EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# EU Biosimilar regulatory framework – Non-Clinical and Clinical Aspects III

**GCC Workshop on Similar Biological Medicinal Products (Biosimilars)**
19-20 April 2011, Riyadh

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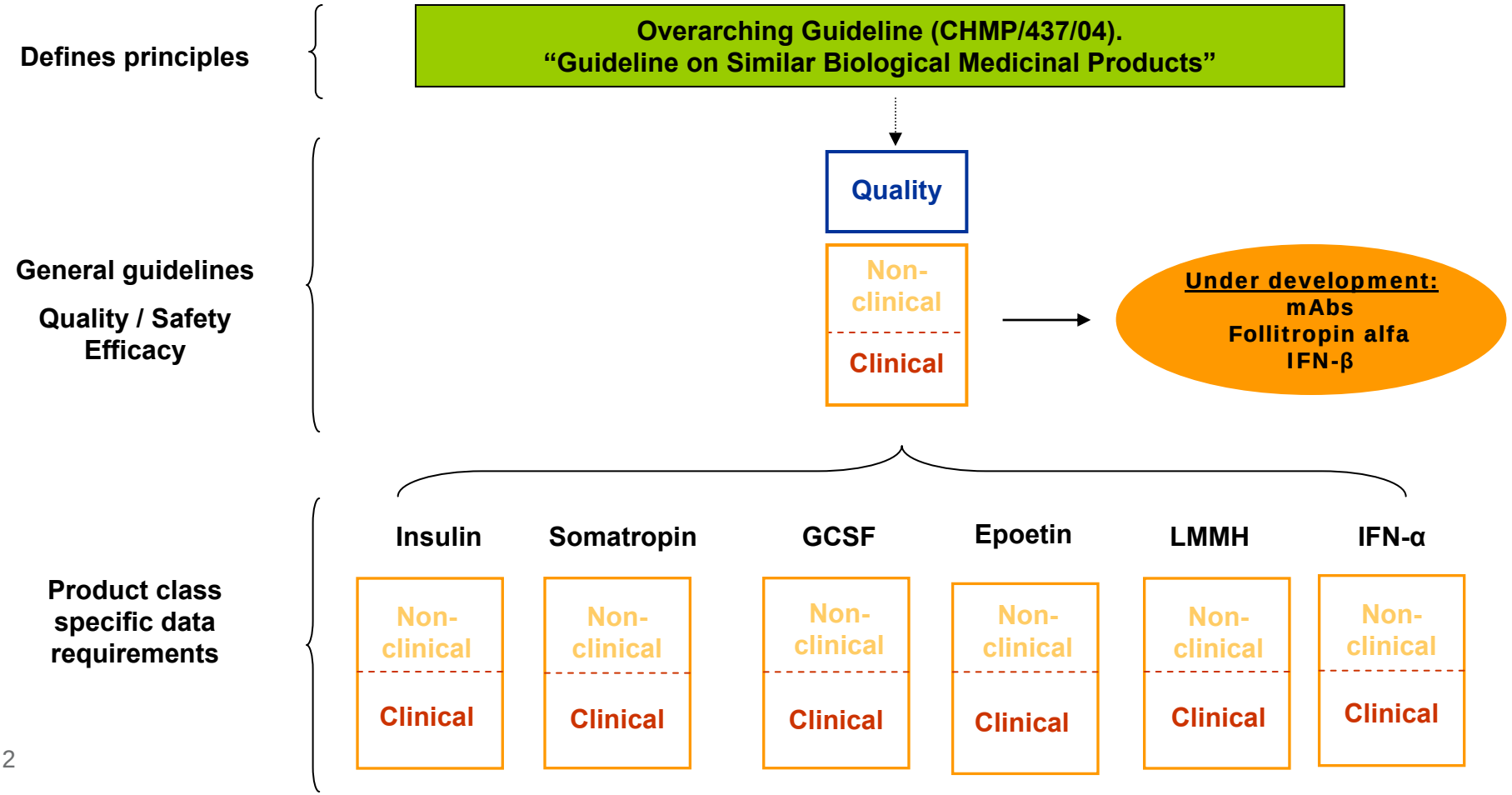
# Guidelines for biosimilars



