

GRIPS Symposium

**International Conference on Biotech
Medicines Innovations in Developing
Countries:**

Peter Richardson, EMEA
19-February-2009





Biosimilars

Implementation

Guidelines

Experience

Future Developments

Overview of presentation

- **Rationale / Introduction**
- EMEA Guidelines
- Vision
- Experience
- Conclusion

The EU Road to Biosimilars

- **Review of Pharmaceutical Legislation ***
 - » Opportunity to assess EU needs
- **Novel approach – “Abridged biologicals”**
 - » Recognising variability in biological products.
- **Scientific principles : Comparability**
 - » Experience of innovators making changes
- **Comparability applied to biosimilars**
 - » Reduce non-clinical & clinical data

* Regulation EC/726/2004 + amended Directive 2001/83EC

Rationale - biosimilar evolution

- **Development of comparability concept**
 - » History of changes to various products
- **New Pharmaceutical Legislation**
 - » (Directive 2001/83/EC, as amended: Article 10.4)
- **“additional data, in particular, the toxicological and clinical profile shall be provided.”**

Rationale for Guidelines

- **Guidelines need to address:**
 - » Types of Product / Classes Applicable
 - » Quality / Safety / Efficacy / Pharmacovigilance
 - » Sufficient detail with flexibility
(Balance of “case-by-case” v recipe)

Biosimilars evolve from generics

- **Regulatory perspective - What is a biosimilar ?**
 - » 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”*

