European perspectives on regulation for biologics

Jean-Hugues Trouvin
Afssaps – DEMEB – Paris, France
Biologics working party – EMEA – London, UK

Overview of presentation

- ✓ Regulation of biologics in EU
- ✓ Organisation and mandate of the Biologics working party (BWP)
- ✓ BWP guidelines and position statements
- ✓ New topics (challenges) under development
  - New technology challenges
  - Advanced therapy medicinal products
  - New concepts in Quality
- ✓ Current topics under discussion
  - Regulation for variations to marketing authorisation
  - Biosimilars
- ✓ Conclusion

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Regulation of biologics in Europe

- Biologics =
  - Vaccine
  - Plasma-derived medicinal products
  - Urine-, or tissue- derived medicinal products
  - Any biological substance of human or animal origin
  - Biotechnology-derived proteins
  - Gene therapy
  - Cell therapy

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Regulation of biologics in Europe

- ✓ EU = 27 Member States and three authorisation procedures
  - National authorisation
  - followed by Mutual Recognition → **CMDh**
  - Decentralised procedure → **CMDh**
  - Centralised procedure → **CHMP**

  → EMEA

- ✓ Centralised procedure
  - mandatory for
    - Biotechnology derived proteins
    - Gene transfer products
    - Recombinant virus vaccine
  - Optional for other biologics

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Regulation of biologics in Europe

- ✓ Three authorisation procedures but
- ✓ Same assessment criteria → 30 years of EU harmonisation:
  - 1965: First EU Directive 65/65: basic principles
  - 1975: Setting up first EU committee → CPMP, Brussels
  - 1987: Concertation procedure for biotechnology-derived products → start of the BWP
  - 1993: Regulation 2309/93 for medicinal products
  - 1995: setting up EMEA and CPMP in London
  - 2001: Dir. 2001/83 → CHMP
  - 2003: Dir. 2003/63 → Biosimilars

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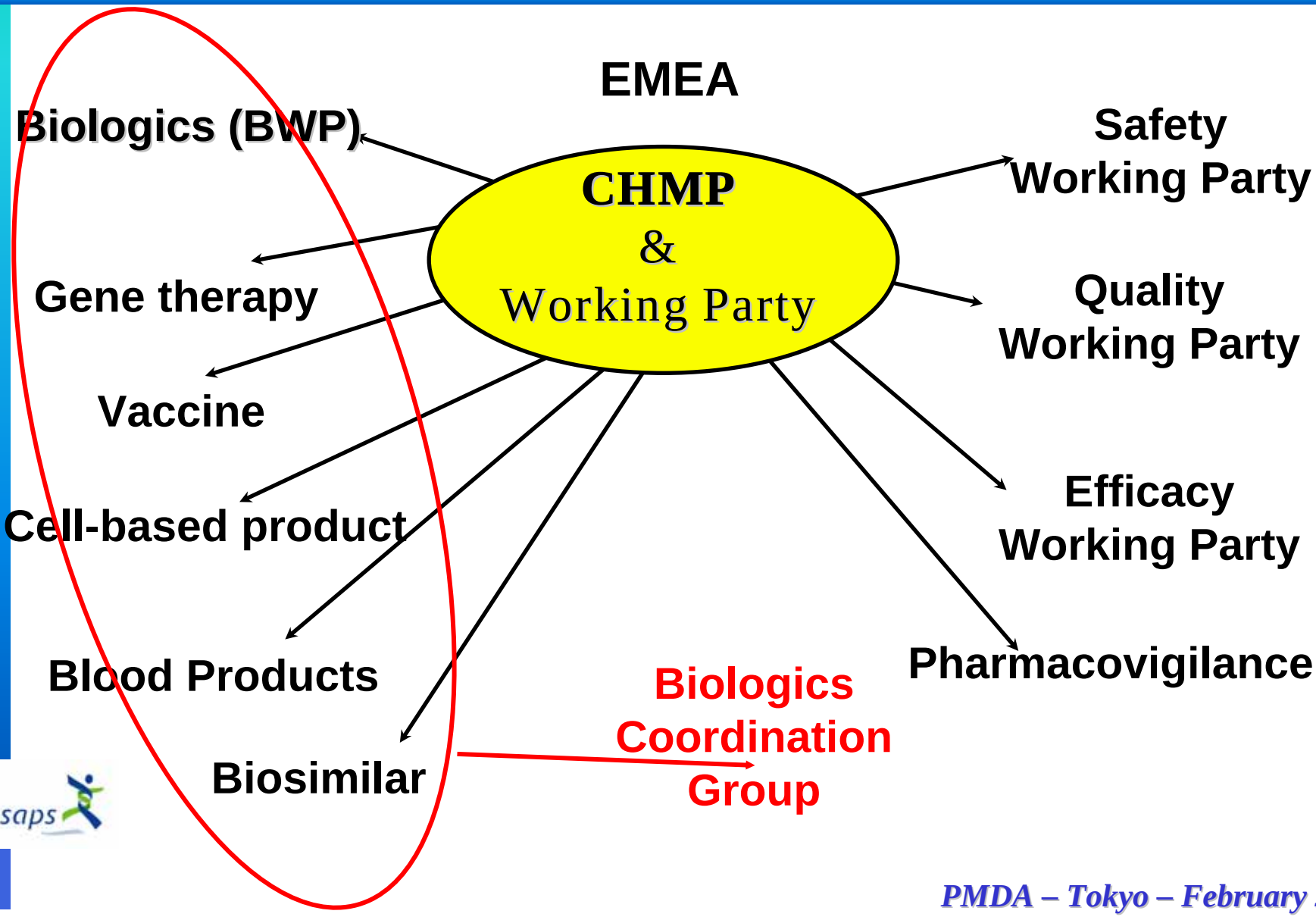
Scientific network



