



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# EU Biosimilar Regulatory Framework II

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**GCC Workshop on Similar Biological Medicinal Products (Biosimilars)**

19-20 April 2011, Riyadh





5 years to built the  
worlds tallest building  
2009

(21 September 2004 –  
4 January 2010)





"I believe that this nation should commit itself to achieving the goal, before this decade is out, of landing a man on the moon and returning him safely to earth."

J F Kennedy, Inauguration speech, 1961



July 20, 1969, American Neil Armstrong



It takes more than 10 years and 1\$ Bn to bring an innovative product with a new active substance on the market

Biologicals are more complex and expensive to develop than small entity drugs

Can/will public sector cope with the continuously rising costs for the health care system?



# What is a biosimilar? - Regulatory perspective

## Biosimilars evolve from generics

Previous Generic Definition - NOT sufficient

- \* “The provisions of Article 10(1)(a)(iii) [i.e. for generic medicinal products] may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, **the toxicological and clinical profile shall be provided.**”

\* Section 4, Part II, Annex 1 (Dir. 2001/83/EC)



## Biosimilars are not generics

### Regulatory perspective – “Biogeneric” ??

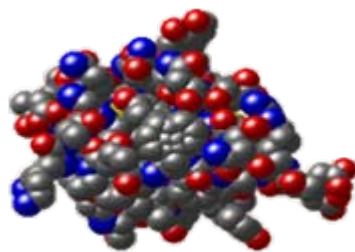
- Is a generic biological possible?
- In THEORY – YES
- In PRACTICE – may be possible where molecule is fully characterised (depends on complexity).
- RESULT – SBMP (Similar Biological Medicinal Product).  
*Informally: “biosimilar”*



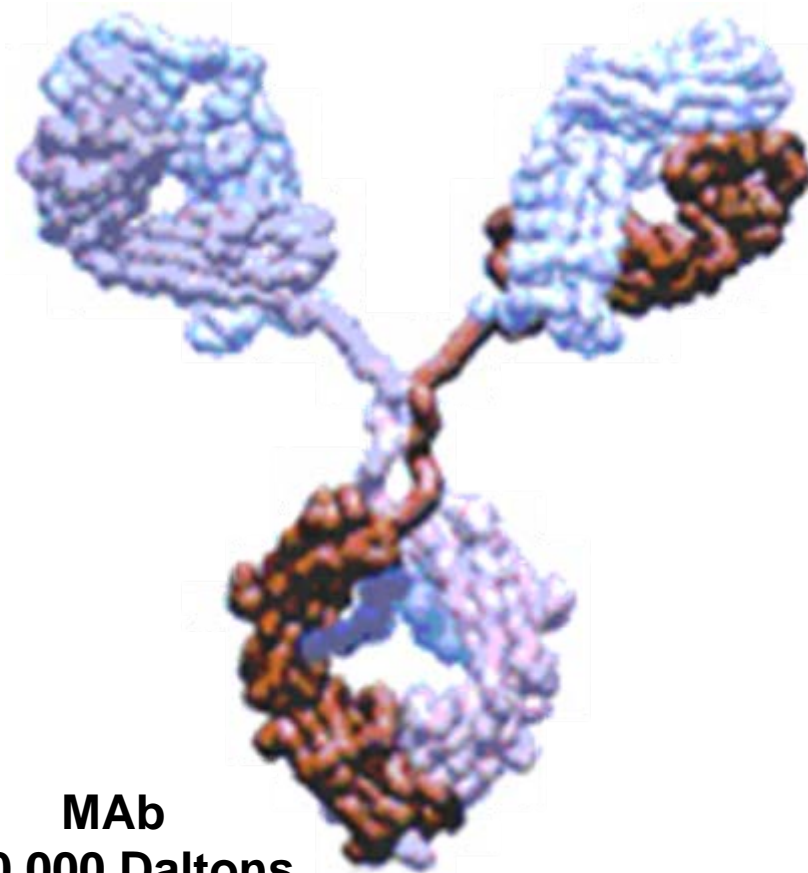
## Why „biosimilar“ (and not „biogeneric“)?



**Aspirin**  
**180 Daltons**



**Insulin**  
**5 700 Daltons**



**MAb**  
**150 000 Daltons**



# Biosimilar Legislation

Updated legislation\* defined legal base for SBMP:

- Where there **are differences** (particularly) in raw materials or manufacturing processes of **biosimilar and reference product**, then results of **appropriate pre-clinical tests or clinical trials** relating to these conditions must be provided.