Biosimilar Legislation

- **New 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

Dossier requirements for biosimilars

Module 1 - Normal Requirements

Module 2 - Normal Requirements

**Integrated CE
(Comparability Exercise)**

Quality, Module 3 - FULL

+ CE

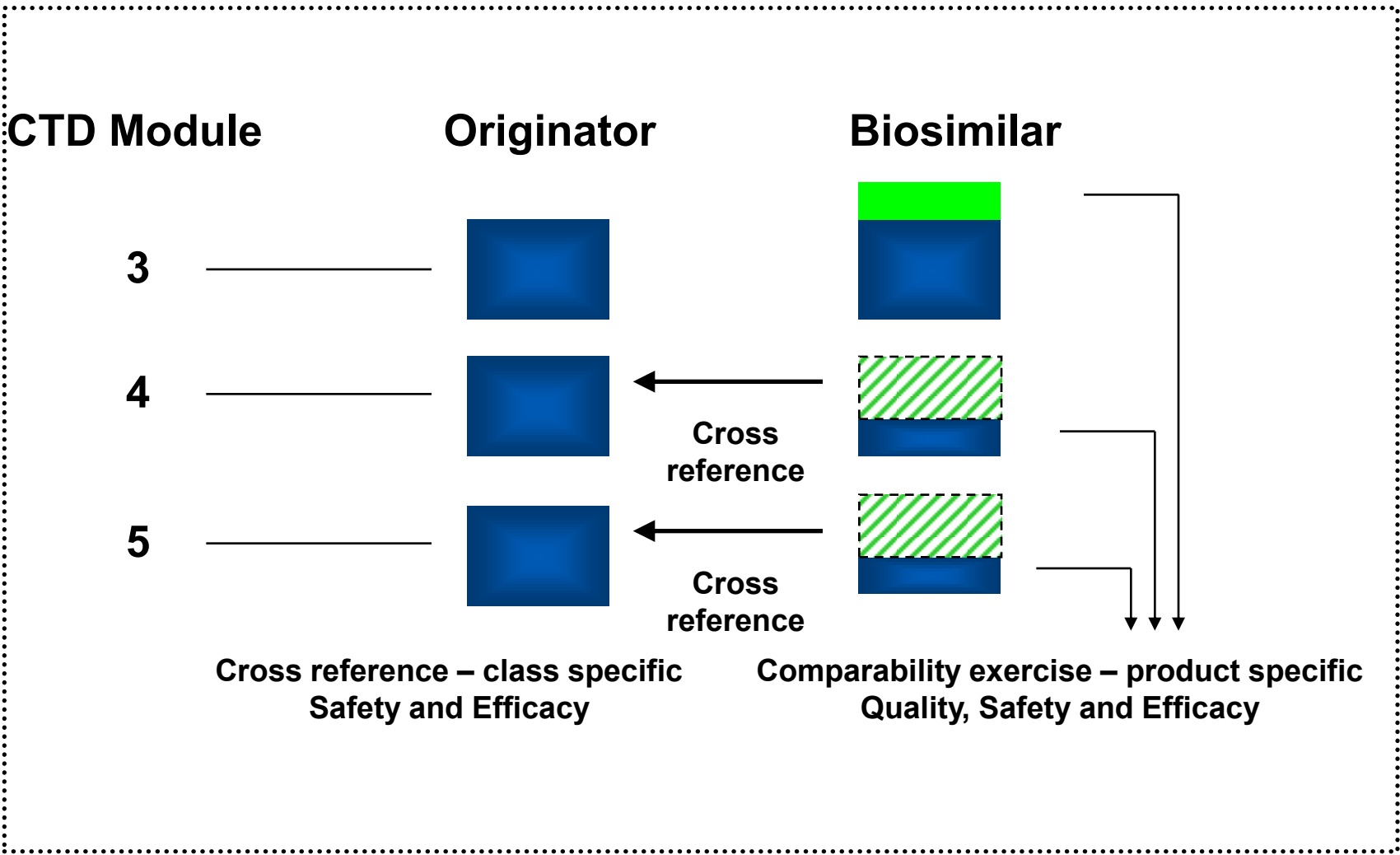
Non-clinical, Module 4 - Reduced

+ CE

Clinical, Module 5 - Reduced

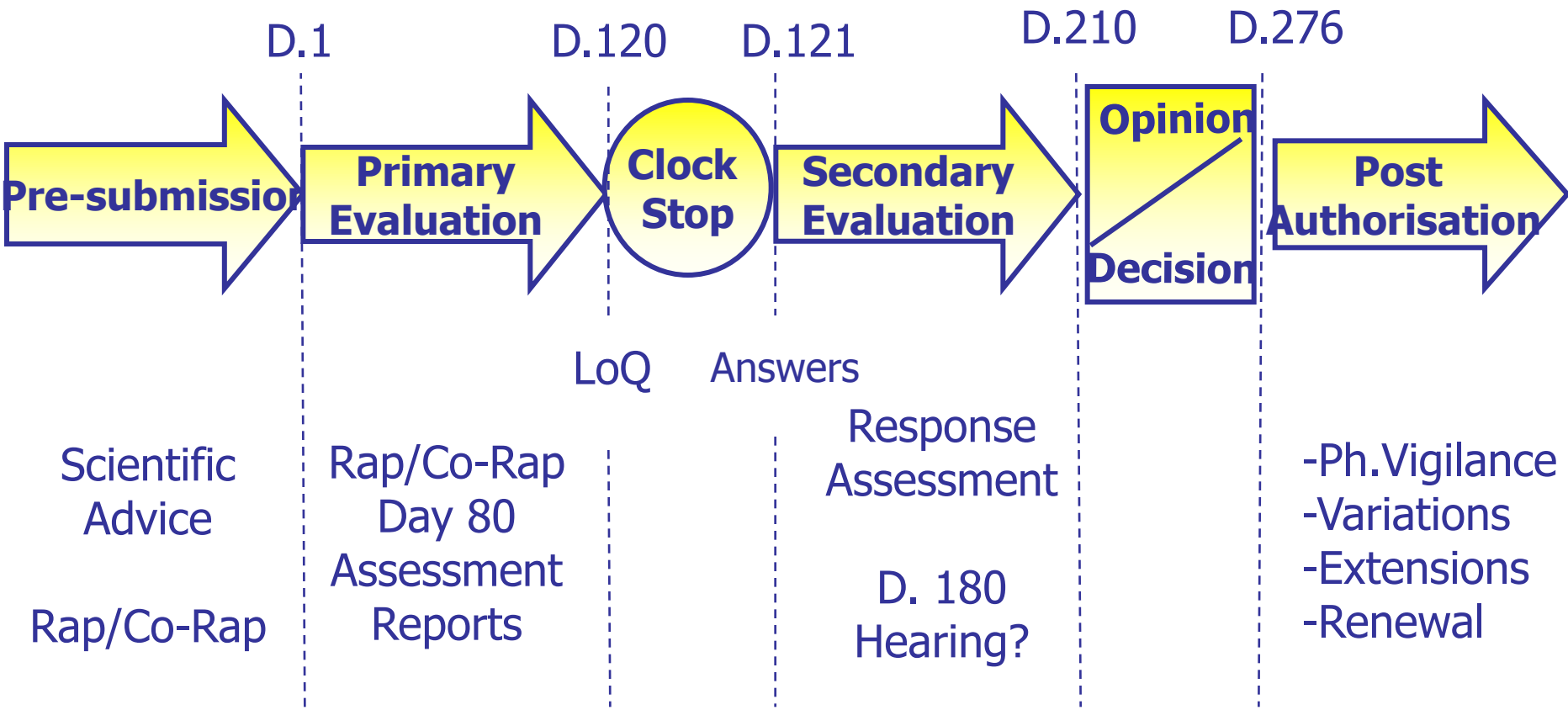
+ CE

Dossier requirements for biosimilars





Overview of Centralised Procedure - Biosimilar Timetable (Full MAA)





