



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Biosimilars in the European Union - regulatory perspectives

ICH GCG ASEAN Training Workshop on ICH Q5C, 30-31 May 2011, Kuala Lumpur

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An agency of the European Union





Content

- Introduction to the European Regulatory Network
- Biosimilar regulation and concepts
- Biosimilar evolution in the European Union
- European guidelines for biosimilars
- Looking ahead/Challenges
 - Increasing complexity – biosimilar monoclonal antibodies
 - International aspects and harmonisation
- Case studies
- Conclusions



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Introduction

- The European Medicines Agency (EMA) is a decentralised body of the EU.
- The mission of the Agency is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health.
- Responsible for centralised procedure and co-ordination of EU network + plays a role in stimulating innovation and research in the pharmaceutical sector.





European Union

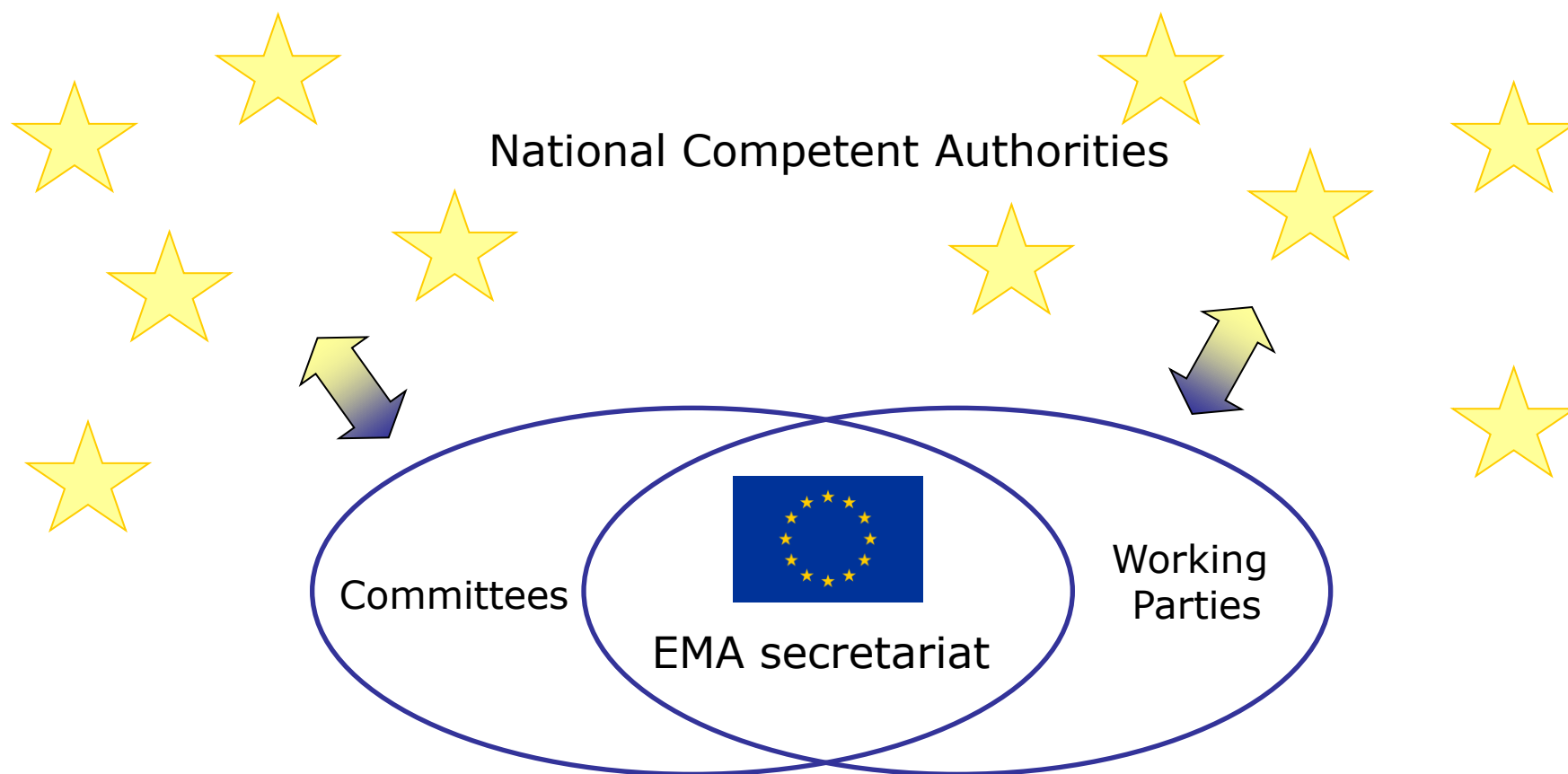
- 500 million users of medicinal products
- 27 EU Member states
- > 40 national competent authorities