\* Article 10(4) of Directive 2001/83/EC, as amended (2004/27/EC)



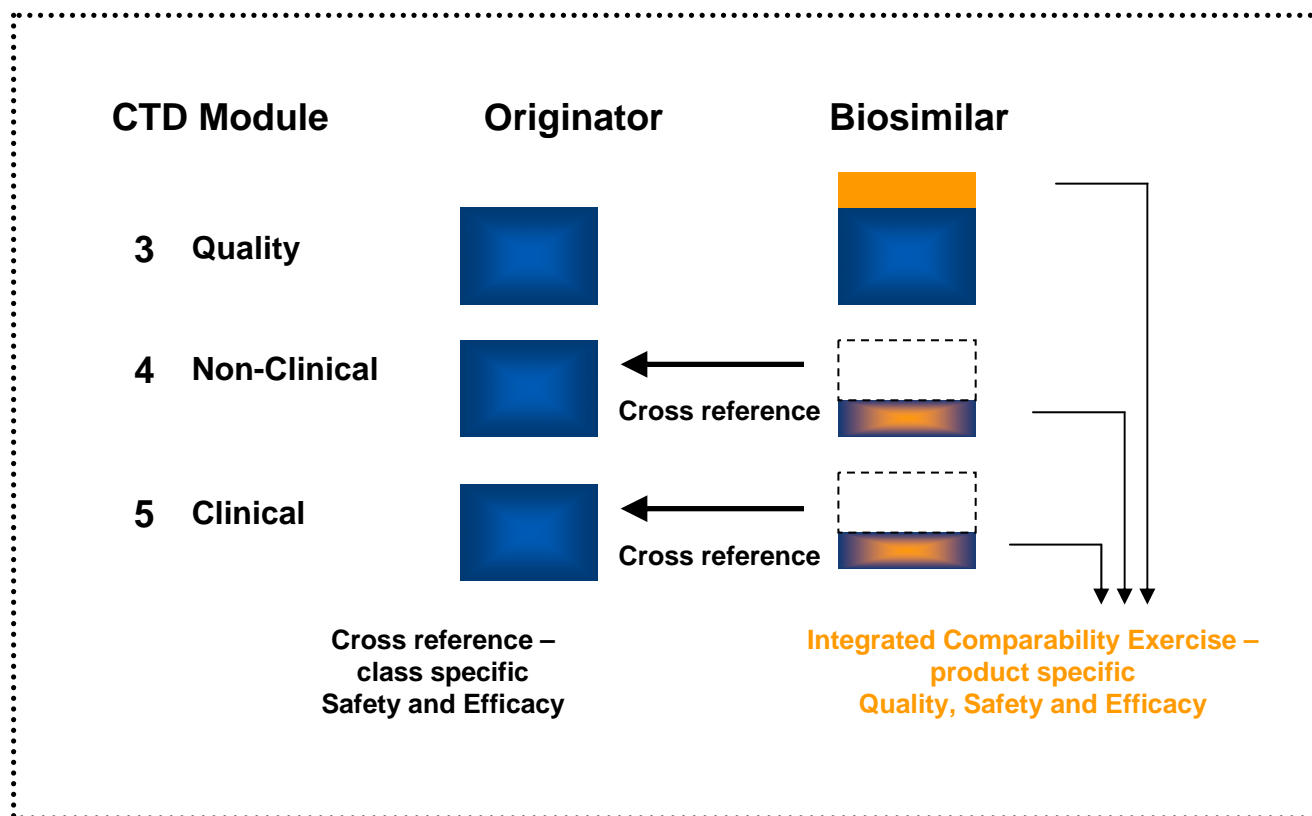


# Comparability exercise

- Stepwise head-to-head comparison at the levels of quality, safety and efficacy to demonstrate that the biosimilar and the reference medicinal product have similar profiles in terms of quality, safety and efficacy.
- Depending on the similarity on the quality profile, the extent of the non-clinical and clinical testing may be reduced compared to a stand-alone development.
- Any differences in the quality attributes require a satisfactory justification of the potential implications with regard to the safety and efficacy of the product.



# Dossier requirements for Biosimilars





## Legislation and its implementation

Legislation (Directive 2001/83/EC, as amended (2004/27/EC) in March 2004:  
Article 10.4)

### Implementation

- Biosimilar Task Force (2004-2007) (EMA transversal group - regulatory / legal / quality / safety / efficacy / PhV competences)