EPAR - European Public Assessment Report

= CHMP AR after deletion of commercially confidential information

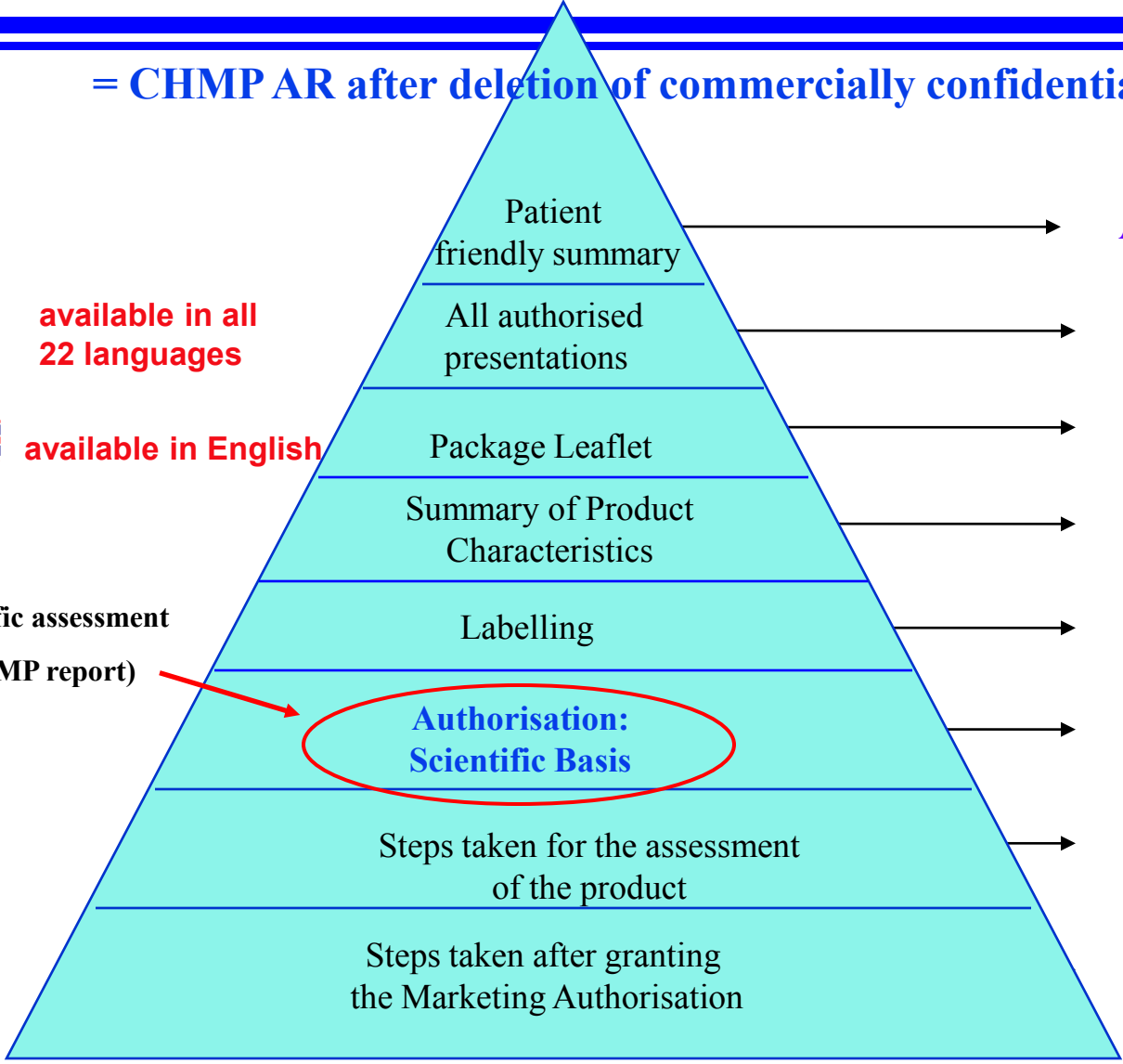


available in all 22 languages



available in English

Scientific assessment (CHMP report)



All readers



All readers



Patients



Health professionals



Pharmacists/patients



Scientific community
Health professionals



Anyone interested



Anyone interested





EPARs - via EMEA homepage

European Medicines Agency

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we work for you

EMEA STRUCTURE

- Overview
- Mission Statement
- Organigramme
- Management
- Staff
- European Experts

EMEA COMMITTEES

- Management Board
- CHMP
- CVMP
- COMP
- HMPC
- PDCO
- CAT

CONTACT & LOCATION

- General Enquiries
- Press Office
- Pharmacovigilance
- Product Defects
- EMEA Certificates
- Documentation
- European Experts
- ICM/Audits
- Business Hours
- EMEA holidays 2009
- How to Find Us

MEETINGS & EVENTS

- Meetings
- Events

RECRUITMENT

- Recruitment Policy
- Job Opportunities

PUBLISHING SERVICES

- Online Mailing service
- Important legal notice
- Copyright Policy

SEE ALSO

- Calls for Tender
- Fees Payable to EMEA

Main EMEA contact details and Product Emergency Hotline

First EMEA workshop on a proposed European paediatric network

Published 30/01/2009

On 16 February 2009, the European Medicines Agency (EMA) will be holding a workshop to discuss and initiate the development of a European paediatric network of existing national and European networks and centres with specific expertise in research studies and clinical trials relating to paediatric medicines. This initiative stems from EU paediatrics legislation that calls for the fostering of high-quality, ethical research on medicinal products to be used in children.

