PMDA February 2009

Peter Richardson, EMEA

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

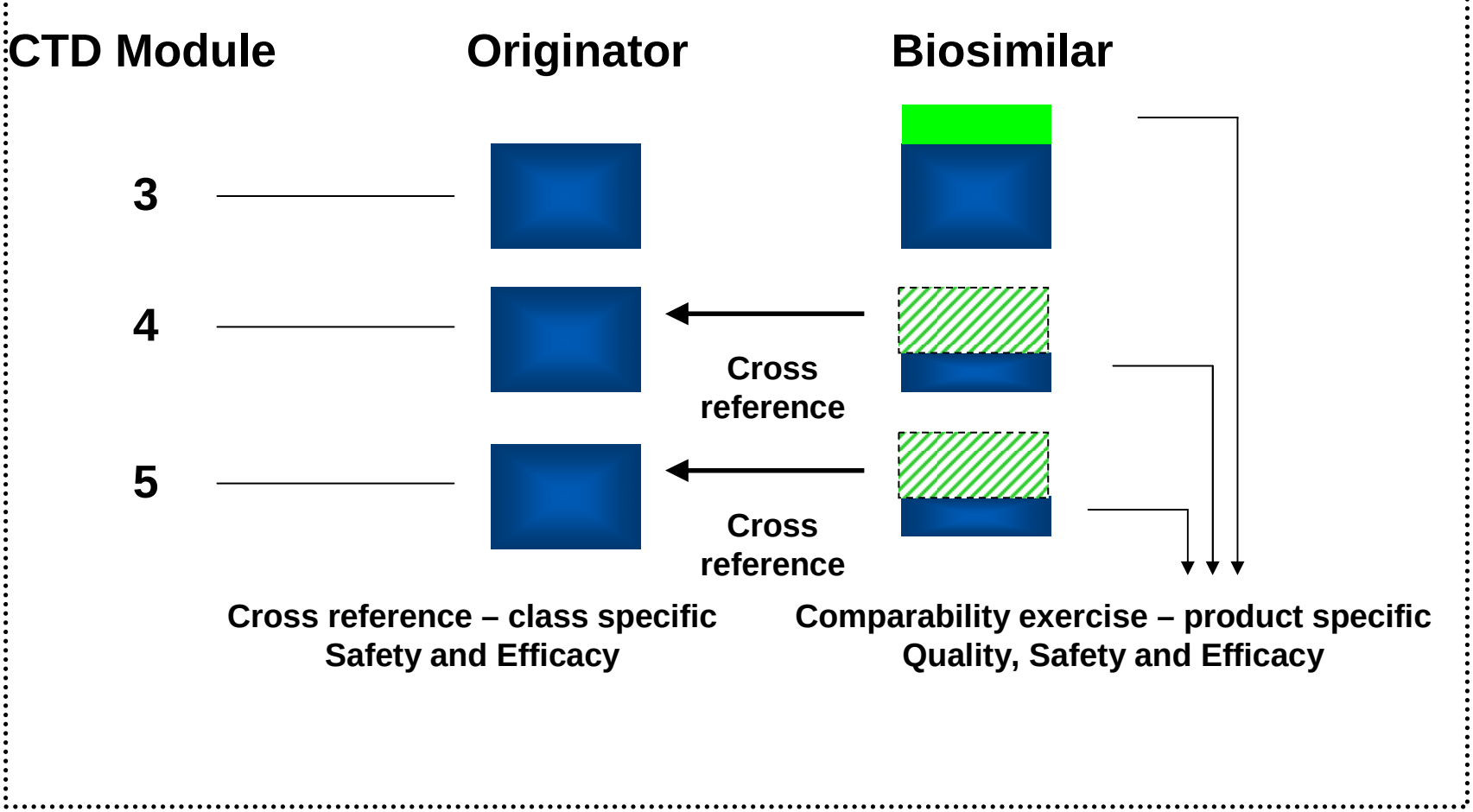
Module 1 - Normal Requirements

Module 2 - Normal Requirements