# 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)

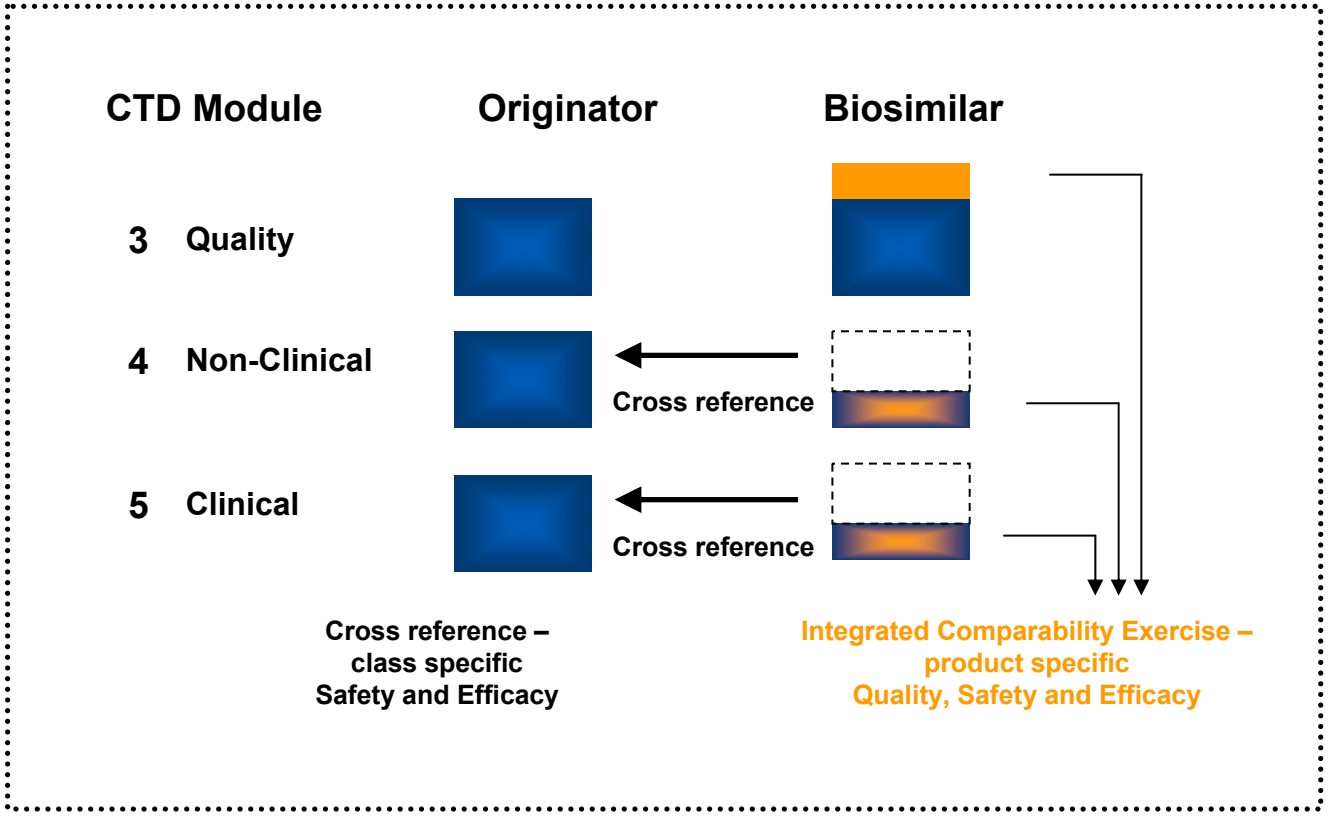
# Comparability exercise

- 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



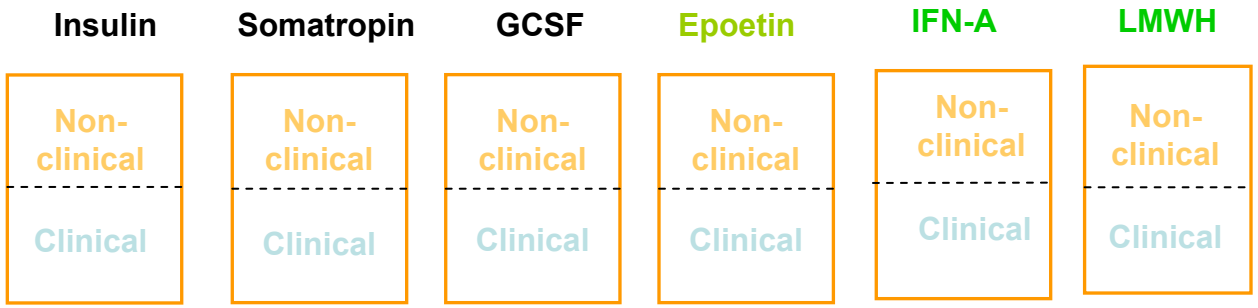
# Evolving scientific thinking

Biosimilars currently authorised are „small biologicals“
**(less complex)**

However

- Different expression systems have been used
  **(Valtropin® = yeast  Humatrope® = E coli)**