For full details see: [EMEA Events](#)

COMP invites comments on draft data requirements for orphan medicines

Published 21/01/2009

The European Medicines Agency's Committee for Orphan Medicinal Products (COMP) has drafted for public consultation the following document:

[Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation \(EMEA/COMP/15893/2009\)](#)

This document is a revision of 'Guideline on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation' (EMA/COMP/66972/2004), released in September 2004, which has now been superseded.

Comments may be sent, until 21 July 2009, by e-mail to: orphandrugz@emea.europa.eu

Latest Press Releases

See [Press Office](#) for archived press releases

30/01/09	EMEA	Public statement on Zimulti (rimonabant) Withdrawal of the marketing authorisation in the European Union
30/01/09	EMEA	Public statement on Acompla (rimonabant) Withdrawal of the marketing authorisation in the European Union
23/01/09	EMEA	Public statement on Zenapax (daclizumab) Withdrawal of the marketing authorisation in the European Union
22/01/09	CHMP	Press Release from the January meeting <i>Conf.</i>
22/01/09	CHMP	Press Release - European Medicines Agency makes recommendations for safer use of Bitalin and other methylphenidate-containing medicines in the EU See also, Questions and answers on the review of medicines containing methylphenidate
22/01/09	CHMP	Press Release - European Medicines Agency recommends new contraindication for Fareston (toremifene) See also - Questions and answers on the addition of contraindications for Fareston (toremifene)
16/01/09	PDCO	Press Release from the 7-9 January meeting
16/01/09	CVMP	Press Release from the January Meeting
16/01/09	EMEA	Press release on inaugural meeting of the CAT See also, Questions and answers on the regulation of advanced-therapy products
16/01/09	EMEA	Press Release - Priority access for children during Myozyme supply shortage
08/01/09	COMP	Monthly Report from the January meeting

See [Press Office](#) for archived press releases

Fast track to a topic...

PRODUCT INFORMATION

- Human Medicines
- Veterinary Medicines
- Safety Announcements
- Withdrawals and Refusals
- Summary of Opinions
- Opinions for Orphan Designation
- Opinions for medicines used outside the EU

MEDICINES FOR CHILDREN

PATIENT GROUPS

MEDICINES FOR THE ELDERLY

ENEPD

SME OFFICE

MEDICINES AND EMERGING SCIENCE

EU ENLARGEMENT

NEW EU LEGISLATION

ROADMAP 2010

EU TELEMATIC

- EudraPharm Website
- EudraCT Website
- EudraCT Helpdesk
- PIM website
- eSubmission Website
- EudraVigilance Website
- EudraVigilance Veterinary Website