Biologics Working Party (BWP)

- ✓Chairperson
- ✓27 members appointed by their National Authorities
- ✓Experts (permanent or ad hoc)
- ✓European Pharmacopea (Observer)
- ✓Commission representative
- ✓EMEA secretariat

Biotechnology Working Party (BWP)

- ✓ 11 meetings per year (1 week before the CHMP)
- ✓ Two-day meeting organized in
  - a plenary session
  - break-out sessions
  - drafting groups
- ✓ Overview of BWP Activities
  - Dossier evaluation (quality/biological documentation)
  - Plasma Master Files
  - Vaccine Antigen Master Files
  - Evaluation on medicinal products (vaccines) according to Art 58 of Reg.726/04/EC
  - Scientific Advice
  - Ancillary Substances
  - Development and maintenance of Guidelines
  - Regulatory Advice
  - Meetings with Interested Parties

BWP Guidelines or position statements

- Production and quality control of rDNA-derived medicinal products
- Production and quality control of cytokine
- Production and quality control of monoclonal antibodies
- Allergen products - 1992
- Radiopharmaceuticals - 1990
- Use of Transgenic Plants for production of medicinal products
- Validation of virus removal and inactivation procedures
- Medicinal products derived from human blood and plasma
- Minimizing the risk of transmission of agents causing spongiform encephalopathies via medicinal products (TSE guideline)
- Gene therapy products (quality aspects)
- Biosimilar (Quality Aspects)
- Harmonization of requirements for influenza vaccines
- Pandemic Influenza vaccine (mock up dossier)
- Potency testing of cell based immunotherapy MPs

Non exhaustive list ….