- Biosimilar class specific guidance has been finalised for **more complex products**, e.g. alpha-interferons or LMWH



# Evolving scientific thinking

***Similar biological medicinal products containing low molecular weight heparins (LMWH) – (Non-)Clinical Issues.***

LMWHs are heterogeneous (polysaccharides)

Mode of action is not completely understood

LMWH are licensed for various indications, including:

- **Treatment and prophylaxis of deep venous thrombosis**
- **Prevention of complications of acute coronary syndromes (unstable angina, non-STEMI and STEMI)**

Recommendation for establishing equivalent efficacy: Prevention of venous thromboembolism (VTE) in surgical patients with high risk

May allow extrapolation to other indications if adequately justified.

# Evolving scientific thinking

*Reflection Paper on Interferon alfa*

**Interferon-alpha** licensed for cancer indications and for treatment of viral hepatitis C

Several PD effects; relation to efficacy unknown and potentially different in the two „major“ indications

Concept of „PD fingerprint“**, ie measurement of PD markers and their comparison even if their correlation to clinical efficacy is unclear:**

- **β2 microglobulin**
- **Neopterin**
- **Serum 2´, 5´-oligoadenylate synthetase activity**

„Biosimilar“ endpoint rather than „benefit“ endpoint
**(virological response at week 12)**

# Biosimilar Epoetins Revision of the guideline 1/2

| Former Guideline | | Updated Guideline |
|---|---|---|
| **Clinical Development** | | |
| 2 Comparability Efficacy studies for **both routes** of administration (iv / sc)<br><br>Trials should include a **correction phase** and a **maintenance phase**<br><br>➢**Pre-dialysis and dialysis** population should not be mixed<br><br>➢**Duration** of efficacy studies :<br><br>at least 3 months, ideally 6 months<br><br>Example :<br>Correction Phase/ SC / Pre-dialysis<br>Maintenance Phase/ IV / Haemodialysis | | **Two approaches**<br><br>• Previous approach:<br><br>Clinical studies in **both routes**<br><br>• Alternative:<br><br>**One Clinical efficacy study (SC)**<br>**Bridging study**: single and multiple dose PK/PD → Endpoint Hb |

# Biosimilar Epoetins Revision of the guideline 2/2

| Former Guideline | | Updated Guideline |
|---|---|---|
| **Immunogenicity:** | | |
| ➢ at least **12-month comparative** data<br>➢ (route not specified) | | ➢ preferably 12-months otherwise sound justification<br>➢ sufficient number of SC treated patients with renal anaemia |
| **Extrapolation of Indication** | | |
| ➢ **Extrapolation** from S&E data in renal anaemia patients to other indications if appropriately justified | | ➢ Since MoA the same for all approved indications and only one known EPO receptor ->**Extrapolation within the same route of administration** |

# BMWP workplan 2011

Guideline on **Immunogenicity** Assessment of **monoclonal antibodies** intended for in vivo Clinical use

Action: Finalisation of guideline

Guideline on Similar Biological Medicinal Products containing **Follitropin alpha**

Action: Preparation of guideline

Guideline on Similar Biological Medicinal Products containing **Monoclonal Antibodies**

Action: Finalisation of guideline

Guideline on Similar Biological Medicinal Products containing **beta-Interferon**

Action: Preparation of guideline

# BMWP workplan 2011

Guideline on Similar Biological Medicinal Product (**Overarching Guideline**)

Action: Revision of guideline

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

Action: Revision of guideline

Guideline on Similar Biological Medicinal Products containing **Recombinant Human Insulin**