CMDh **CMDv**

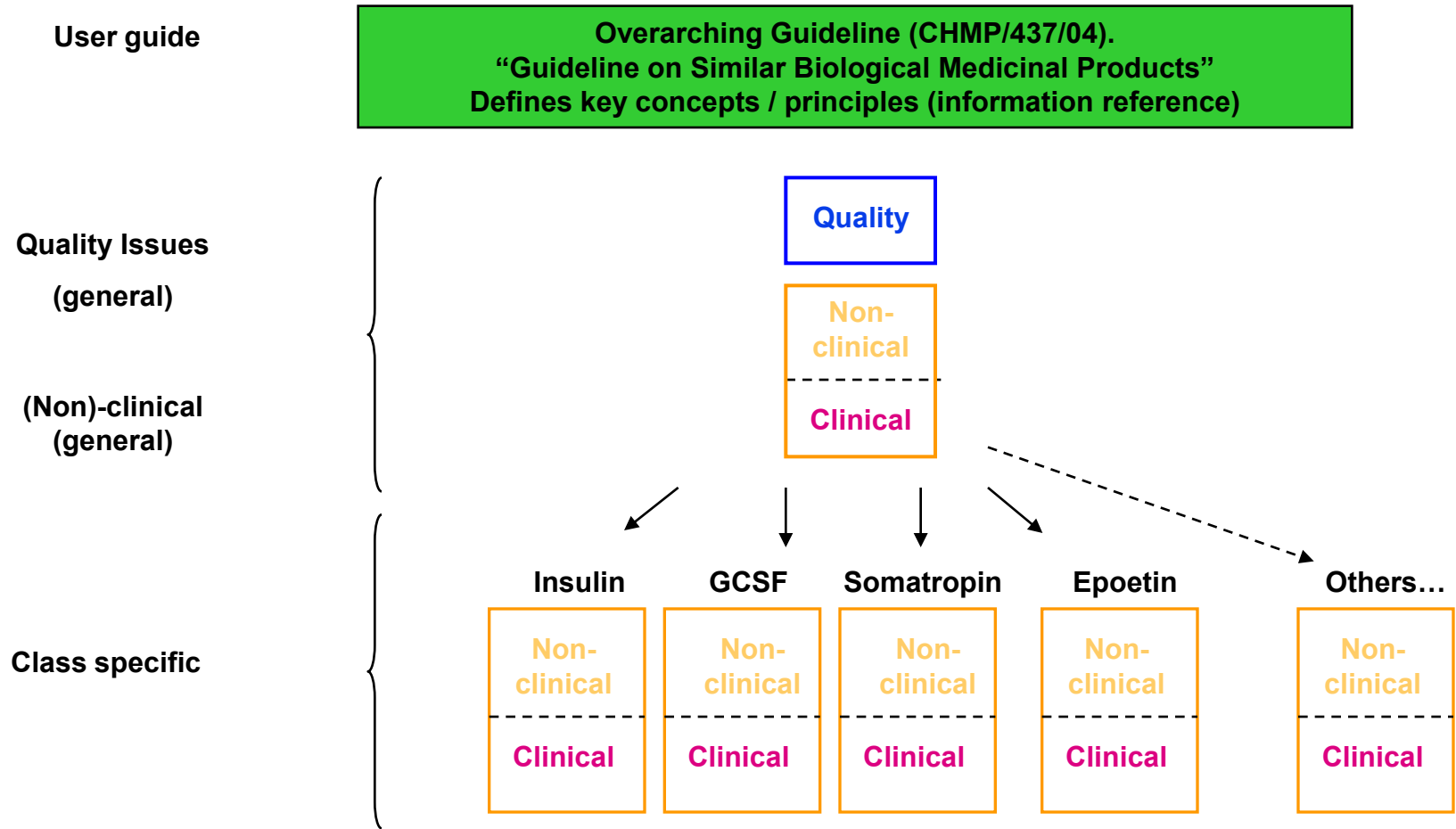
Overview of presentation

- Rationale / Introduction
- **EMEA Guidelines**
- Vision
- Experience
- Conclusion

Preparing the network

- **Legislation refers to Guideline**
 - » General principles (“ overarching”)
- **EMEA tasks**
 - » Coordination by Secretariat / BMWP / BWP
- **Consult with stakeholders**
 - » Workshop – Paris 2005 / comments during drafting
- **Assessor training**
 - » EMEA, October 2007 (app. 50 assessors)
 - » Immunogenicity workshop 2007

Biosimilar Guidelines - Summary (2006)



Biosimilar - Guidelines

- **Overarching guideline**
- **Quality guideline**
- **(non)-clinical guideline on SBMP**
- **Product-class specific guidelines on SBMP - (non)-clinical**

Overarching Guideline

- **Guideline on Similar Biological Medicinal Products. CHMP/437/04 (CHMP Adopted).**
- **Main points:**
 - » Outline concepts and basic principles
 - Biological, Biotech. (rDNA), Immunological & Blood / plasma derived products
 - » Considerations: analytical methods, processes, clinical and regulatory experience.
 - » Choice of Reference Product
(EU Reference for comparability exercise)

Quality guideline

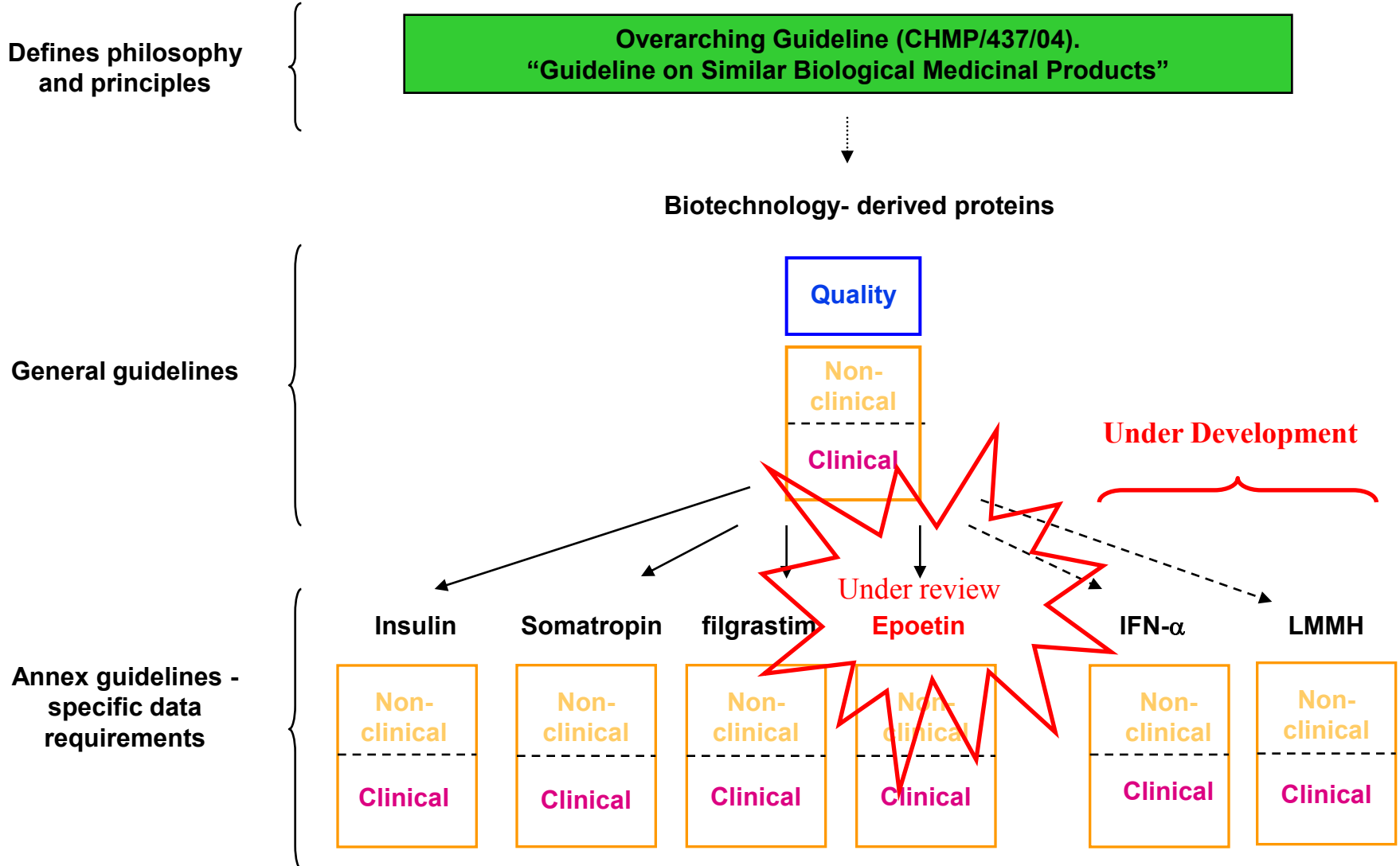
- **Specific for rDNA derived proteins**
- **Main issues**
 - » state-of-art analytical methods to characterise both similar and reference products
 - » Manufacturing process should be well developed
 - » Avoid changes, i.e. additional Comparability Exercises during development

