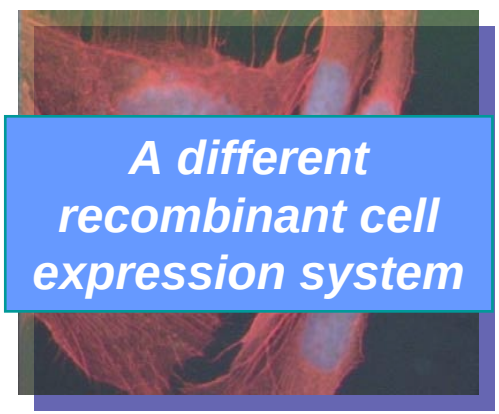
**Transfer into Host Cell, Expression**



*A different fermentation process*

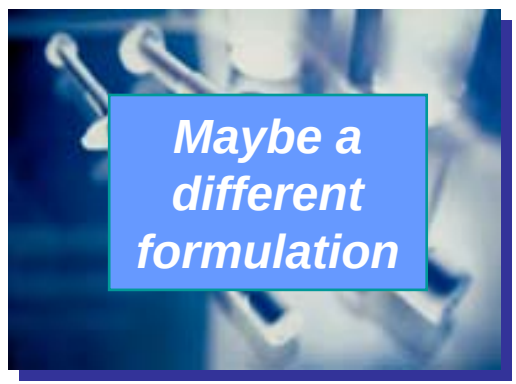
**Downstrea**

*Different in-process controls*



*A different recombinant cell expression system*

**Large-Scale Fermentation**



*Maybe a different formulation*

e.g., bacterial or mammalian cell

**Formulation**

# Microheterogeneity

## *t-PA (Alteplase)*

**A 527-amino acid residue protein containing 17 S-S bridges and 3 glycosylation sites**

**Possible sources of heterogeneity (experimentally observed variations only !)**

Variability in N-linked carbohydrate side chains

Parekh, RB et al. (1989) Biochemistry **28**, 7670–7679
Spellman, MW et al. (1989) J. Biol. Chem. **264**, 14100–14111
Wittwer, AJ et al. (1989) Biochemistry **28**, 7662–7669

Single-chain and two-chain forms

Rijken, DC & Collen, D (1981) J. Biol. Chem. **256**, 7035–7041

Additional O-Glycosylation

Harris, RJ et al. (1991) Biochemistry **30**, 2311–2314

Proteolysis at Arg-X

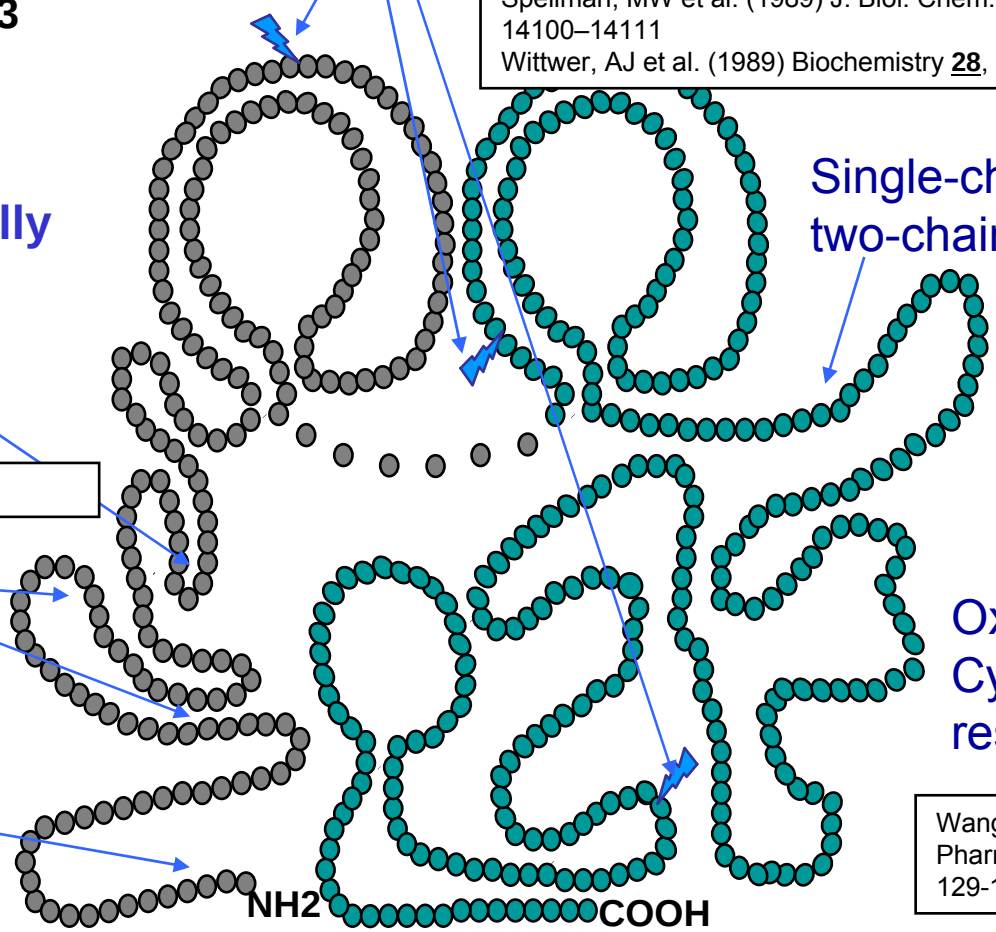
Nguyen, TH & Ward, C (1993) Pharmaceutical Biotechnology **5**, 91–134