BWP at the international level

- ✓ BWP contributes to the ICH network and development of international guidelines:
  - Genetic stability (Q5C)
  - Stability testing for biological products (Q5B)
  - Viral safety of products derived from cell lines (Q5A)
  - Cell substrates (Q5D)
  - Specifications for biotech products (Q6B)
  - Safety studies for biotech products (S6)
  - Comparability
- ✓ New guideline(s) to come ?
  - Integration of Q8, Q9, Q10 in a "new approach"

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Recent development: Guideline on Viral safety for investigational medicinal products (IMP)

- ✓ To provide scientific guidance relating to the viral safety of biotech derived products used for clinical trials
- ✓ Guidance is provided with respect to:
  - the criteria for and the extent of viral safety evaluation studies, especially validation studies, that are required prior to and during clinical development.
  - the extent to which manufacturers are able to refer to in-house experience concerning virus safety evaluation.
  - the risk assessment which should form part of the safety evaluation.
- ✓ Bulk of the guidance provided is directed towards materials for phase I and II studies. For phase III materials, validation studies should be performed essentially as described by ICH Q5A (see section 4)
- ✓ The aim of virus safety studies for biotechnological IMPs is to demonstrate an acceptable level of safety for clinical trial subjects.

EMEA/CHMP/BWP/398498/05

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Other challenges under development -1-

- ✓ Expression system: new cell lines:
  - Mammalian cell lines: regulation of cyclin-dependent kinase, anti-apoptic protein –BCl2, PRC-6
  - Yeast strain humanized for N-linked glycosylation
  - Other alternative expression systems:
    - Insect cells (SF9, Hi5)
    - Transgenic plants (Maize, tobacco, potatoes)
    - Transgenic animals (goat, sheep, rabbit, …)
- ✓ Production system: Serum free media
  - Cell-culture systems
  - Structure and post-processing modifications
  - Impact on yield and consistency of the production
- ✓ Purification system:
  - New resins
  - New product-dedicated purification (Ab-selection)
  - Use and re-use of the columns, and monitoring of their capacities
  - Consequences on yield, reproducibility and respect of the « natural » micro-heterogeneity
  - Consistency

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Other challenges under development -2-

- ✓ New analytical tools available
  - For nucleic acid (PCR, ..)
  - For proteins (CZE, Glycan analysis)
  - Real time analysis
  - Biological methods
- ✓ But ….. more and more product-specific technics
- ✓ Impact on the quality control strategy and batch release specifications

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Other challenges under development

Future products to come:

- ✓ Recombinant proteins from
  - Transgenic plants
  - Transgenic animals
- ✓ Gene therapy
- ✓ DNA vaccines
- ✓ Cell therapy
- ✓ Tissue engineered products

Advanced therapy medicinal products

K. Cichutek presentation

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Other challenges under development

New "quality vision"

Develop or harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science."

Q8: Pharmaceutical Development

Q9: Quality Risk Management

Q10: Pharmaceutical Quality System

ICH Brussels 2003

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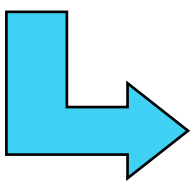
Q8: Implementation of new concepts

- ✓ Process Analytical Technology
- ✓ Real time release
- ✓ Design Space
- ✓ Formal experimental design
- ✓ Lifecycle: update to support new knowledge
- ✓ Continual improvement
- ✓ Knowledge versus data



Flexible regulatory approach
Risk based regulatory decisions

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New quality vision for biologics

- ✓ These principles should now be extended to active substances and to biologics…
- ✓ Even if, for biologics, due to their inherent variability, the concept of "space design" "PAT" or is routinely applied,
- ✓ There will be practical consequences of implementing these principles in terms of
  - Format of dossier for submission
  - Respective role of the assessors, inspectors
  - On the organisation of the variation regulation

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Revision of the variation regulation

- ✓ Review project launched in 2006
- ✓ More coherence between EU regulatory framework
- ✓ **Simplification of existing legislation**, without compromising human health:
  - Clearer, Simpler, More flexible
  - Reduce administrative burden
  - Further harmonise between EU member state
  - Adapt to ICH concepts

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Revision of the variation regulation

- ✓ Implementing new concepts (discussed also at the ICH level)
  - Design space, PAT (Q8)
  - Risk management, (Q9)
  - quality systems (Q10)
- ✓ More flexible approach to post-authorisation changes