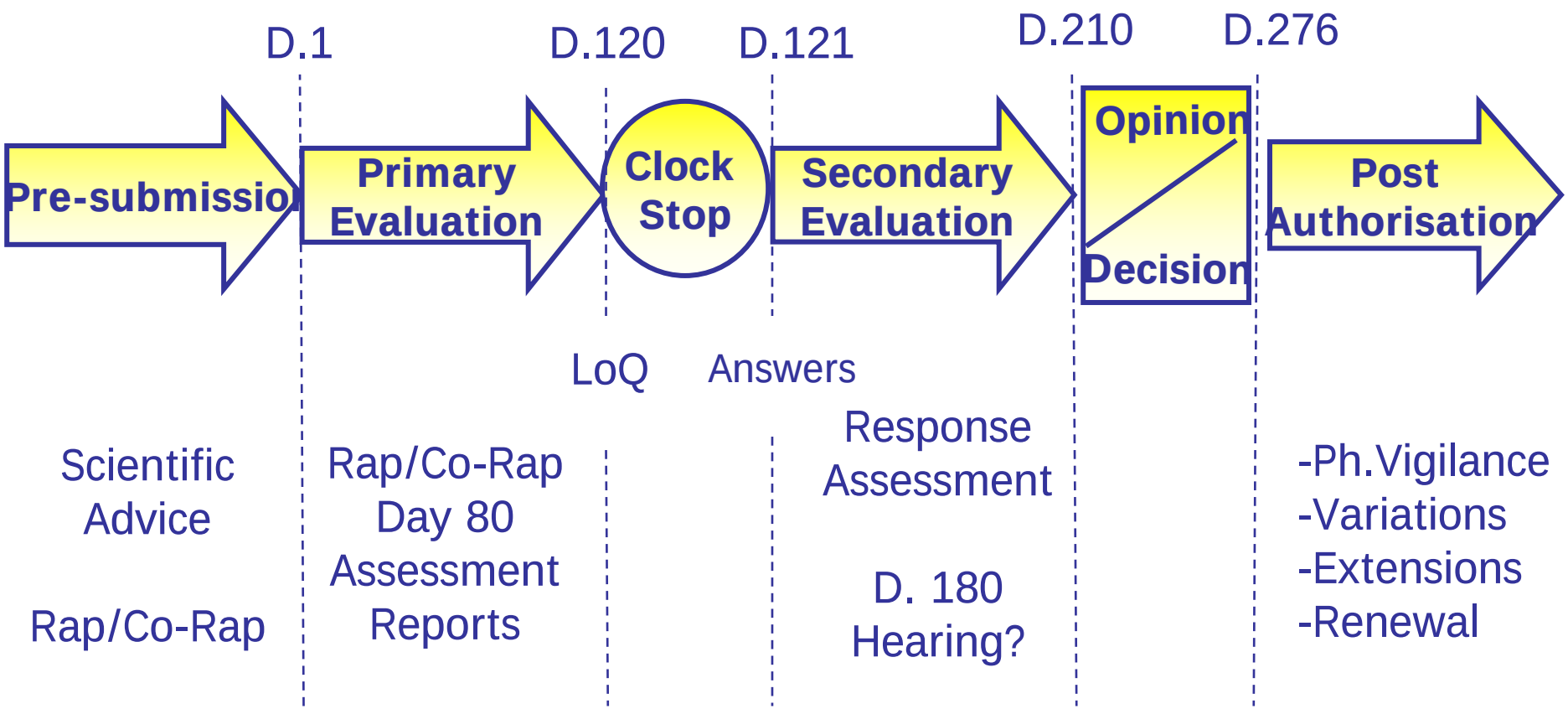
Integrated CE
(Comparability Exercise)

Quality, Module 3 - FULL	+ CE
Non-clinical, Module 4 - Reduced	+ CE
Clinical, Module 5 - Reduced	+ CE