### Structures

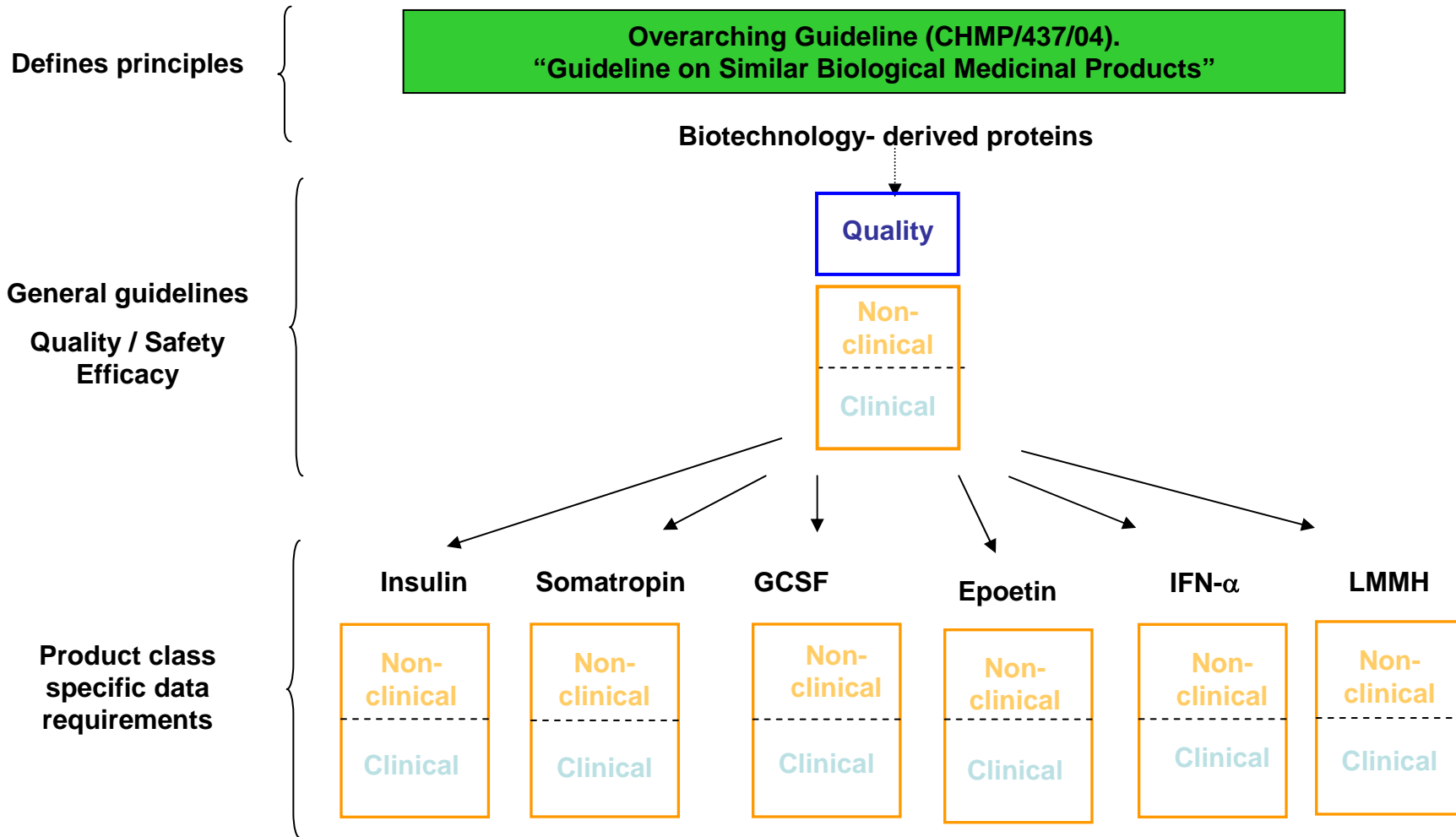
- Initial guidance (2Q 2004)
- Biosimilar Working Party (BMWP) (established 2005, multidisciplinary)

### Products

- Scientific advices
- First Biosimilar opinion and marketed Biosimilar in the European Union (2006 Omnitrope)
- Currently 17 centralised procedures completed (cut-off August 2010)