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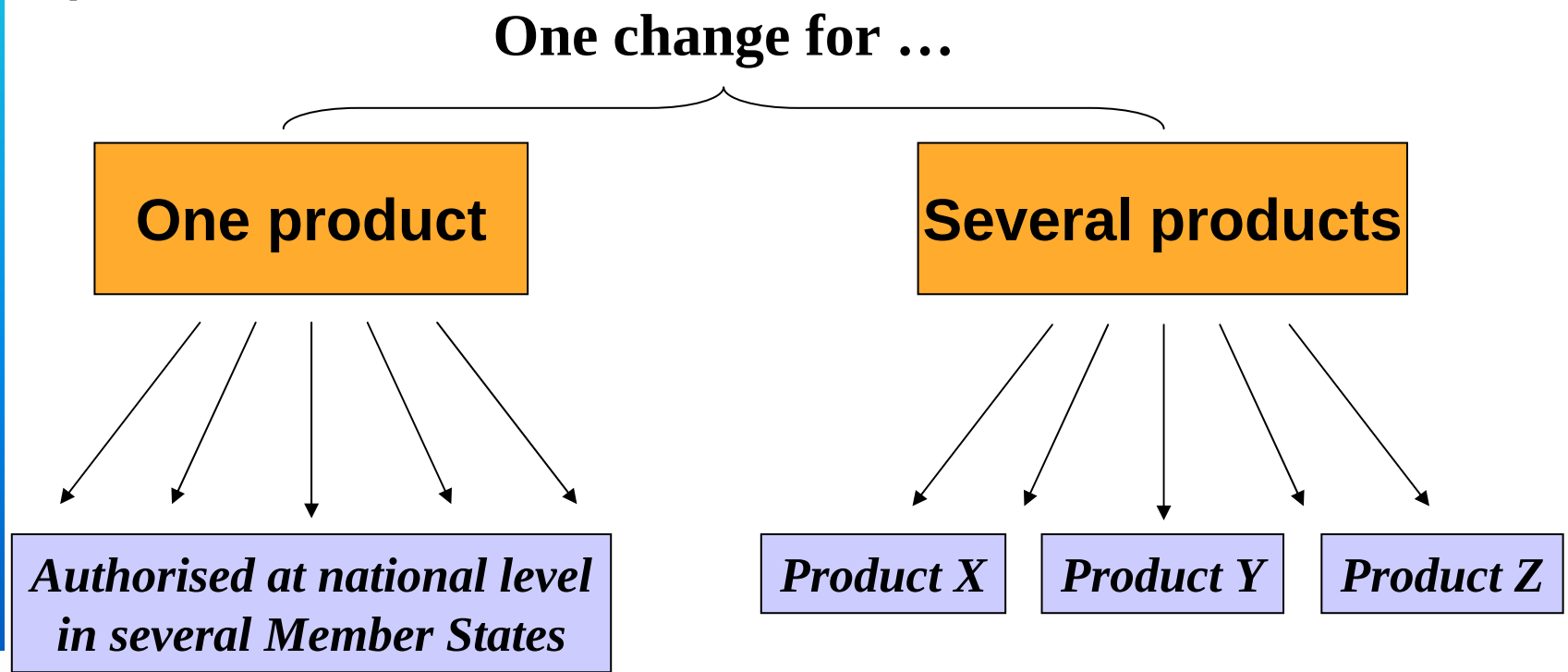
Revision of the variation regulation

- ✓ Addressing the new pharmaceutical industry organisation → globalisation of the production



Revision of the variation regulation

- ✓ Project submitted in Dec. 2006 by the EU Commission,
- ✓ To be further elaborated with competent bodies (National Agencies, EMEA and its scientific committees)
- ✓ Consultation with industry