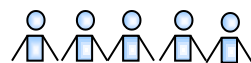
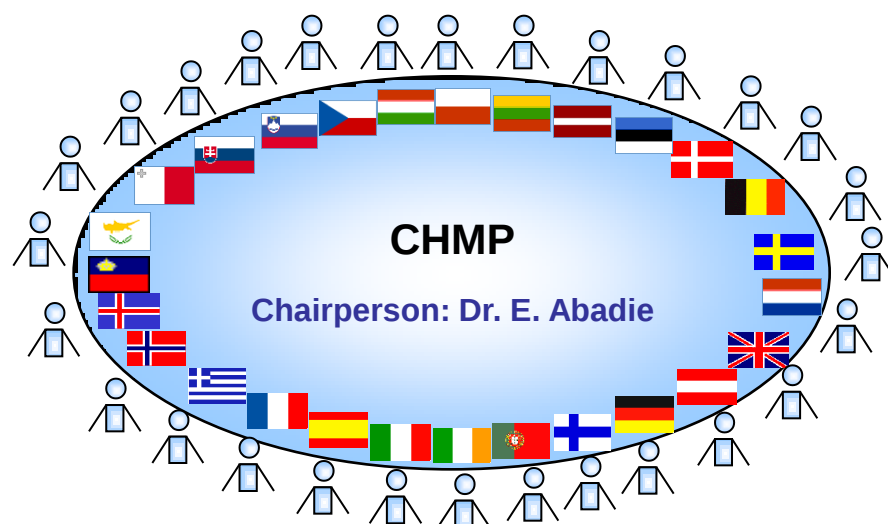
European Regulatory Network

4,500 European experts

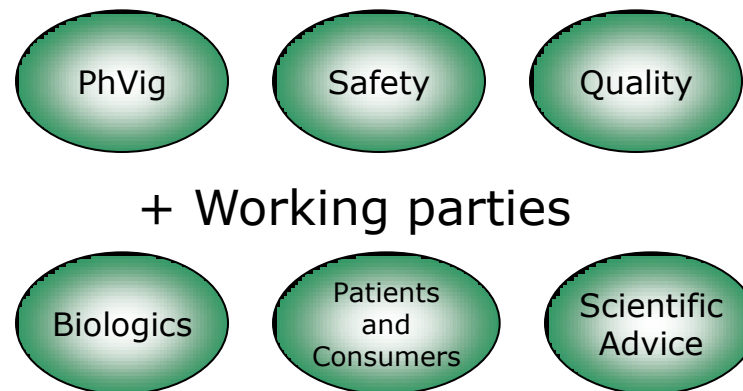




Committee for Medicinal Products for Human Use



max. 5
Co-opted
CHMP
members



+ *Ad hoc* working parties
e.g. Biosimilar Medicinal Products Working Party



Working parties

Biosimilar medicinal products working party

- Established in 2005
- Face-to-face meetings 3 times per year
- Responsible for non-clinical/clinical and overarching aspects of biosimilars
- Comparability and immunogenicity aspects for all biologicals

Biologics working party

- Initially established in 1986
- Face-to-face meetings 11 times per year
- Quality aspects relating to biological and biotechnological medicinal products (including biosimilars)



Working parties

Working parties' tasks include:

- Preparation and revision of guidelines
- Provide scientific input to the CHMP and Scientific Advice Working Party
- Contributing to international co-operation with other regulatory authorities
- Liaising with interested parties (e.g. briefing meetings with industry)
- Organisation of workshops and trainings (e.g. biosimilar mAbs workshop, immunogenicity workshop, assessor trainings)



Centralised Procedure

Mandatory scope:

- Medicines derived from biotechnology and other high-tech processes (including biosimilars)
- Advanced-therapy medicines
- Medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases
- Designated orphan medicines intended for the treatment of rare diseases.