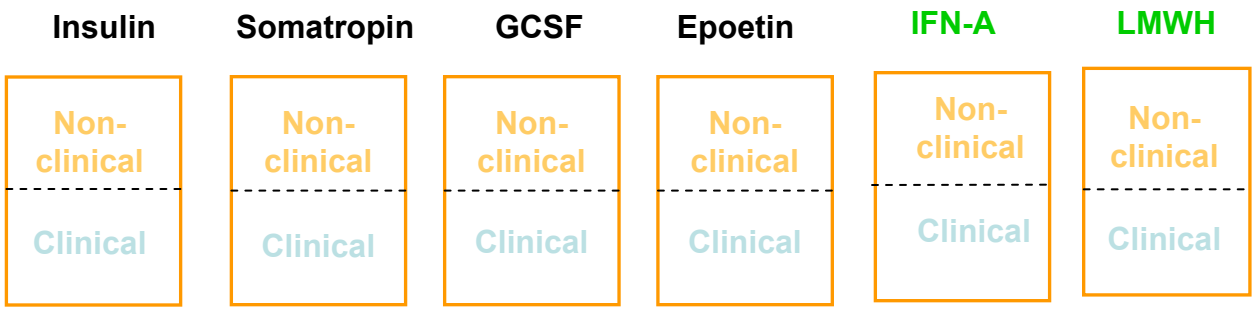
Action: Revision of guideline

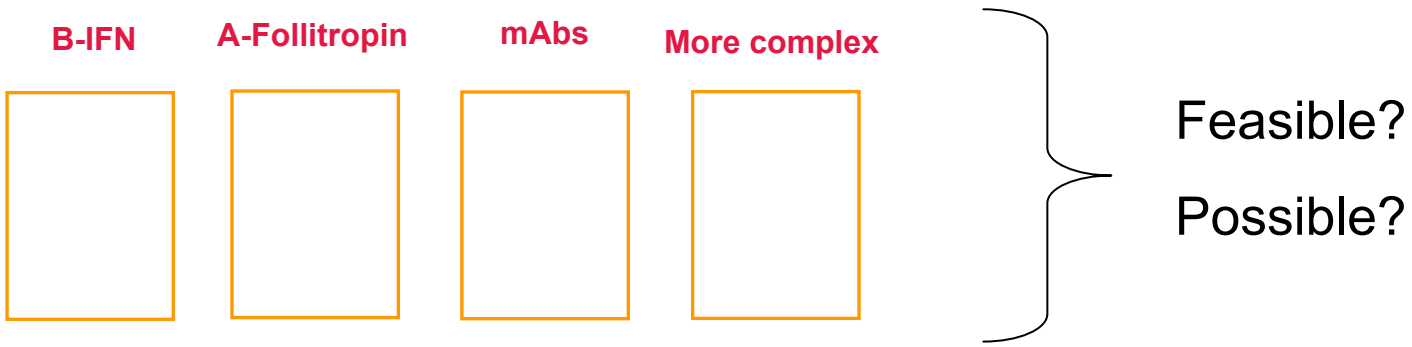
Guideline on Similar biological medicinal products containing **low-molecular-weight-heparins**