Dossier requirements for biosimilars

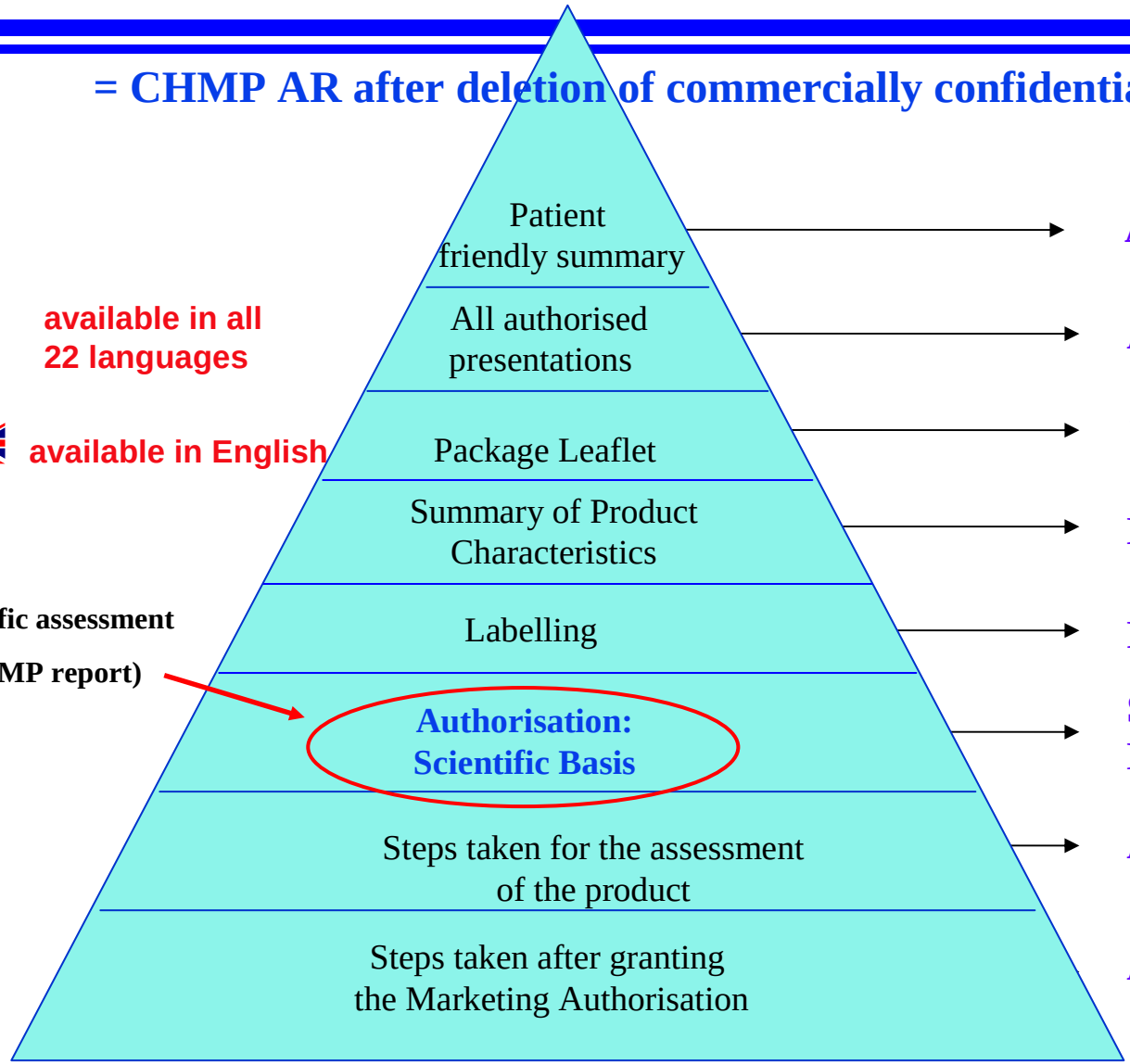


Overview of Centralised Procedure - Biosimilar Timetable (Full MAA)