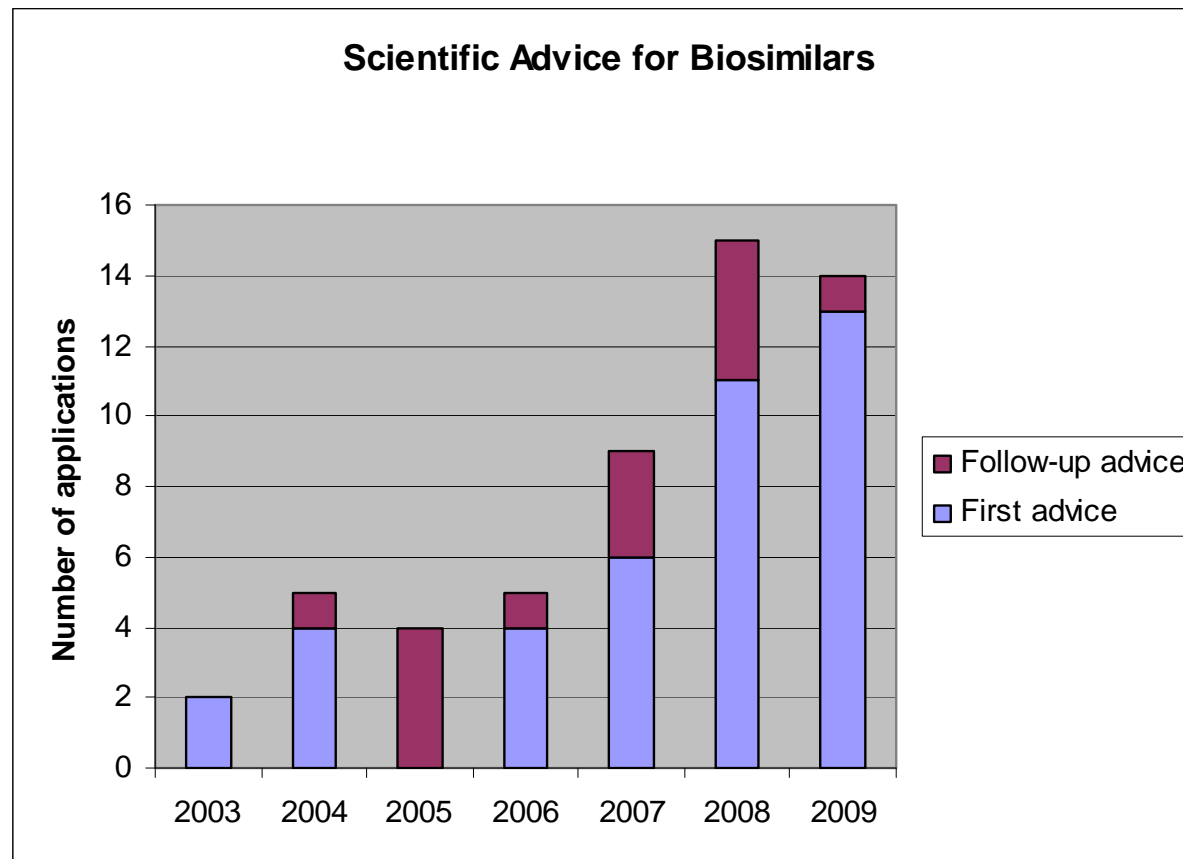


# Biosimilar References





# Scientific Advice





# Biosimilar MAA Procedures

status August 2010

|    |                                             |                      |            |
|----|---------------------------------------------|----------------------|------------|
| 1  | Omnitrope (somatropin)                      | Sandoz               | Authorised |
| 2  | Valtropin (somatropin)                      | Biopartners          | Authorised |
| 3  | Alpheon (interferon alfa)                   | Biopartners          | Negative   |
| 4  | Binocrit (epoetin alfa)                     | Sandoz               | Authorised |
| 5  | Epoetin alfa Hexal (epoetin alfa)           | Hexal                | Authorised |
| 6  | Abseamed (epoetin alfa)                     | Medice               | Authorised |
| 7  | Silapo (epoetin zeta)                       | Stada                | Authorised |
| 8  | Retacrit (epoetin zeta)                     | Hospira              | Authorised |
| 9  | Insulin Marvel Short (human insulin)        | Marvel Life Sciences | Withdrawn  |
| 10 | Insulin Marvel Intermediate (human insulin) | Marvel Life Sciences | Withdrawn  |
| 11 | Insulin Marvel Long (human insulin)         | Marvel Life Sciences | Withdrawn  |
| 12 | Filgrastim Ratiopharm (filgrastim)          | Ratiopharm           | Authorised |
| 13 | Ratiograstim (filgrastim)                   | Ratiopharm           | Authorised |
| 14 | Biograstim (filgrastim)                     | CT Arzneimittel      | Authorised |
| 15 | Tevagrastim (filgrastim)                    | Teva                 | Authorised |
| 16 | Filgrastim Hexal (filgrastim)               | Hexal                | Authorised |
| 17 | Zarzio (filgrastim)                         | Sandoz               | Authorised |
| 18 | Nivestim (filgrastim)                       | Hospira              | Authorised |