Action: Revision of guideline

# How far can we go?

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

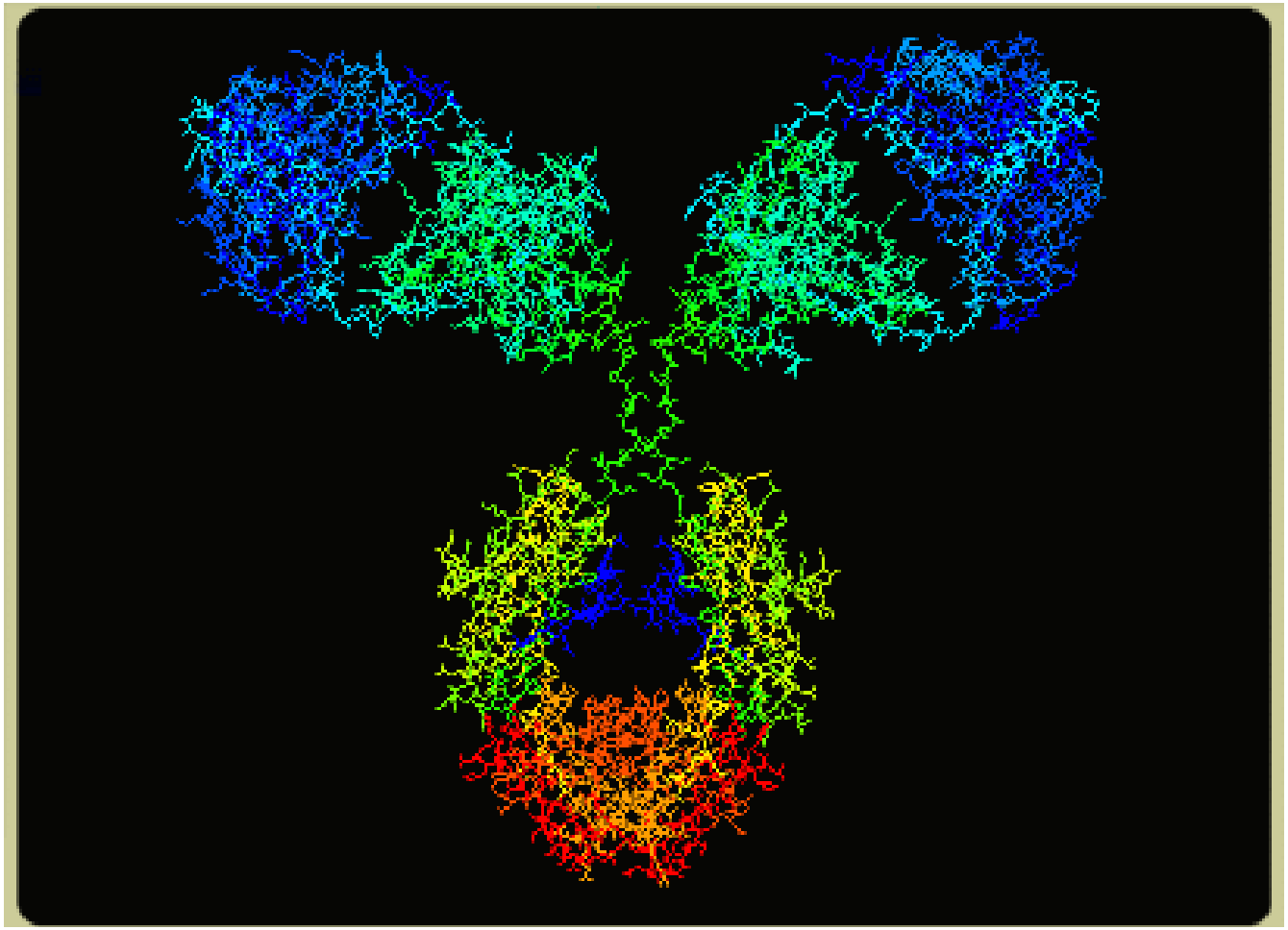


# Biosimilar Monoclonal Antibodies?

- Monoclonal antibodies are complex molecules
  - High level of microheterogeneity, there will always be differences
  - The mode of action is complex and may involve contributions from multiple mechanisms

- The challenge: to demonstrate that differences between the biosimilar and the reference medicinal product do not have a significant impact on clinical efficacy and/or safety
  - Even small differences may have significant effects.
  - Need to combine physicochemical results with functional assays (e.g. antigen-antibody binding assays and cell-based assays) and the qualification in preclinical and clinical studies



# EMA Workshop on Biosimilar Monoclonal Antibodies

**European Medicines Agency, 2nd July 2009**

**Chair:** Christian Schneider (BMWP chair)

**Session Quality:** Jean-Hugues Trouvin (BWP chair)

**Session Non-clinical:** Beatriz Silva-Lima (SWP chair)

**Session Clinical:** Christian Schneider

**EMA:** Falk Ehmann (BMWP scientific secretariat)

**Open discussion on pros and cons of biosimilar mAbs**

- Possibility and feasibility
- No conclusion (yet)……but scientific evolution
- Questions put to audience as a starting point
- Focussed presentations, not meant to be exhaustive, but to initiate discussions.