Oxidation of Cys or Met residues

Wang, 1999, Int. J. Pharmaceutics **185**, 129-188

N-terminal sequence length variation (non-recombinant t-PA only)

Wallen, P et al. (1983) Eur. J. Biochem. **132**, 681 - 686




Deamidation of Asn residues

Zhang, W & Czupryn, MJ (2003) J. Pharmaceutical and Biomedical Analysis **30**, 1479 - 1490

# Microheterogeneity: t-PA

## Total possible variants: $1.09 \times 10^9$

| Modification | Number of possible or described variants |
|---|---|
| Single/two chain ratio | **2** |
| N-terminal sequence | **1** |
| N-glycosylation at $Asn_{117}$ | **7** (6 different oligosaccharides + unglycosylated) |
| N-glycosylation at $Asn_{184}$ | **25** (12 different oligosaccharides with and w/o sialic acid + unglycosylated) |
| N-glycosylation at $Asn_{448}$ | **25** (12 different oligosaccharides with and w/o sialic acid + unglycosylated) |
| O-linked fucose at $Thr_{61}$ | **2** |
| Cleavage at $Arg_7$-$Asp_8$ or $Arg_{27}$-$Ser_{28}$ | $2^2$ = **4** |
| Deamidation of $Asn_{37,58,177,184,205}$ | $3^5$ = **243** (formation of Asp or IsoAsp) |
| Oxidation at $Cys_{83}$ | **2** |
| Oxidation at $Met_{13,\ 207,455,\ 490,\ 525}$ | $2^5$ = **32** |

"Madness of permutation" or presence of a large number of molecular species, with unknown impact on efficacy and safety?

# Points to Consider

**Comparing a Biosimilar to a Reference Product**

- A pure comparability approach is not applicable to products made by independently developed processes because a biosimilar cannot be strictly identical to the reference product
- Public standard material or commercial products are not suitable to establish evidence for quality comparison
- Quality assessment alone cannot guide non-clinical and clinical similarity assessment

# „SAME“ safety and efficacy achievable?

Pictures taken from:
http://savingsandclone.com/news/press_room.html

**“..it could be expected that there may be subtle differences between similar biological products from different manufacturers or compared with reference products which may not be fully apparent until greater experience in their use has been established“**

CHMP Guideline on Similar Biological Medicinal Products, CHMP/437/04, 2005

# Safety is a priority

# Safety: critical considerations

**Tryptophan-eosinophila myalgia syndrome**

Production strain changed-Purification modified

Unrecognised impurity caused EMS

(>1300 cases, 38 deaths)

**Immunogenicity of GM-CSF**

Non-immunogenic: immunosuppressed patients

ABs in non-immunosuppressed patients

**Thrombopoietin immunogenicity**

Pegylated rHuMGDF: highly immunogenic

persistent thrombocytopenia

=> development programme stopped

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

Related to formulation change (change HSA to Tween 80)

Appearance of neutralising ABs to EPO

Leachates from uncoated stoppers reacting with Tween 80

SC route was withdrawn in most countries

Source: Dr Chris Holloway, PRA

## Importance of a REGULATORY FRAMEWORK to ensure:

- **SAFE** and **EFFICACIOUS** biosimilars/FOBs are placed on the market
- Consistent Quality **EVERY TIME, ALL THE TIME**

**A framework should also allow any potential issue to be identified and addressed diligently via RM and pharmacovigilance**

# Key issues for biosimilars (1)

**Clinical data is absolutely critical**

- **To compare with innovator product**
- **To evaluate the risk**
  - Test immunogenicity – NEW immunogenic profile
  - Follow-up with strict pharmacovigilance procedures
  - To inform properly about the amount of data generated from an efficacy and safety perspective

    => Importance of ***informed decisions***

# Key issues for biosimilars (2)

**Risk management plans (RMP) are required e.g. in EU**

- **Part of approval process**
- **Need even stronger for biosimilars e.g. for additional data post-authorisation**
  - Because biosimilars/follow-on biologics can benefit from the concept of "*accelerated development*"
  - Timelines to fulfil these commitments should be clearly identified in order to make ***informed decisions***

