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# **PMDA February 2009**

**Peter Richardson, EMEA**





# Biosimilars

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**Implementation**

**Guidelines**

**Experience**

**Future Developments**

# Overview of presentation

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- **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

# Rationale - biosimilar evolution

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- **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

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- **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**

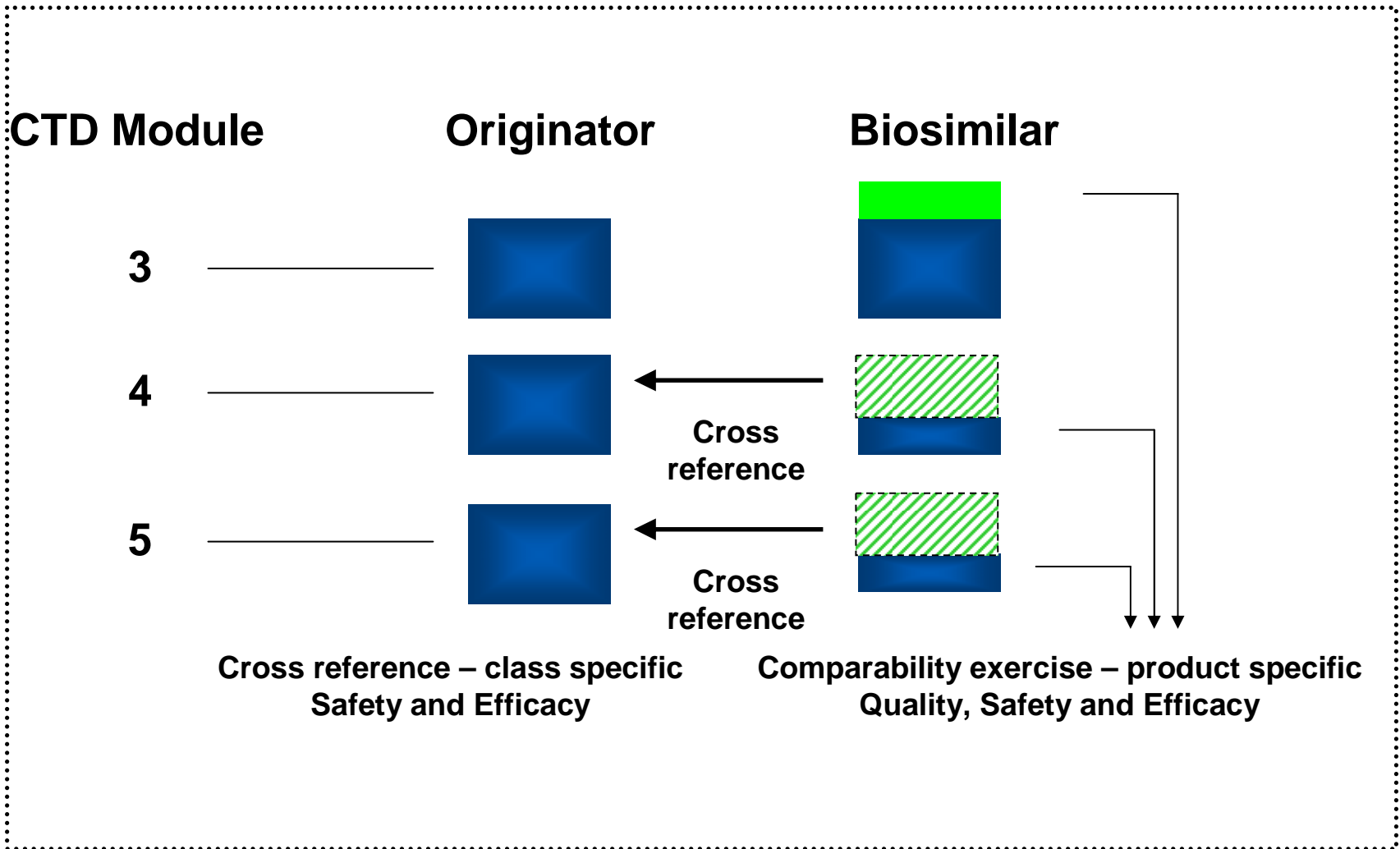
**Non-clinical, Module 4 - Reduced**

**+ CE**

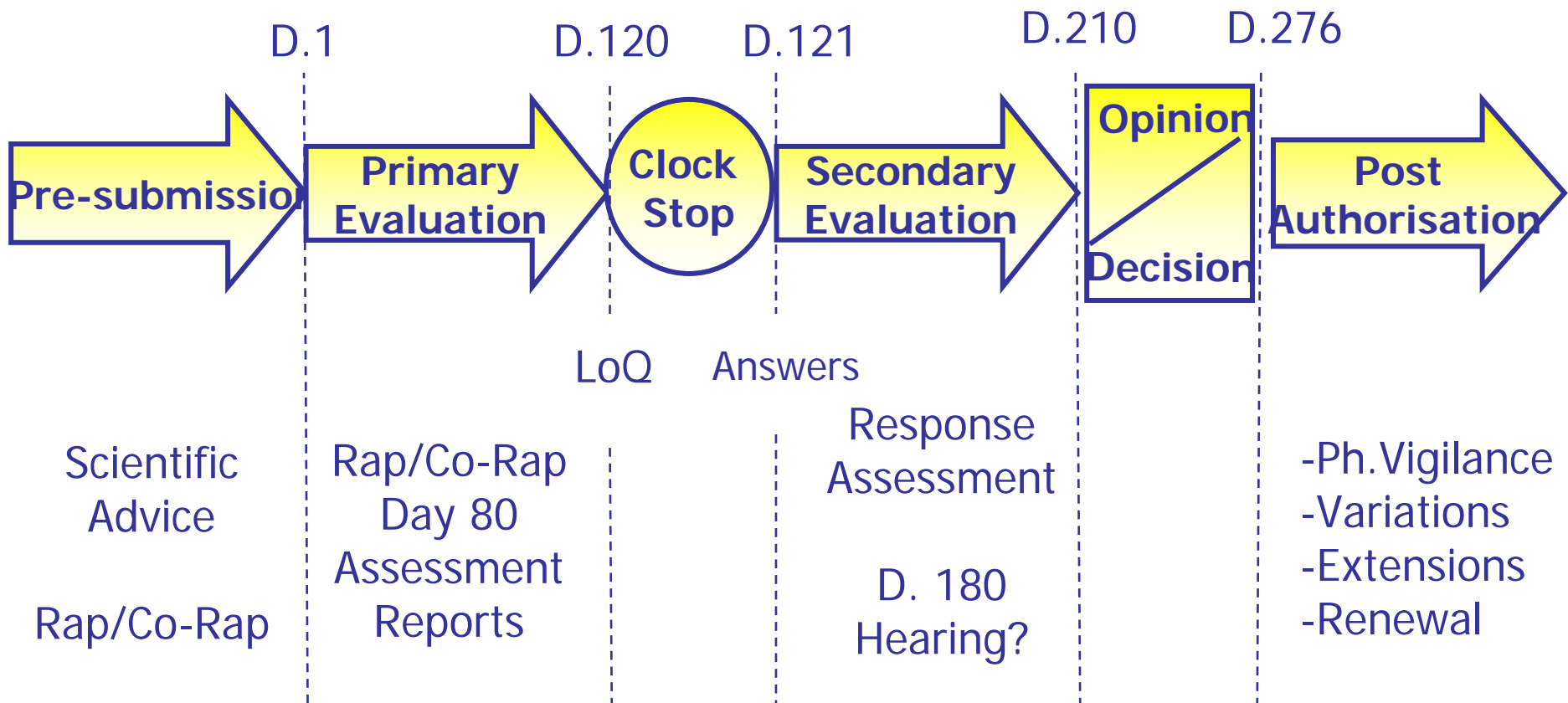
**Clinical, Module 5 - Reduced**

**+ CE**

# Dossier requirements for biosimilars

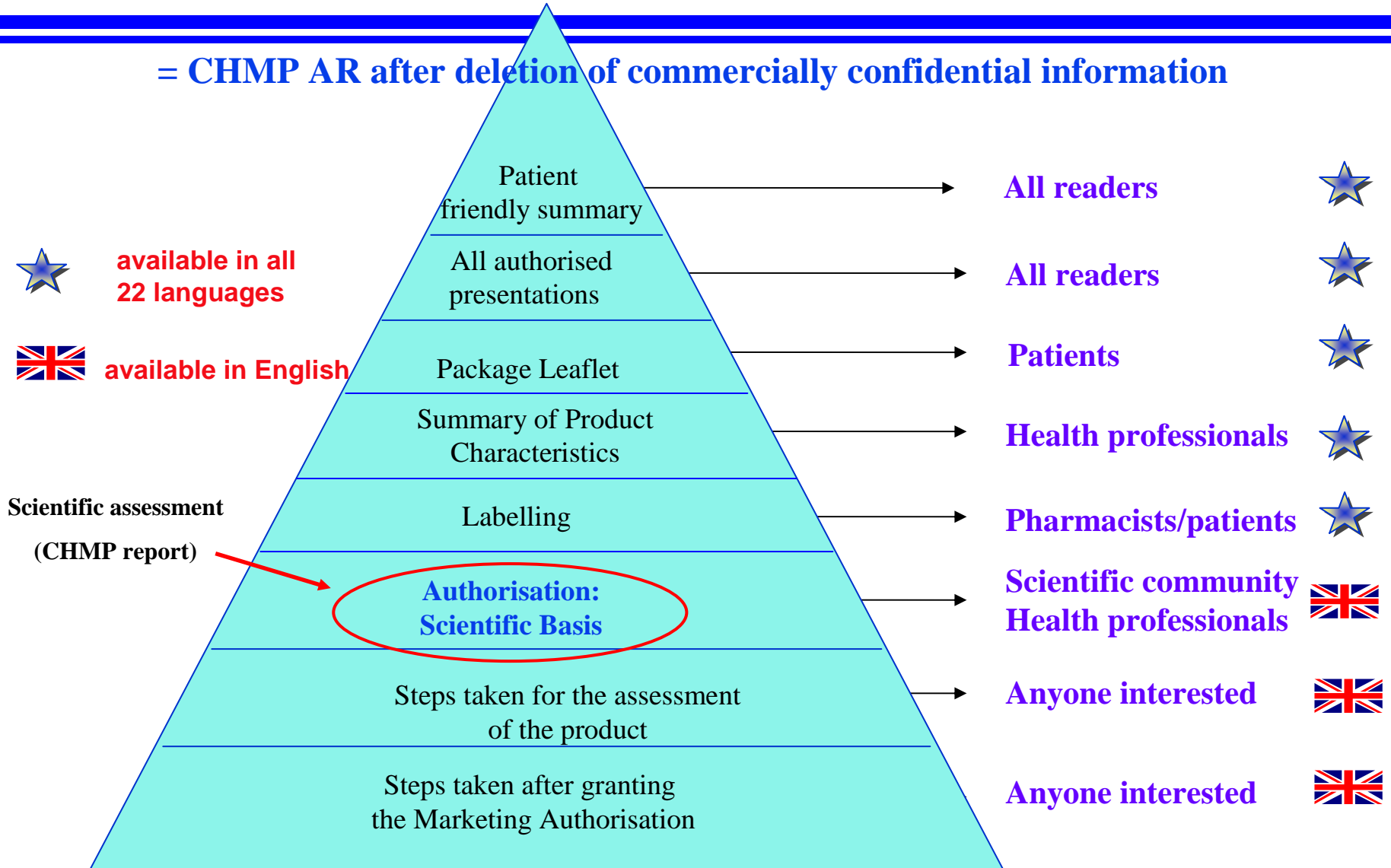


# Overview of Centralised Procedure - Biosimilar Timetable (Full MAA)



# EPAR - European Public Assessment Report

= CHMP AR after deletion of commercially confidential information



# EPARs - 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
- IQM/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: [orphandrugs@emea.europa.eu](mailto:orphandrugs@emea.europa.eu)