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 – EMEA homepage

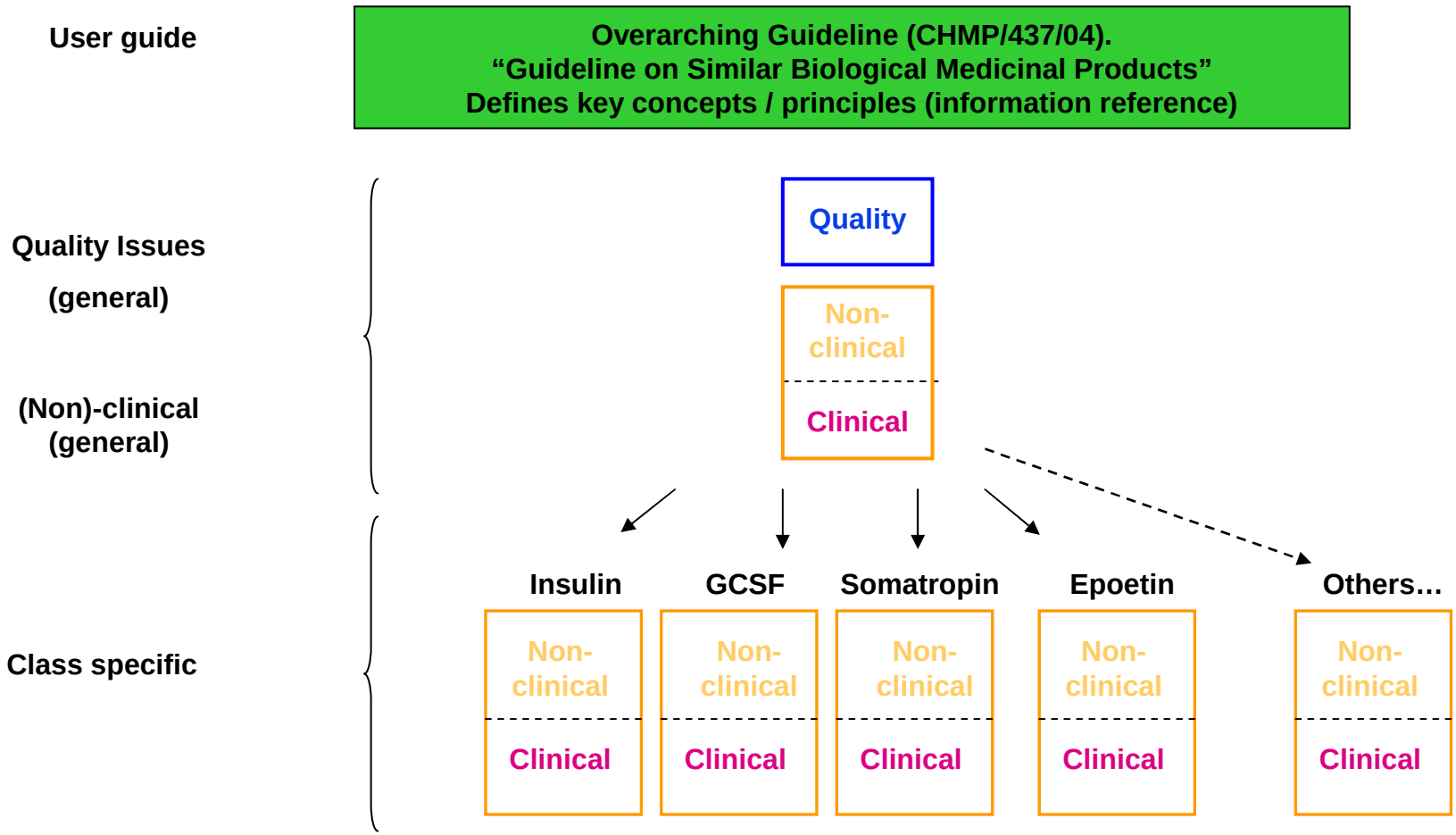
Overview of presentation

- 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
- **Asessor training**
  - » EMEA, October 2007 (app. 50 assessors)
  - » Immunogenicity workshop 2007

Biosimilar Guidelines – Summary (2006)



Biosimilar – Guidelines

- **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)