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Biosimilars

- ✓ Why the "Biosimilar" question emerged:
- ✓ In the early 2000s, for some biological products, patent will soon expire: hGH, EPO, G-CSF, etc.
- ✓ But, it is also acknowledged that biological products (proteins) are complex macromolecules due to
  - their origin (extraction, biotechnological process)
  - their structures which are not easy to characterize and quality control,
  - Quality of the manufactured product is highly depending on the production process(es)
  - Acceptability of the product: is not only depending on quality criteria, but has also to be validated with safety and efficacy data

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Biosimilars

Change to the **quality** profile

May impact the **safety and efficacy** profile

Biosimilars

- ✓ Considering that
  - Biological products are partly defined by the production process
  - Biological activity depends on the consistency of the manufacturing and formulation processes, on the storage conditions, etc…
  - Immunogenic profile is one of the safety elements which depends on numerous parameters, among which quality criteria
  - → all these elements cannot be assessed by the only bioequivalence study ("generic" approach)
- ✓ Is the « generic » approach possible for biological products ?
- ✓ The answer would be: → **NO**

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From generics to « biosimilars »

- ✓ Complexity of biologicals (drug substance and drug product) is such that quality, « similarity » cannot be established by analytical techniques only
- ✓ Development of the concept of
  - Comparability (to establish similarity)
  - Similar biological product → biosimilars

Biosimilars: European Legislative framework

- ✓ Directive 2003/63 (amending Dir. 2001/83)
  - Essentially similar medicinal product : not applicable to biological products
- ✓ Directive 2004/27
  - Article 10.4 Biological Medicinal Products :

Where a biological Medicinal Product which is similar to a reference biological product does not meet the conditions in the definition of a generic medicinal product owing to differences relating to raw materials or differences in manufacturing processes of the biological medicinal product. The results of appropriate pre-clinical and clinical trials relating to these conditions must be provided.

- ✓ Marketing authorisation procedure: via the centralised marketing authorisation (MA) when the “biosimilar” is a recombinant protein

Biosimilars – development of guidelines

- ✓ To accompany the setting of the new « biosimilar » approach : preparation of guidelines
- ✓ The first guideline (2000-2001) dealt with the question of « comparison »
  - Following a change introduced in the manufacturing process of a biological medicinal product
  - For a biological product prepared by a new manufacturer

- → CPMP/BWP/3207/00: Note for guidance on comparability of medicinal products containing biotechnology-derived proteins as drug substance
- → CPMP/3097/02: Annex on non-clinical and clinical considerations
- → ICH guideline Q5E: Comparability of Biotechnological/Biological Products subject to changes in their manufacturing process