# Key messages from the workshop

## Discussion on Quality

- Guidelines for quality sufficient **(mAbs quality guideline; biosimilar quality guideline).**
- Impossible to replicate exactly **the innovator which is in itself moving over time (**"moving target"**). Variability is set by the innovator in terms of production process and variability,** not so much in impurity profile **(which can be different and needs to be justified).**
- Different expression systems can be used**, but might be source of many difficulties.**
- **Analytical tools:** Paradoxical situation **that some blunt bioassays on one side but very sensitive tools on the other => combination.**
- **Main question: How to assess** impact **on safety and efficacy**

# Key messages from the workshop

## Discussion on non-clinical

- Reduced non-clinical programme may be possible **(and ethically maybe better acceptable); should focus on the specific needs and mechanism of action (e.g. as regards the requirement to show comparable impact on signalling events).**

- Toxicity **mostly related to** target-related **toxicity.** Use of non-relevant species not appropriate **(agreed by majority).**

- **For "unknown" impurities: Alternative approaches preferred, e.g. tissue cross-reactivity, reduce impurities, …**

- No consensus **if tox studies have to be** comparative**.**

# Key messages from the workshop

Clinical discussion

- Most sensitive model vs the clinically most relevant model
  - **(do we need the data in the most severe patient population and risk that the data are confounded?) => no consensus**
  - („slight majority“ for most sensitive model?)
- Several people mentioned that **endpoint should be the most sensitive one,** not necessarily the one initially chosen **by the innovator or the one recommended by the guidelines (secondary endpoint?)**
- PK/PD can be different between indications; modelling approaches?
- Understanding of mechanism of action not complete yet. **Not known to what extent** subpopulation of molecular species **contribute to activity in an indication, so has to be shown “somehow” with data.**
  **=> Will be the** totality of evidence **that leads to a convincing dossier.**

# Draft guideline on biosimilar mAbs

(EMA/CHMP/BMWP/403543/2010)

**- For public consultation until 31 May 2011 -**

Scope:

- Non-clinical and clinical data requirements for biosimilar monoclonal antibodies. Principles may also apply to certain fusion proteins (-cept molecules).

Non-clinical:

- A risk-based approach to evaluate mAb on a case-by-case basis is recommended to decide on the choice and extent of *in vitro* and particularly *in vivo* studies.

PK/PD:

- Comparative pharmacokinetic study in a sufficiently sensitive and homogeneous study population (healthy volunteers or patients)
- Pharmacokinetic data can be helpful to extrapolate data on efficacy and safety between different clinical indications
- PD studies, if feasible, can provide strong support for biosimilarity

# Draft guideline on biosimilar mAbs

(EMA/CHMP/BMWP/403543/2010)

Safety/Efficacy:

- Should normally be demonstrated through a phase III equivalence trial
- Trial designed to demonstrate similar efficacy and safety compared to the reference product, not patient benefit per se
- Choose most sensitive population
- Extrapolation of indications possible based on overall evidence of biosimilarity

RMP and PhVig plan:

- Required as for all biosimilars
- Post authorisation safety studies may be required

# Experience during Product evaluation

# **Omnitrope** (somatropin)

- Reference medicinal product: Genotropin
- Changes during development (active substance manufacturer). Increase in complexity of demonstration of comparability
- Additional steps introduced to reduce levels of Host Cell Protein
- Very high levels of (non-neutralising) antibodies, up to ~ 60% (for material used in clinical trials – manufactured according to old process)
- Additional liquid formulations added in the post-authorisation phase, posology unchanged

# **Valtropin** (somatropin)

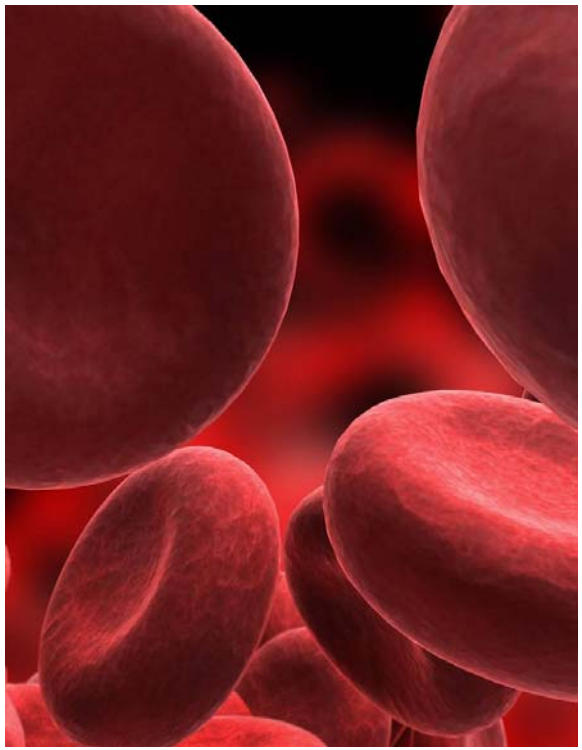
- Reference medicinal product: Humatrope
- Different expression system compared to reference medicinal product (*S. Cerevisiae* vs *E.coli*). Process specific HCP (yeast) assay required
- Changes during development subject to additional comparability
- Clinical trial:
  - initially calculated to demonstrate non-inferiority
  - US sourced reference product used (considered supportive)
- Indications differ from Omnitrope (Different reference medicinal product used)
  - Paediatric indications for Omnitrope only: Small Gestational Age (SGA), Prader-Willi Syndrome (PWS)