**Latest Press Releases**

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

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

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 TELEMATICS**

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

**CMDh** **CMDv**

# Overview of presentation

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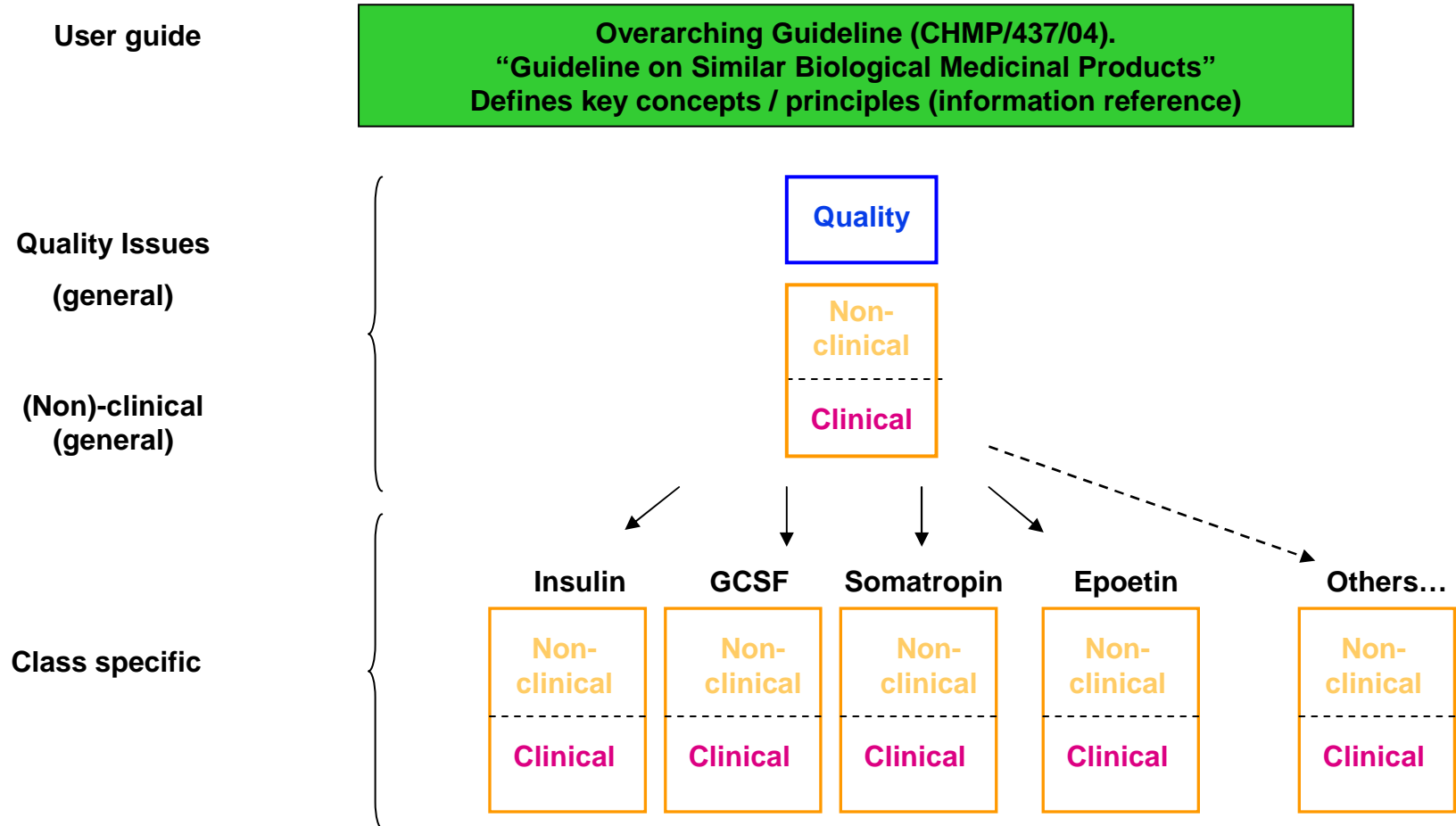
- Rationale / Introduction
- **EMEA Guidelines**
- Vision
- Experience
- Conclusion

# 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

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- **Overarching guideline**
- **Quality guideline o**
- **(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