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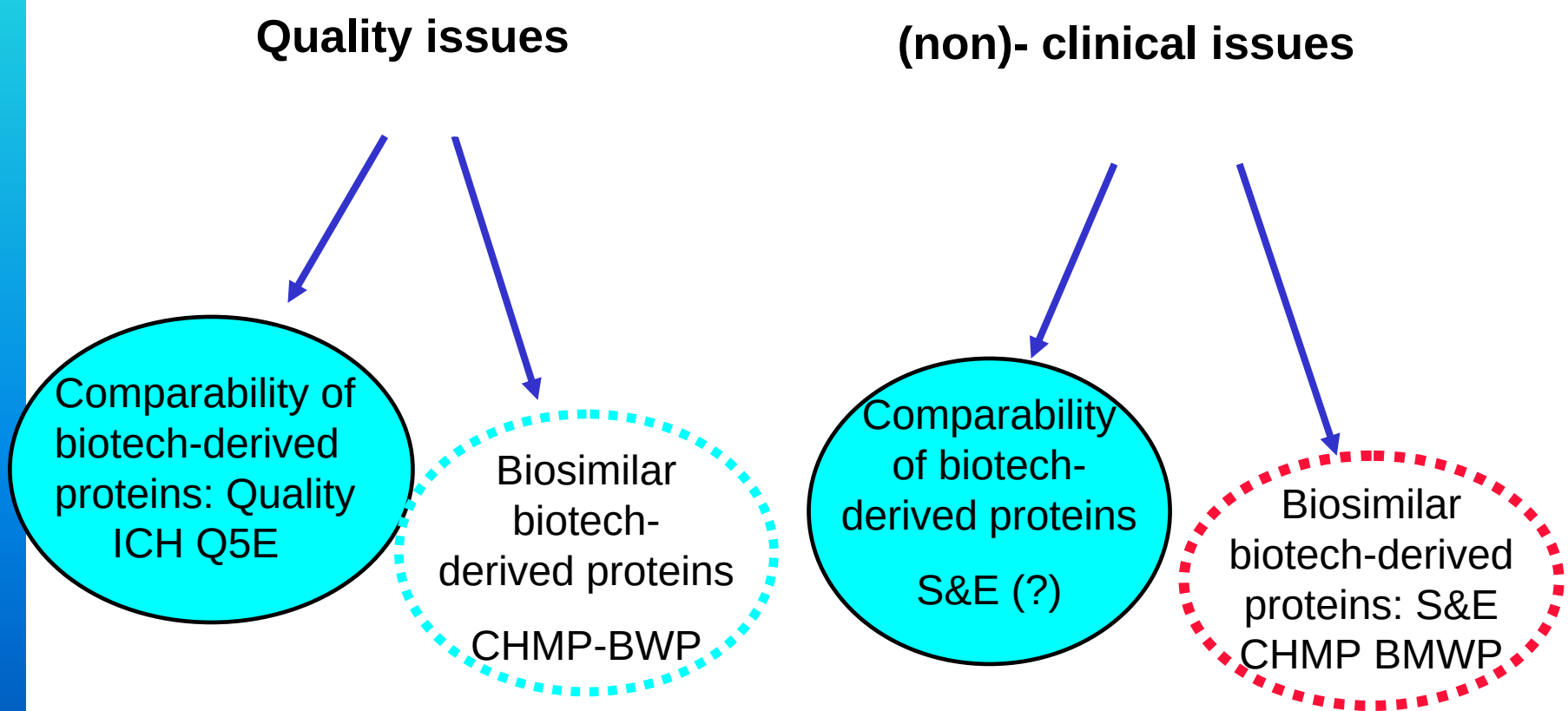