# **Binocrit** (epoetin alfa)

- Reference medicinal product: Erypo/Eprex (epoetin alfa)
- Extensive characterisation and quality comparability exercise
- Structural comparisons
  - Qualitatively similar
  - Quantitative differences seen (Increase in high mannose-6-phosphate, Decrease in N-glycolyl-neuraminic acid)
  - Differences were justified
- PRCA (Pure Red Cell Aplasia) issue with Reference medicinal product
  - Subcutaneous (SC) route contraindicated (chronic kidney disease, CKD patients) until May 2006
  - SC route most sensitive for potential immunogenicity
  - Consequence: No comparative SC studies (CKD)
  - SC route in immunocompetent individuals contraindicated for biosimilar (further studies needed)
  - Risk minimisation required to avoid off-label SC use

# **Silapo** (epoetin zeta)

- Reference medicinal product: Erypo/Eprex (epoetin alfa)
- Extensive characterisation and quality comparability exercise
- Structural comparisons
  - Qualitatively similar
  - Quantitative differences seen (Increase in des o-glycan forms, Decrease in N-glycolyl-neuraminic acid)
  - Differences were justified
- SC route initially contraindicated as for Binocrit. SC indications added post-authorisation upon availability of data



# Current Guideline on Filgrastim

***Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor***

**Pharmacokinetics study** : single dose cross-over studies IV and SC

**Clinical Efficacy studies** : Two different approaches

**1 / Comparability efficacy study in the recommended clinical model**

Prophylaxis of severe neutropenia after cytotoxic chemotherapy

in a homogenous patient group

→ *Primary endpoint : Duration of severe neutropenia*

**2 / Alternative model : Pharmacodynamics comparability studies in healthy volunteers**

Scientific advice is highly recommended

→ *Primary endpoints : Absolute Neutrophil Count* $ANC_{AUC}$ *and* $ANC_{Cma}$

**Extrapolation of indication** if Mechanism of Action is the same

**Clinical Safety assessment :** Total follow-up of at least 6 month

# Experience with Biosimilar Filgrastims 1/2

| Name | Applicant | Date of Approval | Scientific Advice | Reference | Approach |
|---|---|---|---|---|---|
| Filgrastim Ratiopharm | Ratiopharm | 15-Sep-08 | 3 | Neupogen | Efficacy studies |
| Ratiograstim | Ratiopharm | | | | |
| Biograstim | CT Arzeimittel | | | | |
| Tevagrastim | Teva | | | | |
| Filgrastim Hexal | Hexal | 06-Feb-09 | 2 | Neupogen | PD studies |
| Zarzio | Sandoz GmbH | | | | |

# Experience with Biosimilar Filgrastims 2/2

| Filgrastim Ratiopharm | Filgrastim Hexal |
|---|---|
| **Clinical Development** | |
| ➢ 2 PK/PD studies in healthy volunteers<br>➢ **1 pivotal placebo controlled comparative efficacy study in breast cancer patients**<br>➢ 2 **comparative** safety studies in lung cancer and non-Hodgkin's lymphome | ➢ No pivotal efficacy study<br>➢ **4 PK/PD studies in healthy volunteers (single and multiple dose)**<br>➢ 6-month **non comparative**, supportive, safety study in breast cancer patients |
| **RMP** | |
| ➢ Routine Pharmacovigilance<br>➢ Routine Risk Minimization Activities (labelling) | ➢ Routine Pharmacovigilance<br>➢ Routine Risk Minimization Activities (labelling)<br>➢ **FUM : 3 post-marketing studies**<br>• Phase IV study in patients with severe chronic neutropenia (SCN)<br>• Safety Follow-up of the SCN patients included in the phase IV study<br>• Follow-up of healthy stem cell donors undergoing PBPC mobilisation |