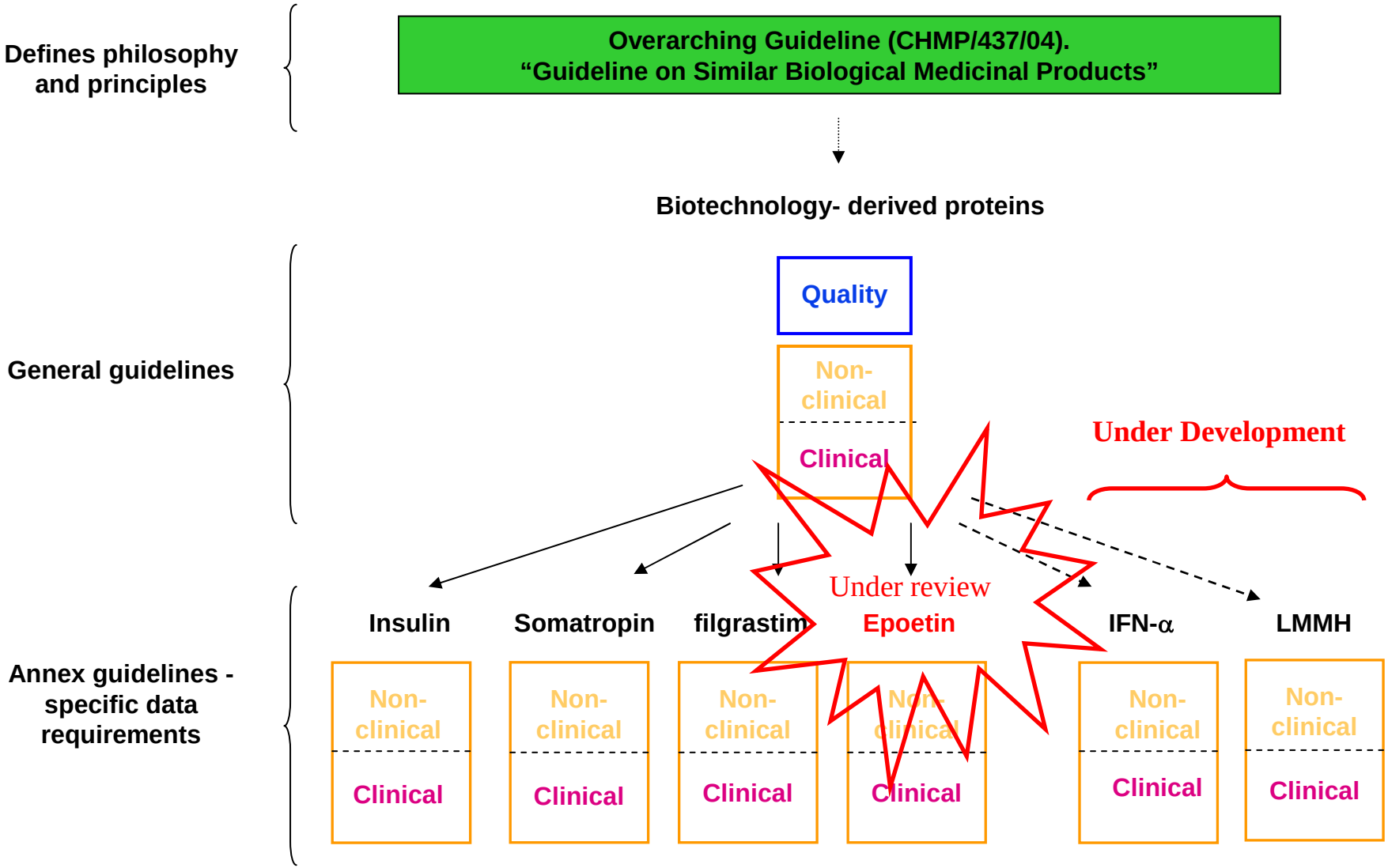
Quality guideline

- **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

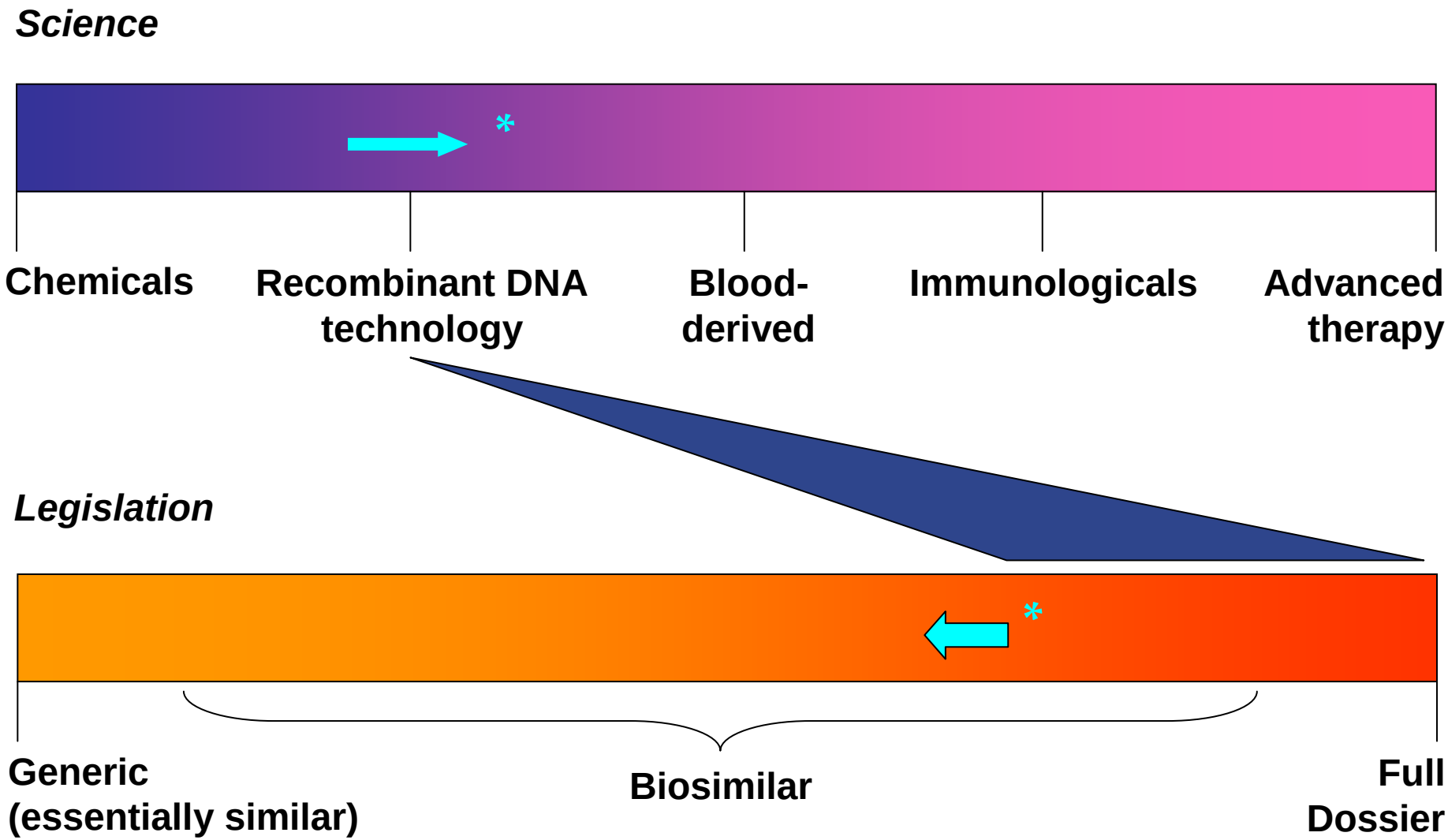
Current applicability - Biosimilars

- **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



* Future Developments ?