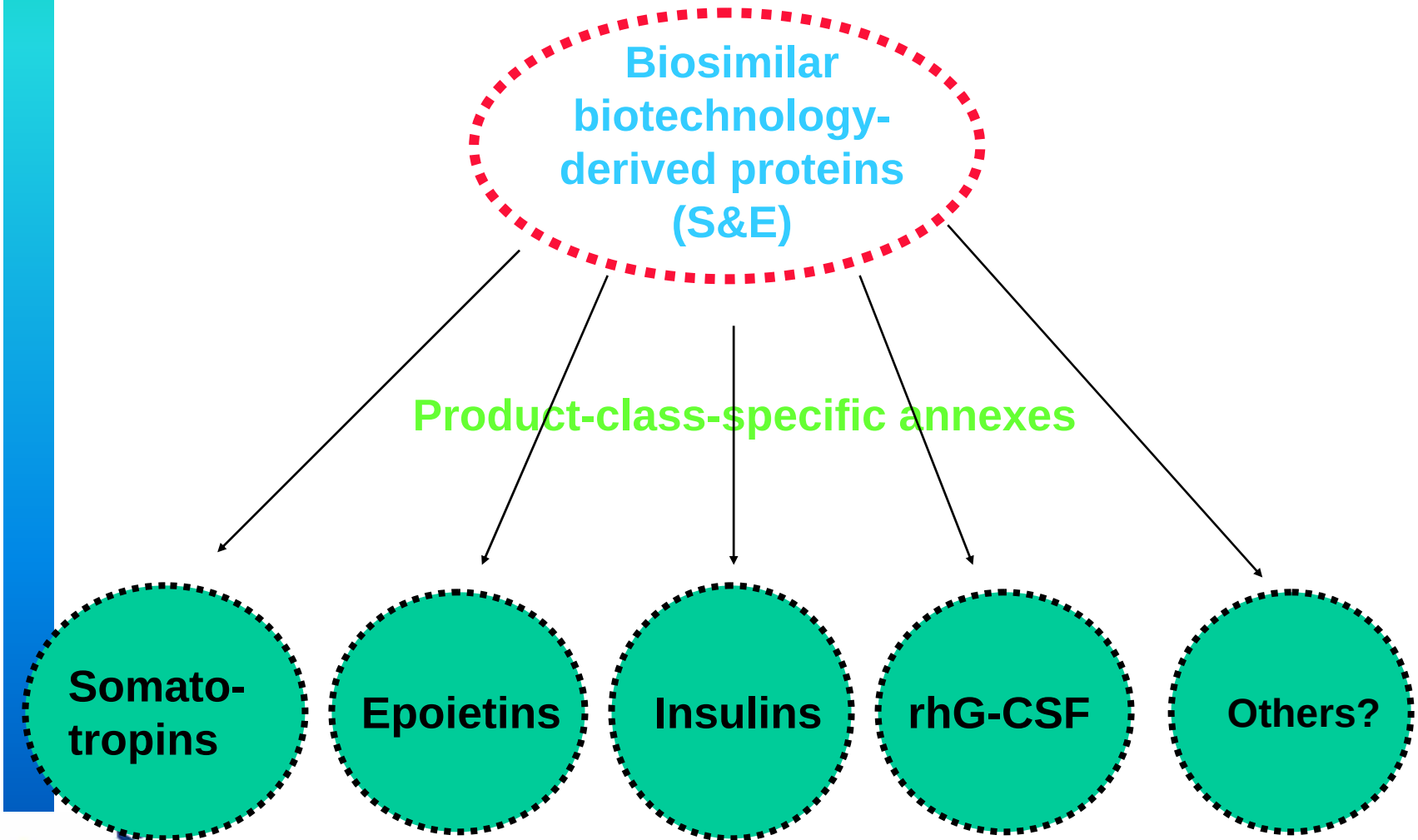
From “comparability” guideline to “biosimilars” guidelines