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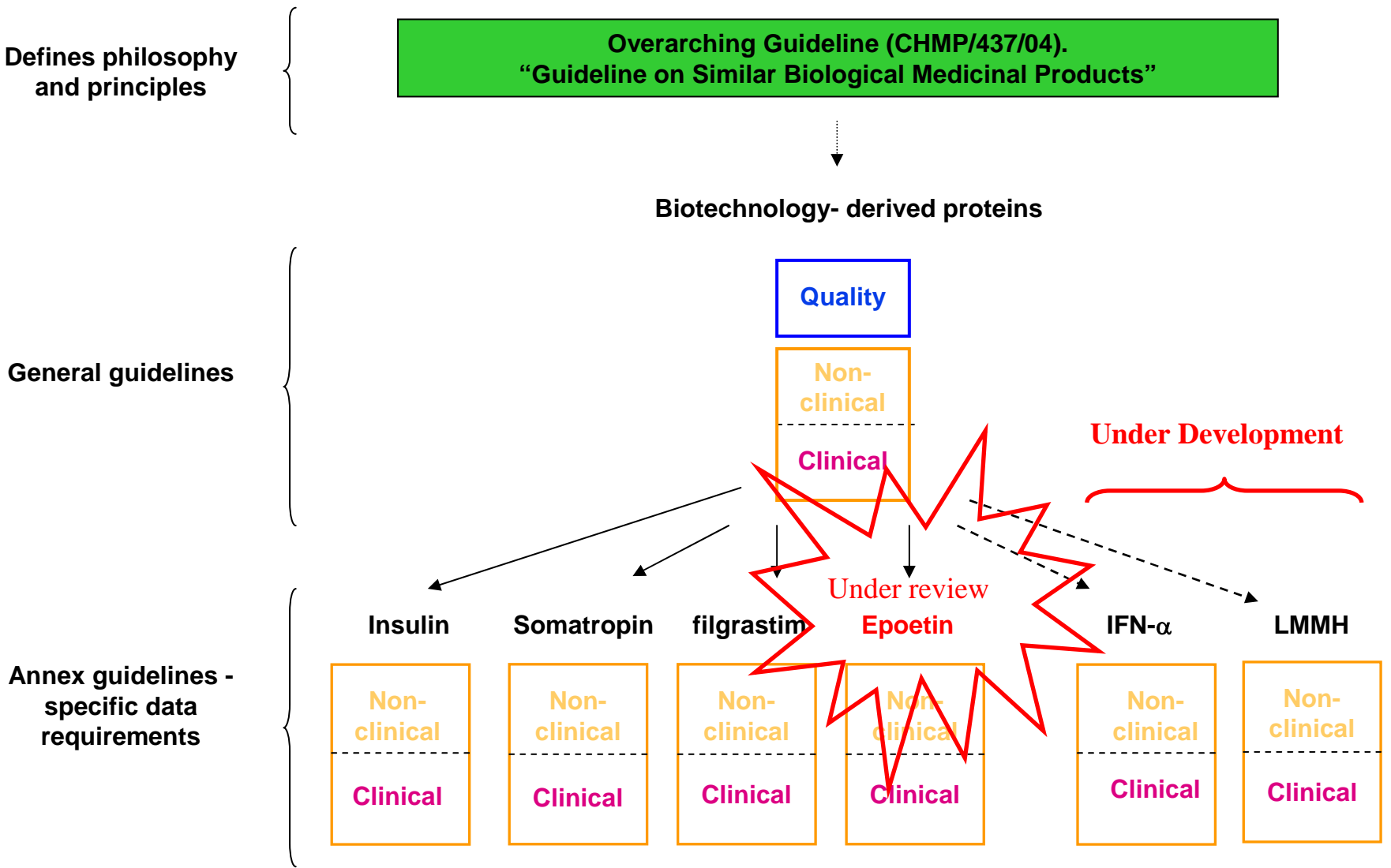
- **Specific for rDNA derived proteins**
- **Main issues**
  - » state-of-art analytical methods to characterise both similar and reference products
  - » Manufacturing process should be well developed
  - » Avoid changes, i.e. additional Comparability Exercises during development

