

European perspectives on regulation for biologics

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Overview of presentation

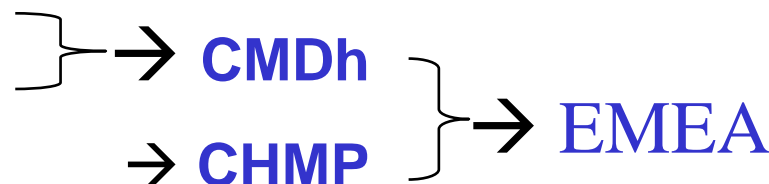
- ✓ Regulation of biologics in EU
- ✓ Organisation and mandate of the Biologics working party (BWP)
- ✓ BWP guidelines and position statements
- ✓ New topics (challenges) under development
 - New technology challenges
 - Advanced therapy medicinal products
 - New concepts in Quality
- ✓ Current topics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

✓ 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

✓ EU = 27 Member States and three authorisation procedures

- National authorisation
- followed by Mutual Recognition
- Decentralised procedure
- Centralised procedure



✓ Centralised procedure

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

- ✓ 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

Scientific network

EMA

**CHMP
&
Working Party**

Biologics (BWP)

**Safety
Working Party**

Gene therapy

**Quality
Working Party**

Vaccine

**Efficacy
Working Party**

Cell-based product

Pharmacovigilance

Blood Products

**Biologics
Coordination
Group**

Biosimilar



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

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"

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.

EMA/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 –BCI2, 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

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

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

Other challenges under development

-4-

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

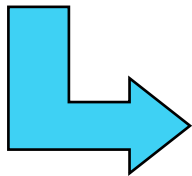
Q9: Quality Risk Management

Q10: Pharmaceutical Quality System

ICH Brussels 2003

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

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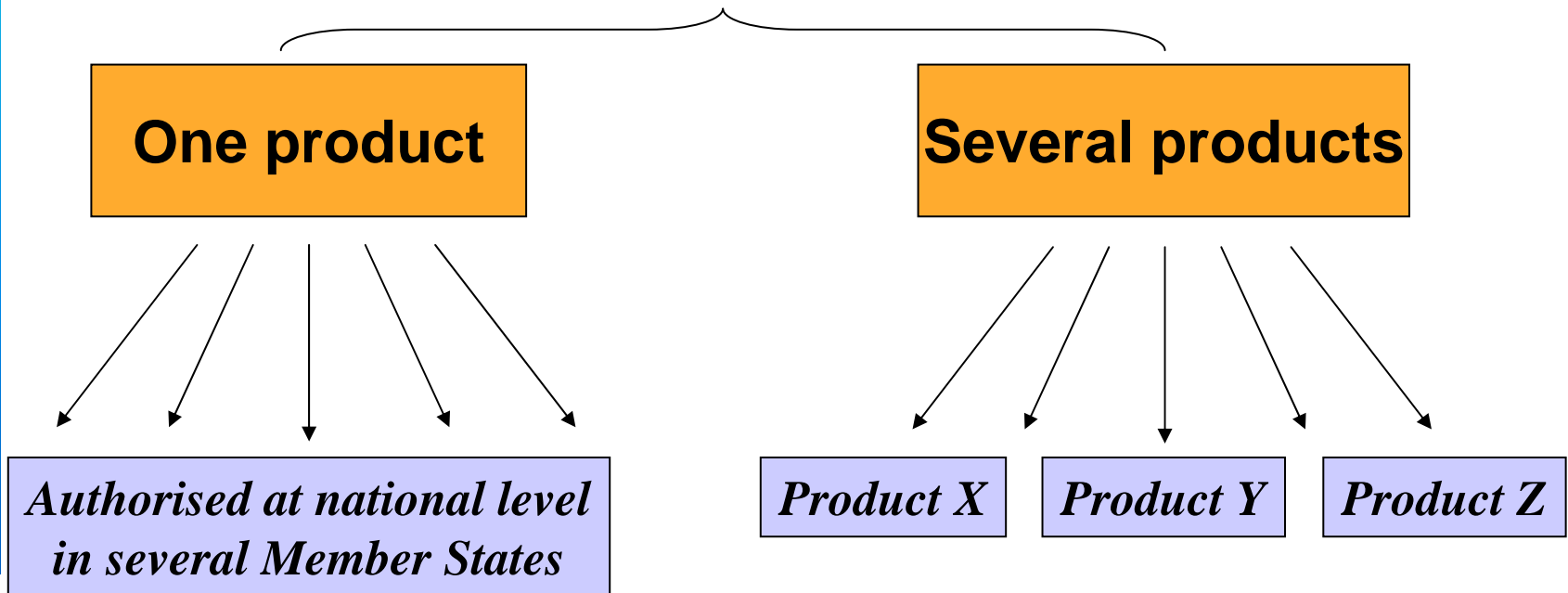
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- ✓ Review project launched in 2006
- ✓ More coherence between EU regulatory framework
- ✓ **Simplification of existing legislation**, without compromising human health:
 - Clearer, Simpler, More flexible
 - Reduce administrative burden
 - Further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

- ✓ 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

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

One change for ...