# Key issues for biosimilars (3)

**Obligation to identify all biosimilar medicines**

- **Use of individual INN names**
- **Use of Brand Name**
- Prevents inadvertent automatic interchangeability/substitution
- Enhances ability to implement active pharmacovigilance

# Worldwide regulatory situation

- Worldwide, the regulatory framework for biosimilar medicines is not harmonised
- The European Union (EU) is currently the most advanced region in terms of having a developed regulatory pathway for these products
- In many other regions national plans are limited or in some cases there are no regulatory processes in place
- This lack of minimum regulatory standards presents a risk for patients because of the potential issues relating to the quality, efficacy and safety of biosimilars developed and approved without defined requirements

# EU Experience

- The Guidelines as well as EMEA's effort (workshop-December 2005) to seek feedback in an open, transparent setting established an important precedent for Europe and the rest of the world
- The scientific and regulatory dialogue was essential to recognise that biosimilar medicines are not generic products, and therefore require different development, assessment, and registration approaches that are adapted to their specific nature and complexity

# Guiding principles

# Basic Philosophy of the Guidance

- Biologicals are complex
- “The process is the product” still the paradigm
- Necessity for demonstration of batch to batch consistency
- Necessity for demonstration of **good and similar quality**
- **Demonstration of quality must always be complemented with non-clinical and clinical studies**
- Immunogenicity cannot be predicted
- The level of similarity is crucial
  - Are the products similar enough?
  - Is the data package suffient enough (accelerated development versus full data package)
  - Risk relating to off-label use or substitution when biosimilar products have important differences with reference product

# Key points to consider

- The manufacture of biosimilars will by definition involve very substantial differences (new cell line, new facility, new process) raising the **relatively high likelihood of clinically important differences**
- The importance for clinicians to be able to make ***informed decisions*** about biosimilar medicines, scientifically driven, based on data generated during development, as well as through risk management and pharmacovigilance
- A regulatory framework needs to maintain incentives for **innovation**
    - Development of biologics is time-consuming, costly and risky
    - Important to encourage innovation and new biological products
    - Efforts from innovators need also protection
        - Patents (e.g. composition of matter, methods of using products and methods of manufacturing)
        - Trade secrets
        - Data and market exclusivity because of high risk investments

# Key concepts for guiding principles

1. **Clear regulatory pathway for new product category distinct from generics: biosimilar medicines**
   - **Open, transparent process with class-specific guidance, including a stepwise approach for products to be covered**
   - **Using reference products that have extensive clinical data and market experience**
   - **Includes a distinct naming and labeling system (market surveillance for safety)**

2. **Adequate quality standards**
   - **Products need to have similar molecular structural properties**
   - **Same quality standards as for innovative products**
   - **Robust comparative physico-chemical and biological characterization to be specified**

3. **Adequate pre-clinical and clinical testing requirements**
   - **Case-by-case approach within the scope of pre-defined non-clinical and clinical requirements**
   - **Clinical data for each indication unless otherwise scientifically justified**
   - **Appropriate risk management and active pharmacovigilance**

4. **Appropriate use**
   - **Science does not support automatic interchangeability/substitution**

# Implementation considerations

# Considerations for Implementing Global Guidelines on Biosimilars

- **Need global principles based on sound scientific, technical and regulatory elements as minimum level of requirements**
- **The EMEA biosimilar guidance can satisfy these principles and may be used as guidance by any authority worldwide**
- **In order to protect patients, countries with limited regulatory expertise can rely on the key principles and on experience in other countries with assessment of the safety and efficacy of biosimilar medicines**

# Conclusion

# Conclusion (1)

- **Biosimilar medicines are different from generics**
  - ⇒ Category of products which needs to be addressed regulatory-wise
  - ⇒ „The process is the product“ still the paradigm
  - ⇒ Safety concerns can have more significant impact compared to small molecules (e.g. immunogenicity)
- **Need to maintain a good balance with innovation**
  - ⇒ Biological products treat serious diseases
  - ⇒ Biological products require significant investments for their development
  - ⇒ Need to continue making progress in addressing unmet medical needs

# Conclusion (2)

- **No appropriate worldwide framework is currently existing (e.g. ICH)**
- **Importance of common guiding principles**
  - ⇒ Protection patients is crucial
  - ⇒ Possibility to generate knowledge and make progress is impossible outside a well defined regulatory framework
  - ⇒ Role of authorities worldwide in establishing these guiding principles
  - ⇒ Use of existing experience as a model to avoid duplication of efforts (experience growing in EU)

# Conclusion (3)

1. **Biosimilar medicines are a new product category distinct from generic products**
   - ⇒ **require a clear regulatory pathway**
   - ⇒ **Exchange of experience and views between authorities worldwide is possible**

2. **Adequate quality standards**

3. **Adequate pre-clinical and clinical testing requirements**

4. **Appropriate use (i.e. labelling, pharmacovigilance and risk management, interchangeability/substitution)**

# Thank you!