# **Tevagrastim** (filgrastim)

- Reference medicinal product: Neupogen
- Extensive characterisation and quality comparability exercise
- Partial use of reference medicinal product sourced in Lithuania before EU accession – could only be considered supportive data
- Clinical data
  - Phase I: Comparative PK/PD studies in healthy volunteers
  - Phase III: Comparative Safety & Efficacy trials in cancer patients undergoing chemotherapy. Efficacy endpoint: duration of severe neutropenia

# **Zarzio** (filgrastim)

- Reference medicinal product: Neupogen
- Extensive characterisation and quality comparability exercise
- Clinical data
  - Phase I: Comparative PK/PD studies in healthy volunteers. Efficacy endpoints: neutrophil and CD34+ cell counts
  - Phase III: Non-comparative (single arm) clinical trial in cancer patients undergoing chemotherapy. Safety focus. Only supportive
- The G-CSF Guideline states:
  - "*The **recommended clinical model** for the demonstration of comparability of the test and the reference medicinal product is the **prophylaxis of severe neutropenia** after cytotoxic chemotherapy in a homogenous patient group (…). Alternative models, including pharmacodynamic studies in healthy volunteers, may be pursued for the demonstration of comparability if justified.*"

# Withdrawn applications - **Insulin Marvel**

- Reference medicinal product: Humulin S
- Three presentations: Short, intermediate (30/70), long acting
- Quality issues
  - Incomplete comparability exercise, particularly for drug product
  - Inadequate validation of manufacturing process
  - Batch traceability missing
  - More data required for extended release forms
- Clinical issues
  - Comparative PK & PD : **euglycaemic clamp – most sensitive model**
  - Similar PK parameters, however not similar PD profiles : **faster absorption** (glucose infusion rate)→ **Risk of hypoglycaemia** (potentially 45% increase in glucose lowering)
  - Applicant resorted to efficacy trial with HbA1C end-point, not sufficiently sensitive
  - Limited immunogenicity data

# Negative opinion – **Alpheon** (rhIFNα-2a)

- Reference medicinal product: Roferon-A
- Quality issues
  - Concerns regarding stability and impurities for drug substance and drug product. Profiles also not matching reference medicinal product
  - Drug product manufacturing process inadequately validated
  - Comparability between batches used for clinical trial batches and commercial batches not shown
- Non-clinical studies were inadequate and indicated differences
- Clinical issues
  - Difference in virological relapse rates
  - Inconclusive data in the response rate for the “difficult-to-treat” genotype 1 patients
  - Different rate of adverse events
  - Inadequate immunogenicity documentation

# RMP (Risk Management Plan)

General:

- RMP required for all medicinal products including Biosimilars
- A RMP is recommended for the originator and all concerned biosimilars, with - if necessary - separate sections for specific product related issues.
- The RMP should address all ‘class-effects’.

# The EU Risk Management Plan

Part I

**Safety Specification**

**Pharmacovigilance Plan**

} **ICH E2E**

Part II

**Evaluation of the need for risk minimisation activities,**

**-> if a need for additional activities**

# Status of RMP

- RMP as a document is kept confidential
- European Assessment Reports (EPAR) contain the summary table of the RMP
- Annex IV – the most strict risk minimisation measures that needs to be ensured by member states
- Detailed summary tables, and potentially other parts of the reference product's RMP may be provided to the MA applicant for a biosimilar product to ensure compatibility of the risk management systems of both products

## Recommendations based on experience

### RMP Class review **(reference products + biosimilars)**

- CHMP press release in October 2007 (http://www.emea.europa.eu/pdfs/human/press/pus/49618807en.pdf)
- Results of new studies available since then, needs to be reflected in the safety specification of all relevant products
- Based on the new safety specification, re-consider a need for additional pharmacovigilance and/or risk minimisation activities

### Co-operation between MAHs

- It is of added value when a common risk management system between MAHs of reference product and biosimilar products is achieved
- The EMEA may facilitate such a dialogue
- RMP for a biosimilar product needs to cover risks known for the reference product and theoretical ones of the biosimilar product

# Conclusions

- EU biosimilar portfolio and related guidelines continue to grow
- EU experience important reference for others
- Challenges for the future:
  - Moving towards more complex biosimilars, such as mAbs
  - Consider the possibility of a global development of biosimilars

# Further reading

EMEA 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
- 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
- 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

# Thank you for your attention

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# Thank you for your attention!


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