(Non)-Clinical Guideline

- **Guideline on general principles**
 - » Clinical equivalence
 - » Safety studies
 - » Immunogenicity
 - » (Pharmacovigilance)



Biosimilar Guidelines - Summary (2009)



BMWP + BWP

- **Current Highlights**

- » Company briefing meetings
- » Scientific advice / MAAs
- » Guidance
 - Finalise LMMH / interferon alfa
 - Revise epoetin guideline
 - Different expression systems
- » Workshop on Monoclonals – 2009

Overview of presentation

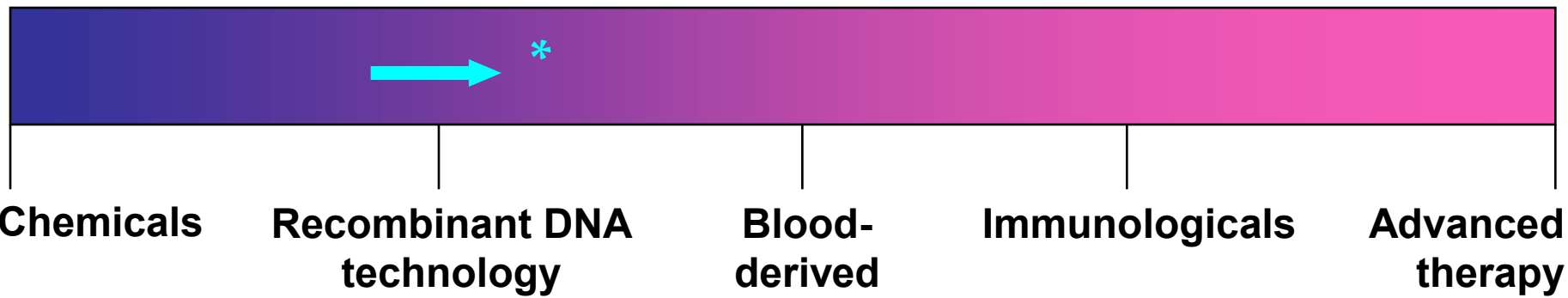
- Rationale / Introduction
- EMEA Guidelines
- **Vision**
- Experience
- Conclusion