Overview of presentation

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

EU Experience - MAAs

15 MAA Procedures Determined - January 2009

Somatropin (2)

Filgrastim (4)

Epoetin (5)

} 11 Products (9MAHs)

Interferon-alfa (1)

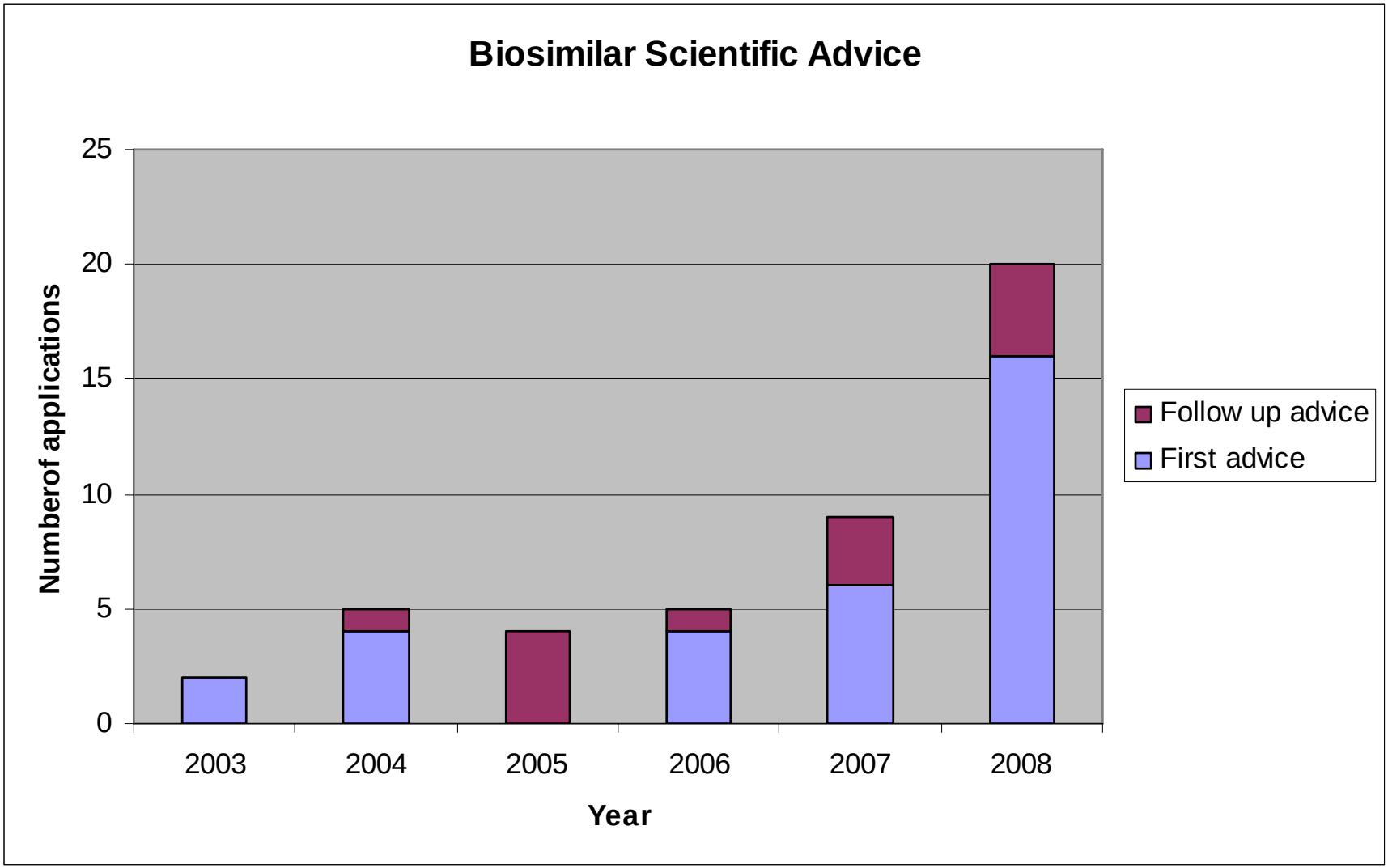
Insulin (3)

+ 2 Positive opinions for filgrastim

Reasons for MAA success

- **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



Overview of presentation

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

Conclusions

- **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