# (Non)-Clinical Guideline

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- **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

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- **Vision**
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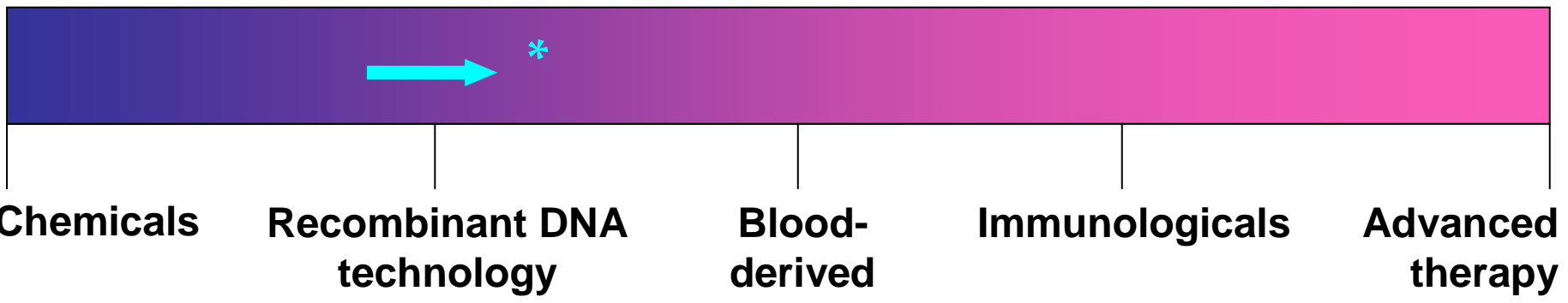


# Current applicability - Biosimilars

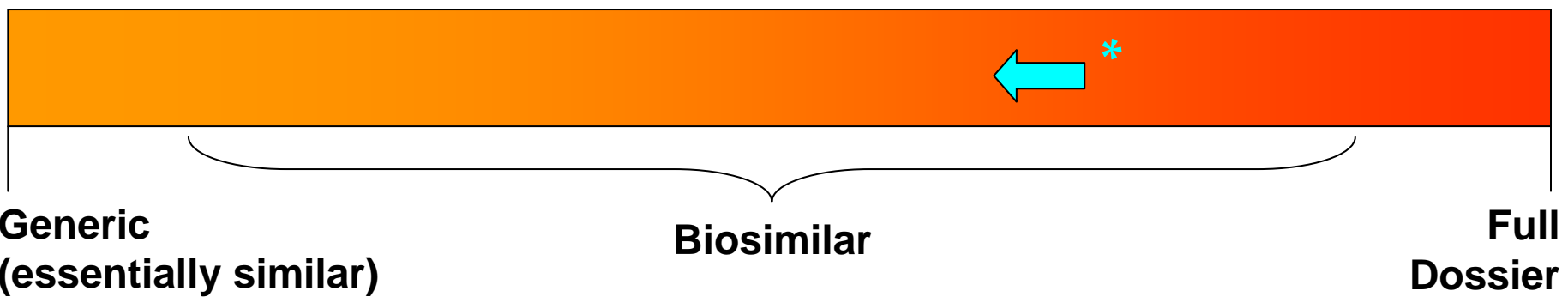
- **Biotechnology-derived: recombinant proteins**
  - » Product complexity – major factor
  - » Data requirements not always the same
  - » Case-by-case approach partly applicable
- **Applications to other biologicals**
  - » Not ruled out
  - » Ability to characterise becomes critical
- **Aims for future**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

# Spectrum of Complexity

## Science



## Legislation



\* Future Developments ?