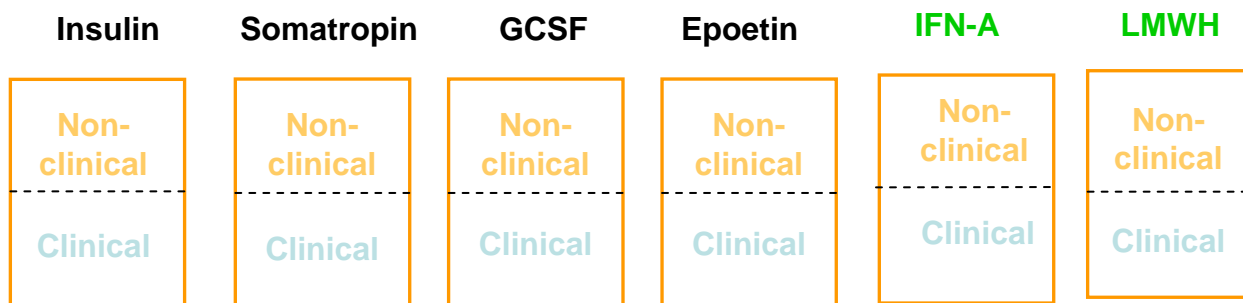
## Perspectives



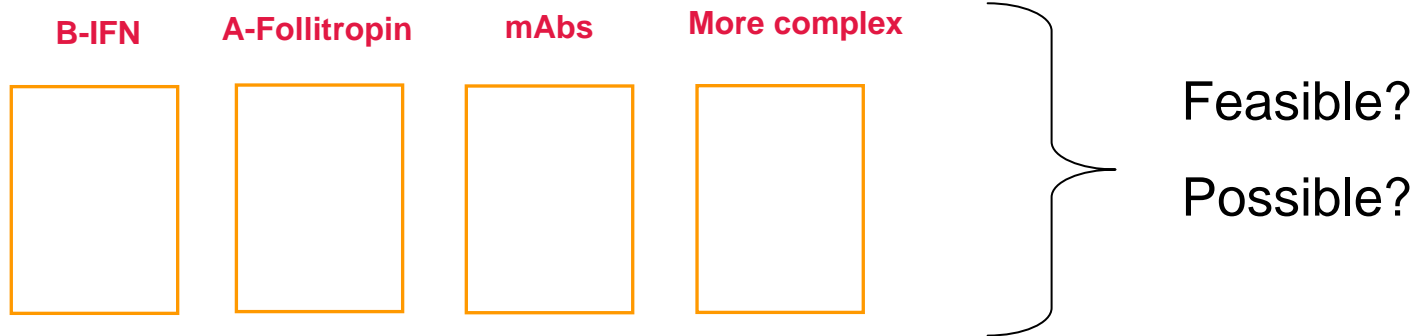
Are we ready for more complex biologicals being authorised via the biosimilar pathway?



Biosimilars currently authorised are „small biologicals“ (**less complex**), however different expression systems have been used (**Valtropin® = yeast**      **Humatrope® = E coli**)



In principle, the concept of “similar biological medicinal products” **applies to any biological** medicine. Guideline CPMP/BWP/437/04







# “Towards Biosimilar monoclonal Abs”

## Pros for biosimilar approach

The structural characterization, manufacture and regulatory history of mAbs are reasonably well established

Readily available potency assays, most of which are relevant (that is, they correlate with the rationale of the product)

In most cases, understanding of mAb function is reasonably well established, facilitating the planning of nonclinical studies as regards endpoints and other criteria

Safety profile is generally reasonably well established

Efficacy profile is generally reasonably well established

## Cons for biosimilar approach

Every mAb is unique and small structural changes can have significant functional consequences. Even the same expression system and similar culture conditions might lead to a distinct product profile (e.g., impurities or microheterogeneity). Some methods for physicochemical characterization might not be sufficiently sensitive to establish similarity conclusively

Potency assays might not be able to discriminate differences (see above)

The efficacy and safety of mAbs are in most cases highly species specific, which makes performing nonclinical studies more difficult and potentially expensive

Safety profile might differ due to factors like differences in impurity profile, immunogenicity and others

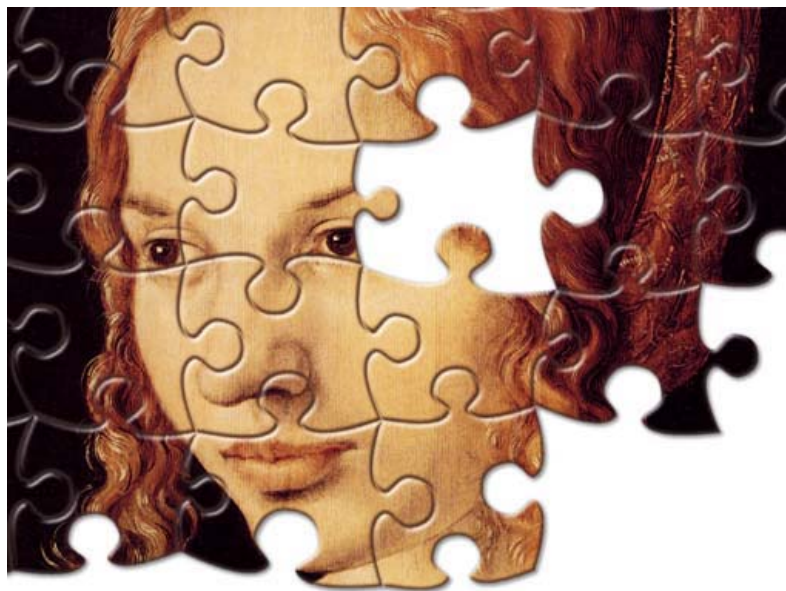
Efficacy from one indication might not be transferable to other indications if the reference product is licensed for several clinical conditions. Equivalence/noninferiority study against reference product might require many more patients than stand-alone trials



# Challenges in a potential expansion of the biosimilar framework to more complex biologicals



# How far can we go?



www.lucky-lions.com

What do we need to know?

How much „similarity“ do we need?



## How to design a biosimilar development programme for a more complex biological?

- What kind of clinical trials can we ask for?
- Therapeutic equivalence?
- Non-inferiority?
  
- Can we ask for all indications?
- Can we extrapolate efficacy?
- Can we extrapolate safety??
  
- What endpoints can we ask for?
- (Activity or Benefit?)
- (Phase II or Phase III endpoints?)