- ✓ 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

- ✓ 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

Biosimilars

Change to the **quality**
profile



May impact the **safety and efficacy**
profile

✓ 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

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

From “comparability” guideline to “biosimilars” guidelines

Guidelines on Comparability

Quality issues

(non)- clinical issues

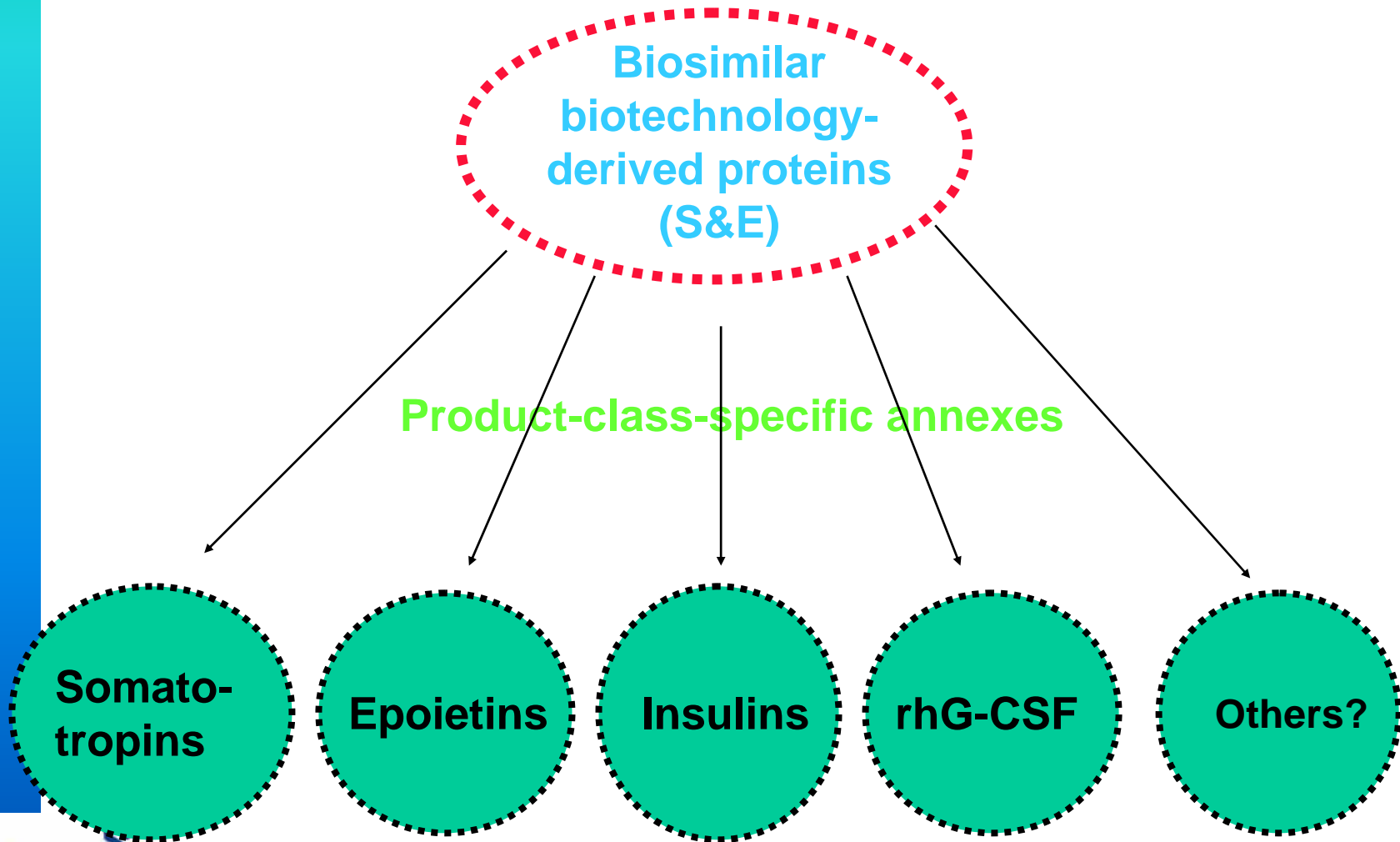
Comparability of biotech-derived proteins: Quality
ICH Q5E

Biosimilar biotech-derived proteins
CHMP-BWP

Comparability of biotech-derived proteins
S&E (?)

Biosimilar biotech-derived proteins: S&E
CHMP BMWP

Biosimilar guidelines



Biosimilar - Quality Guideline

**Similar biological
medicinal product**

**Manufacturing
process DS/DP
'own'**

**Comparability
exercise
'Ref'**

**Specifications
(ICH Q6B principles)**


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

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 ?

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