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- Vision
- **Experience**
- Conclusion

# EU Experience - MAAs

## 15 MAA Procedures Determined - January 2009

**Somatropin (2)**

**Filgrastim (4)**

**Epoetin (5)**

**11 Products**

**(9MAHs)**

**Interferon-alfa (1)**

**Insulin (3)**

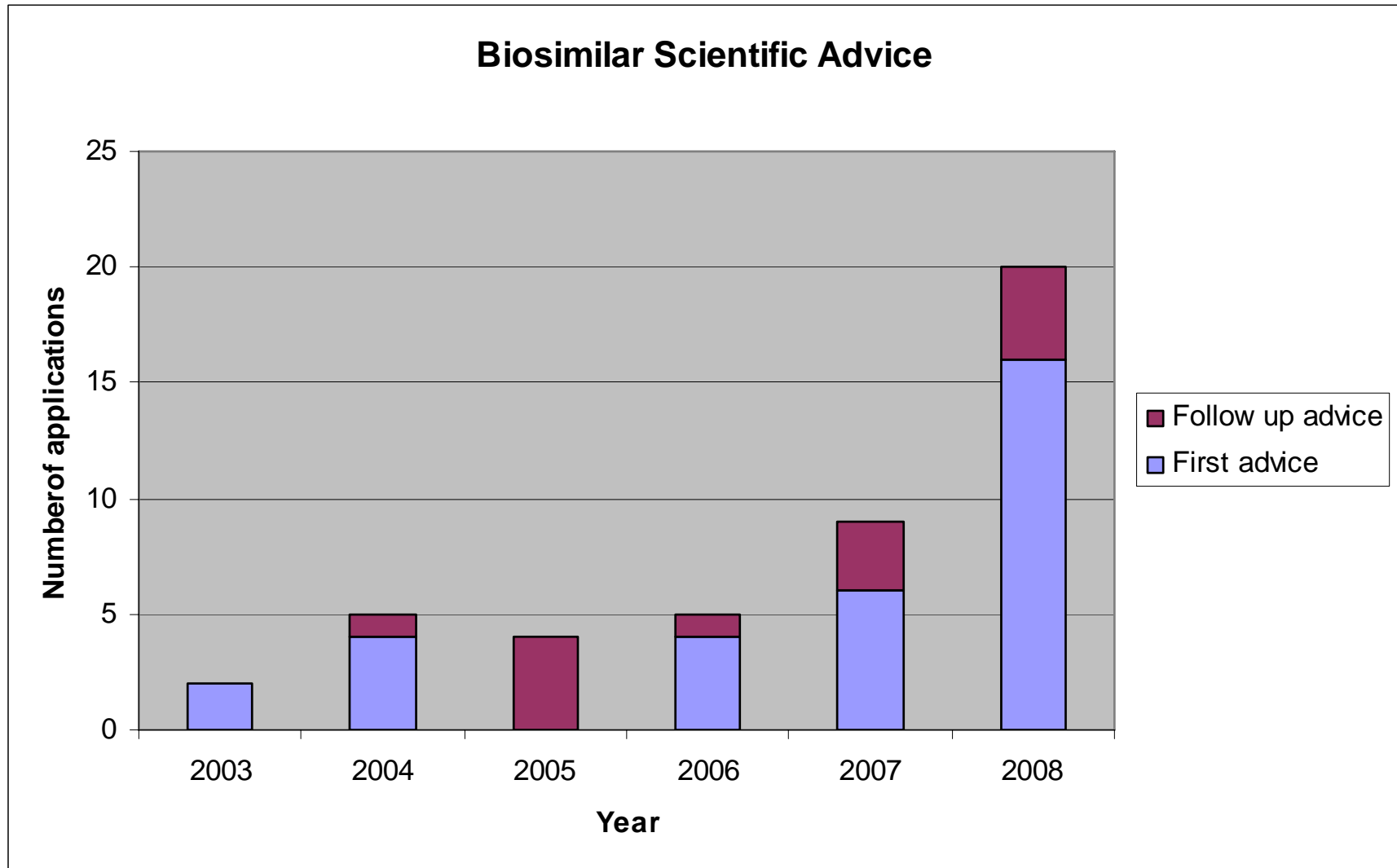
+ 2 Positive opinions for  
filgrastim

# Reasons for MAA success

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- **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



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# Conclusions

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- **Promote early meetings with EMEA**
  - » Legal / Regulatory
- **Scientific Advice**
  - » Comparability / Complexity / Study Design
- **Continued growth in interest in biosimilars**
  - » International : Health Canada, Japan, Others
  - » USA – legislative proposals
  - » WHO guidance under development