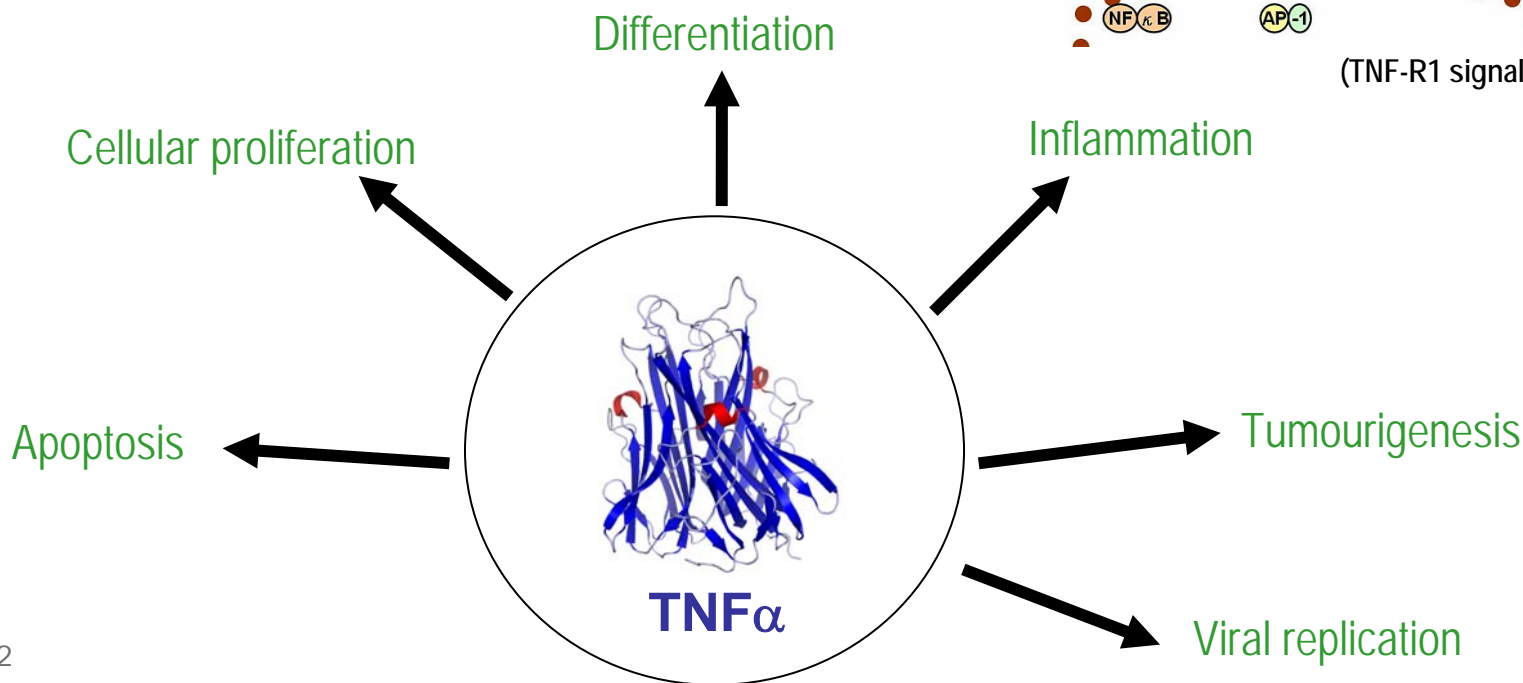
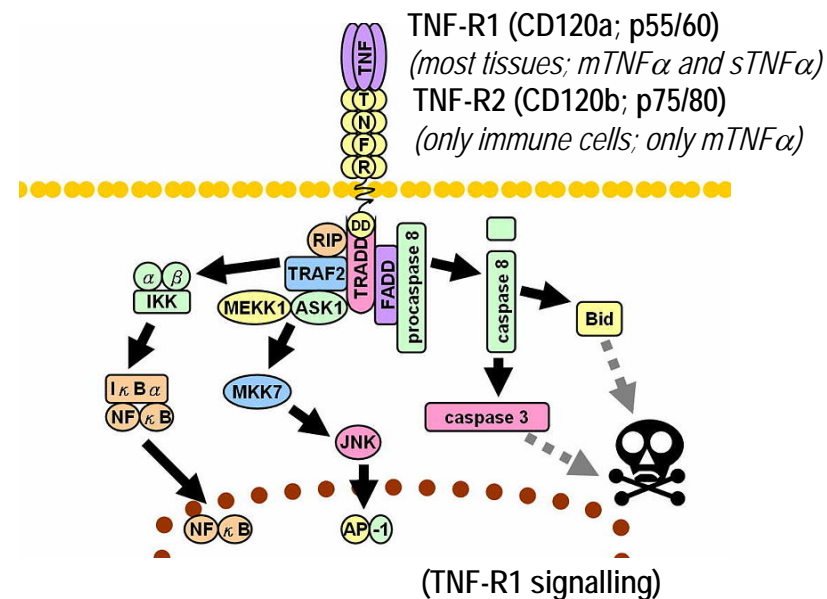
# Extrapolation of Indication

(Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues):

- „*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.***“
- „*In **certain cases** it may be possible to **extrapolate** therapeutic similarity shown in one indication to other indications of the reference medicinal product.*“
- „*Justification will depend on e.g., clinical experience, available literature data, **whether or not the same mechanisms of action or the same receptor(s) are involved in all indications.***“
- „*Possible safety issues in different subpopulations should also be addressed.*“

# Mechanisms of action can be complex!

Example:  $\text{TNF}\alpha$  antagonism





# Challenges

## Extrapolation of indications:

- What if mechanism of action is poorly understood? (e.g. interferons)
- What if clinical endpoints for other indication(s) are not sensitive enough?
- What if Biomarker endpoints have no known correlation with clinical outcome?

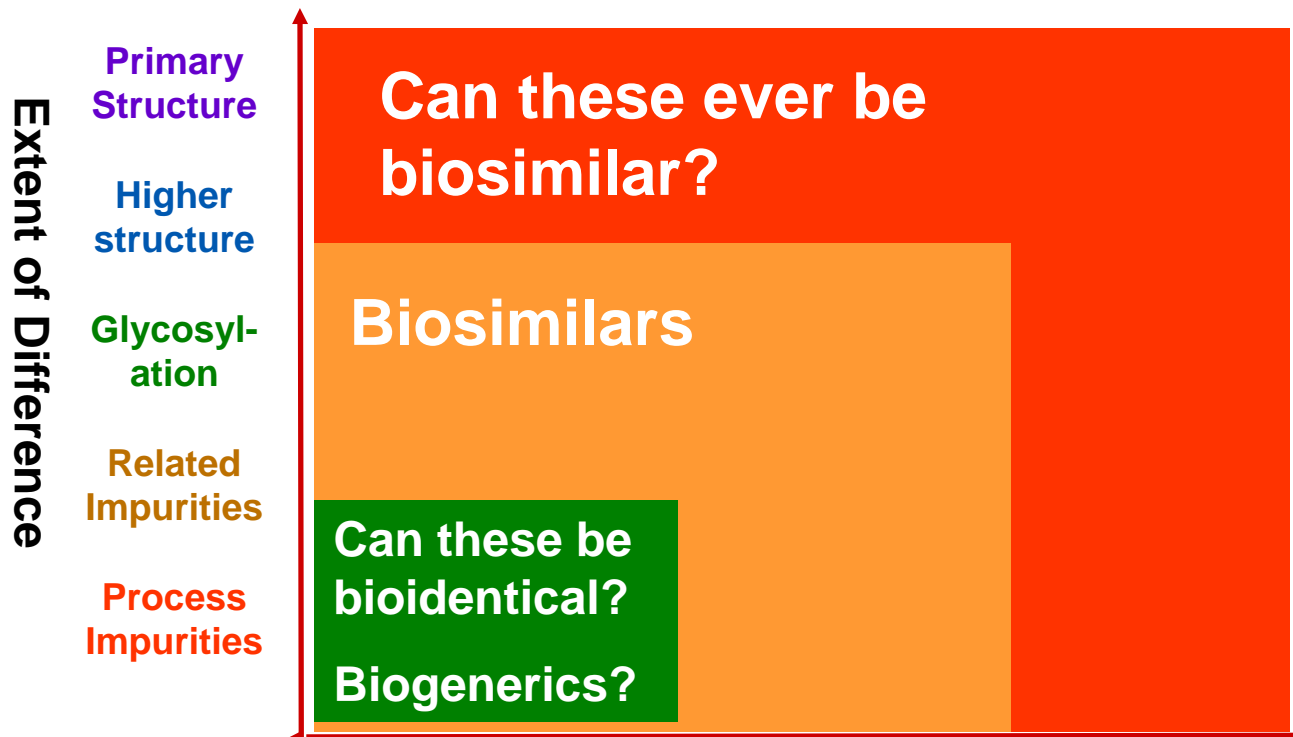
What about „true“ 2nd generation proteins (the „real“ „follow-on“ biologicals?)

- Examples: Fully human anti-TNF alpha mAbs
  - Full development programme?
  - Only one indication, rest PD markers?

To what extent is risk-assessment relevant with regards to structural differences?



# Spectrum of Uncertainty







# Global Regulatory Challenges of the biosimilar framework



## International aspects

Published guidance on Biosimilar/FOPP/SEB/FOB in several regions

Possibility that different concepts in different regions developed (EU / India / Korea / China / US?)

Avoid double standards or

- India and Korea already authorised “Biosimilar” monoclonal Abs and Insulin analoga

WHO guideline

- for entire world

Clear definition of EU Biosimilar concept





# Challenge for a global BS development

EU **definition** of '*reference medicinal product*': Article 10 point 2 (a): 'reference medicinal product' shall mean a medicinal product authorised under article 6, in accordance with the provisions of Article 8'.