Current applicability - Biosimilars

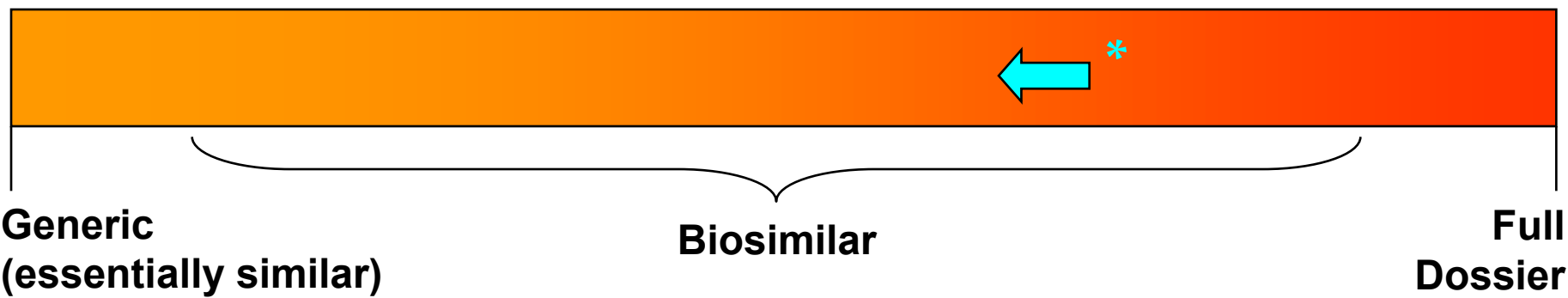
- **Biotechnology-derived: recombinant proteins**
 - » Product complexity – major factor
 - » Data requirements not always the same
 - » Case-by-case approach partly applicable
- **Applications to other biologicals**
 - » Not ruled out
 - » Ability to characterise becomes critical
- **Aims for future**
 - » Extend to other biologicals – mAbs ?
 - » Reduce data requirements where possible

Spectrum of Complexity

Science



Legislation



* Future Developments ?

Overview of presentation

- Rationale / Introduction
- EMEA Guidelines
- Vision
- **Experience**
 - » Marketing Authorisation Applications
 - » Comparability: Quality and Clinical aspects
- Conclusion

EU Experience - MAAs

**15 MAA Procedures
Determined - January 2009**

Somatropin (2)

Filgrastim (4)

Epoetin (5)

11 Products

(9MAHs)

Interferon-alfa (1)

Insulin (3)

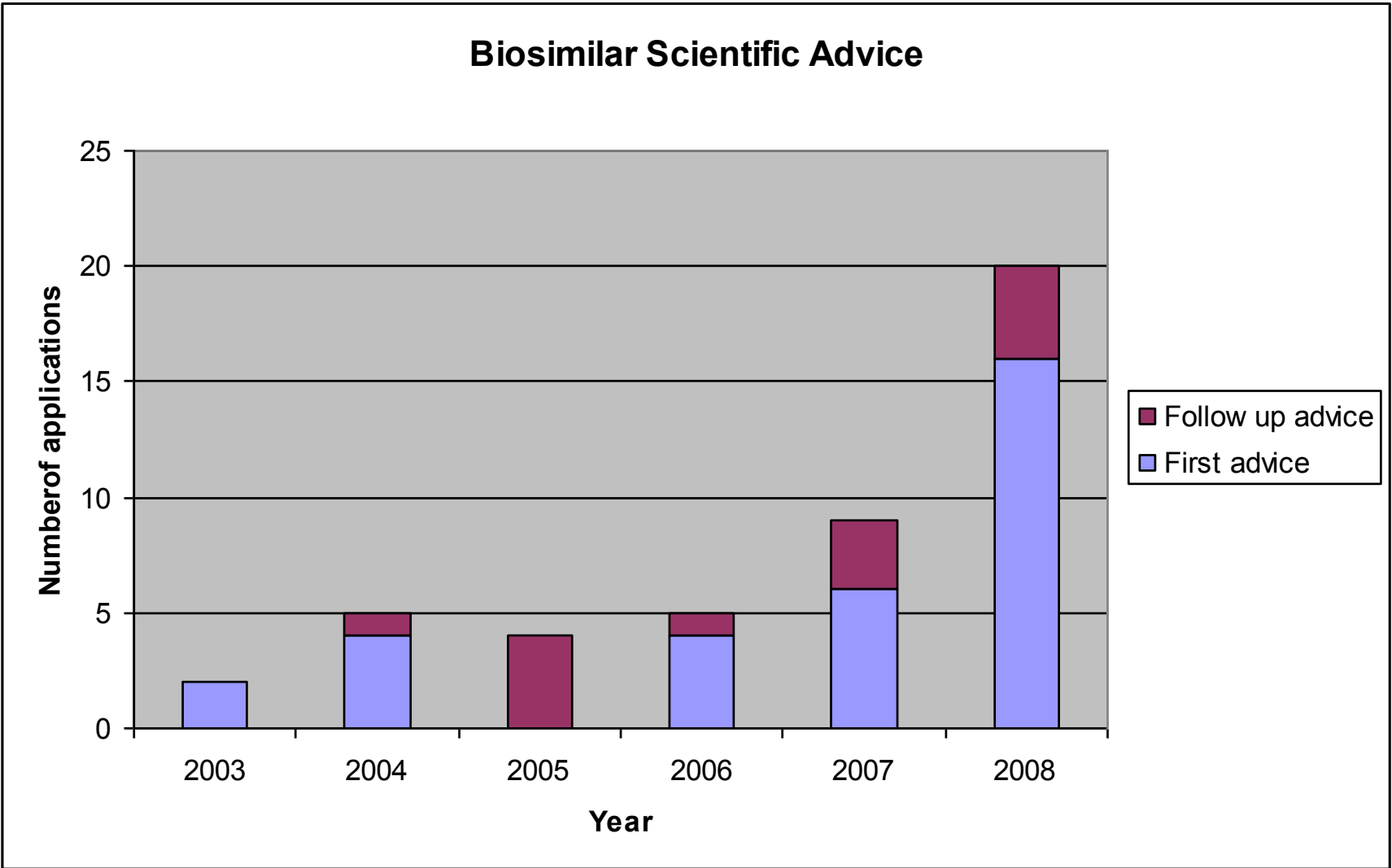
**+ 2 Positive opinions
for filgrastim**