Guidelines on Comparability



Dr Pekka Kurki, Chair CHMP Biosimilar WP – DIA Euro meeting Lisbon, 8 March 2005

Biosimilar guidelines



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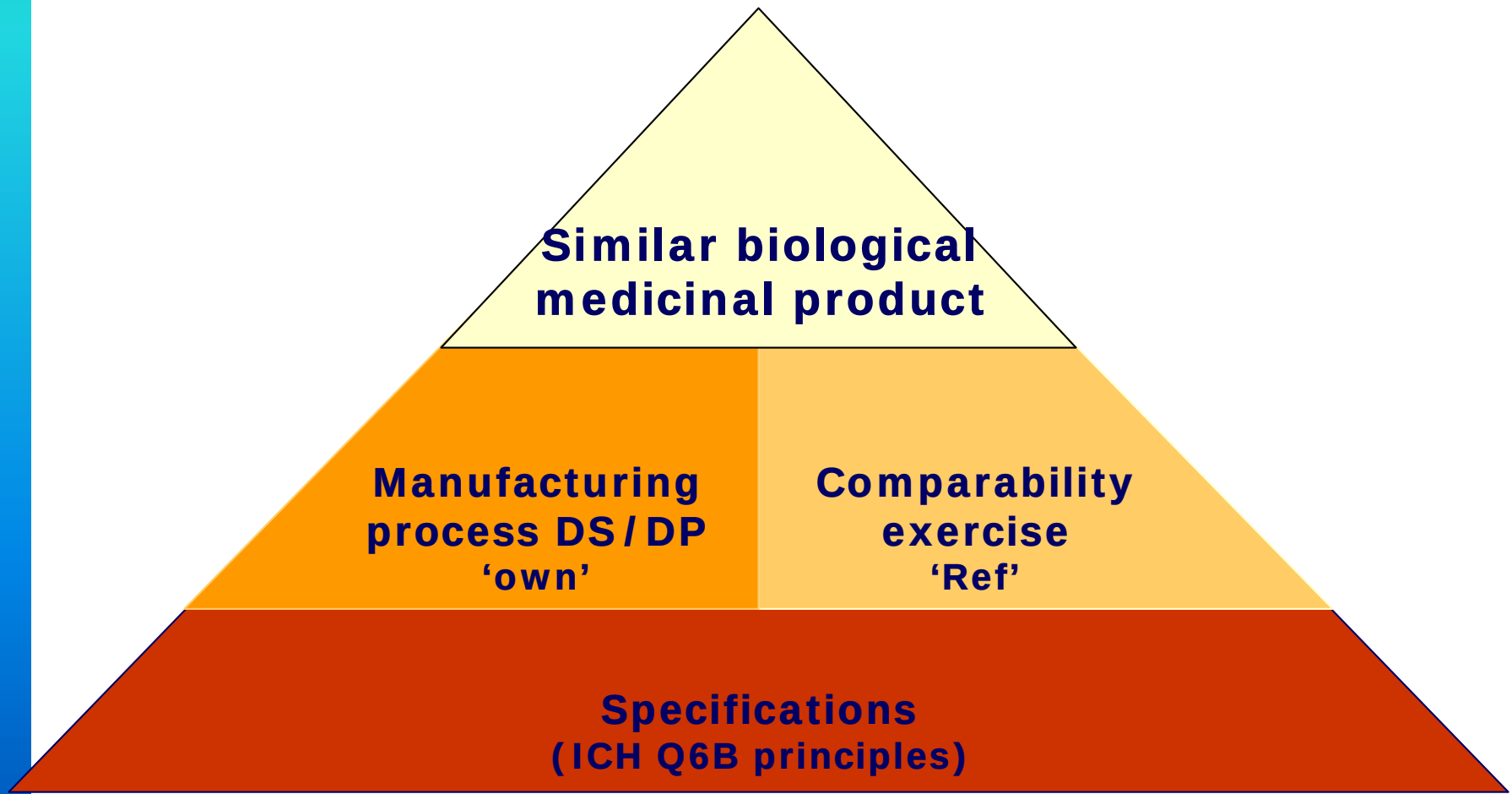
Biosimilar - Quality Guideline



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Current situation (end 2006)

- ✓ Guidelines into force since end 2005
- ✓ Several submissions of MA dossiers
  - Centralised procedure
  - One authorisation granted (recombinant hGH)
  - One EPO application under review
  - Other products submitted and under evaluation
  - Requests for scientific advice
    - Questions on quality, in particular on the « comparability » program
    - Questions on clinical protocols

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Some unresolved questions

- ✓ Some products have several indications in different therapeutic fields (e.g. IFN)
  - What clinical data to be submitted
- ✓ Depending on the manufacturing system, the impurity profile may be different
  - Consequences on efficacy
  - Consequences on long term tolerance (immunogenicity)
- ✓ Improvements in the analytical methods → the biosimilar product is better studied and characterised than the reference product (characterised 10 years or more before)
  - differences not yet suspected may become obvious
  - clinical consequences ?

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Conclusion

- ✓ Biologics are complex products
  - To develop, produce and monitor
  - To regulate
- ✓ EU proposes an harmonised approach, which takes into account experience gained on established technologies (e.g. recombinant proteins)
- ✓ EU contributes in convergence and International cooperation (EDQM, WHO, ICH)
- ✓ Biologics in the future will cover
  - New therapeutic indications (advanced therapy)
  - New threat (pandemic flu)
  - New therapies (e.g. cell-based)
  - New technologies (e.g. pharmacogenetics, nanotechnologies)
- ✓ In the context of globalisation, there is a need for an harmonised approach