Art. 10(2) lit. (a) of Directive 2001/83/EC contains the requirement that a MA has **been granted for the reference product in the Community**.

- Directive does not specify for the development product set up.
- "Overarching" Biosimilar guidance (CHMP/437/04) states: "...the chosen reference medicinal product must be **authorised** in the Community, on the basis of a complete dossier..."

Points to consider:

- Biosimilars evolved from generics legislation - therefore same principles are applied for reference product.
- At time of drafting GL no external reference product with the potential of poor(er) quality and no accessible dossier was desired.
- Comparability should provide a homogenous data set through all disciplines - using different products dilutes comparability assessment



# Challenge for a global BS development I

**Current EC policy foresees the requirement to use a reference medicinal product authorised in the EEA (authorisation + batch release within the EEA).**

- '(...)batches sourced from non-EU countries **cannot, from a legal viewpoint**, be considered as valid **reference for demonstration of 'biosimilarity'**. Scientific arguments on the interchangeability of the same product sourced in different regions are irrelevant in this context. Data from comparability studies based on those batches can only be used as **supportive data.**'
- CHMP Guideline on similar biological medicinal products (CHMP/437/04) where it is stated that “data generated from comparability studies with medicinal products authorised outside the Community may only provide supportive information”.

## **BMWP scientific rationale for alternative approach:**

- “...supported by ethical considerations (avoid repetition of clinical trials).:
- - *Batches from different sources may have different specifications; however the quality could still be similar. Therefore the applicant could be asked to demonstrate that the quality of the non-EU sourced product is similar to the one of the EU-sourced product.*
- - *Clinical bridging strategy could be performed, e.g. phase I PK/PD comparison with 3 arms (non EU sourced reference, EU sourced reference, test product). A stepwise approach could be followed in this case. Multinational programs should be further discussed...”*



# Challenge for a global BS development II

## Points to be considered:

Would the “global development” term as such include any region or only US / ICH?

- Which regions should be included for a “global development”?
- Under which provisions and requirements determined regions may be eligible?

Scientific arguments for the “global development” of biosimilars (previous slide) should be studied in conjunction with other key regulatory elements and its consequences such as:

- Applicability to classical generics as well?
  - The current policy requires the use of a reference product authorised and batch released in one EEA Member State.
- The quality of a reference product should take into consideration not only “specifications” requirements but also GMP provisions.
  - Products sourced outside the EEA from third countries where no MRA is in place need to comply with the cGMP requirements of the EEA in line with the general rules set up for the performance of clinical trials.



## Interchangeability / Substitution I

- Substitution policies and interchangeability are decisions outside the remit of the EMEA.
- Interchangeability may have different meanings in different territories
- The EMEA, based on the assessment of the Marketing Authorisation Application (MAA), provides information on quality, safety and efficacy data and as for all products a Plan for Risk Management and Pharmacovigilance.
- This information can be considered by Health Authorities and Health Care Professionals when making decisions on interchangeability or substitution of medicines.



## Interchangeability / Substitution II

### Relevant Scientific elements:

- Product related
  - Conclusion on similarity of the product
  - Comparative Pre-Clinical and Clinical data
  - Experience with biosimilars and originator
  - Safety profile of the originator
  - RMP specifications
  
- Patient related
  - Therapeutic indication
  - Naïve vs. previously treated patient
  - Patient monitoring
  - Information to patient



## Comparability exercise snapshot or during whole lifecycle?

### Comparability exercise snapshot of two products at time of comparison / marketing authorisation

#### Divergent development of Originator and Biosimilar

- Like for other Biologicals a Biosimilar Marketing authorization is an independent MA which can have its own development.
- Comparison between pre and post change is requested for each step, however a comparison to the product state at time of authorisation is not requested

#### Open questions:

- What is required if the Biosimilar claims a new route of administration / dosing / indication that has not been approved for the originator?
  - GL states: When the pharmaceutical form, the strength or the route of administration is **not the same**; **additional data** in the context of the comparability exercise should be provided. Any differences between the similar biological medicinal product and the reference medicinal product will have to be **justified** by appropriate studies on a case by case basis.
- Clinical comparability exercise in non-authorised indication (most sensitive model)?
- Can a Biosimilar claim an indication what is not approved for the reference product?
- Is the biosimilar regulatory pathway a one way only (e.g. can the originator cross refer to characteristics (dosing, route of administration, indication) of its Biosimilar)?
- **Change of reference product specifications during BS exercise**





## Further reading

EMA Website:

<http://www.ema.europa.eu>

- European Public Assessment Reports (EPARs):  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar\\_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125)
- Biosimilar Guidelines:  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000408.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002958c](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002958c)
- Directive 2001/83/EC, as amended:  
[http://ec.europa.eu/health/files/eudralex/vol-1/dir\\_2001\\_83\\_cons/dir2001\\_83\\_cons\\_20081230\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_cons/dir2001_83_cons_20081230_en.pdf)



# Thank you for your attention

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# Thank you for your attention!

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