Reasons for MAA success

- **Pay attention to quality requirements**
 - » State of the art techniques
 - » Justify differences
- **Request (and adhere to) Sci. Advice**
 - » SA still helpful when guidance available
- **Demonstrate comparability**
 - » Well developed process
 - » Care with in-licensing

Scientific Advice



Comparability issues - quality related



Omnitrope - 1st Biosimilar

- **Development**
 - » **Process changes: active substance manufacture (Covance to Sandoz)**
 - » **E. coli : Host Cell Proteins + immunogenicity (up to 57% anti-hGH Abs)**
 - » **Additional purification steps added**
- **Lyophilised Product**
 - » **2 liquid formulations added post-authorisation**
 - » **Different concentrations / formulations**
 - » **Posology NOT changed.**

Valtropin

- **Historical authorisations: Eutropin (LG Life Sciences)**
- **Authorised shortly after Omnitrope (somatropin)**
- **Reference product for comparability – Humatrope**

- **Manufacturing process**
 - » **Valtropin : *S. cerevisiae***
 - » **Humatrope : *E. coli***

- **Comparability**
 - » **State of art characterisation : no structural difference**
 - » **Changes during development subject to additional comparability**
 - » **Process specific HCP (yeast) assay required.**



Binocrit (epoetin alfa)

- 1st biosimilar epoetin
- Reference product epoetin alfa (Erypo/Eprex)
- Extensive comparability – characterisation
- Structural comparisons
 - » Qualitatively similar
 - » Quantitative differences seen
- Increased: high mannose-6-phosphate
- Decreased: N-glycolyl-neuraminic acid
- Differences have been justified



Silapo (epoetin zeta)

- Reference product epoetin alfa (Erypo/Eporex)
- Formulation similar to Neorecormon (epoetin beta)
- Extensive comparability – characterisation
- Structural comparisons
 - » Qualitatively similar
 - » Quantitative differences seen
- Increased: des o-glycan forms
- Decreased: N-glycolyl-neuraminic acid
- Differences have been justified

Insulin Marvel

- **Three presentations**
 - » **Short, intermediate (30/70), long acting**
- **Withdrawal EPAR (Day 120 CHMP report)**
- **Main issues:**
 - » **Incomplete comparability exercise (particularly for product)**
 - » **Inadequate validation + stability data**
 - » **Poor linkage of lot for comparability with clinical batches**
- **More data required for extended release forms**

Comparability issues - clinical aspects

Somatropin

- **Two Biosimilar Products:**
 - » **Omnitrope & Valtropin**
- **Two Reference Products:**
 - » **Genotropin & Humatrope**
- **Summary of Product Characteristics (SmPC) differ**
 - » **Section 4.1 Therapeutic Indications**
- **Paediatric (Omnitrope only)**
 - » **Small Gestational Age (SGA)**
 - » **Prader-Willi Syndrome (PWS)**

Epoetin alfa

- **Biosimilars - Binocrit (epo. alfa), Silapo (epo. zeta)**
- **Reference Product – Erypo / Eprex**
- **PRCA issue with Eprex**
 - » **Subcutaneous (s/c) route contraindicated (chronic kidney disease, CKD patients) until May 2006.**
 - » **s/c route most sensitive for potential immunogenicity**
- **Consequence: No comparative s/c studies (CKD)**
 - » **Biosmilars currently do not have this route of admin.**
 - » **Required to complete comparative s/c in CKD as part of Risk Management Plan (see EPAR)**
 - » **Risk minimisation required to avoid off-label s/c use**

Insulin Marvel

- **Biosimilar Guideline**
 - » **Comparative PK & PD : euglycaemic clamp – most sensitive**
- **Main issues (see withdrawal EPAR)**
- **Similar PK parameters (i.e. OK for a generic), 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 accepted due to lower sensitivity**
- **Additionally, limited immunogenicity data**

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Conclusions

- **Biosimilars are abridged biologicals (NOT generic)**
- **EU biosimilar : “comparable quality, safety and efficacy” to originator’s reference product**
- **Labelling (i.e. SmPC) may not be the same as the reference product**
- **Prescriber awareness required, e.g. of the authorised indications**
- **Biosimilars are individual products**
 - » **Pharmacovigilance activities need to identify the product being prescribed.**

EMA Website

For your information:

- **EMA Website:**

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

» **EPARs:**

<http://www.emea.europa.eu/htms/human/epar/eparintro.htm>

- **Biosimilar Guidelines:**

<http://www.emea.europa.eu/htms/human/humanguidelines/multidiscipline.htm>