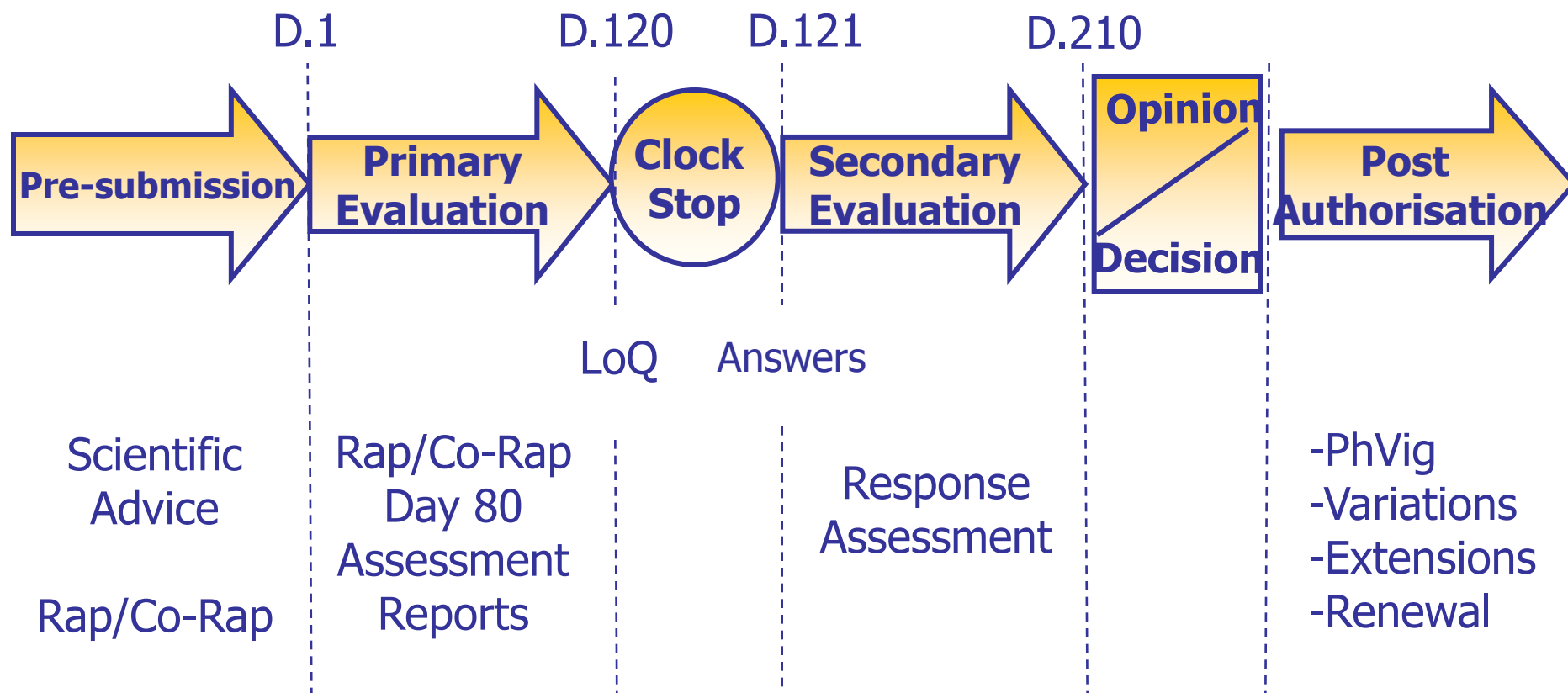
1 Scientific Opinion

1 Commission Decision valid throughout the EU

1 Product Information translated into all official EU languages



Centralised Procedure





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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



Can we have “biogenerics”?

In THEORY – YES

In PRACTICE – may be possible where molecule is fully characterised (depends on complexity)

RESULT – Similar Biological Medicinal Product,
Informally: “biosimilar”

Biosimilar legislation

Legislation states:

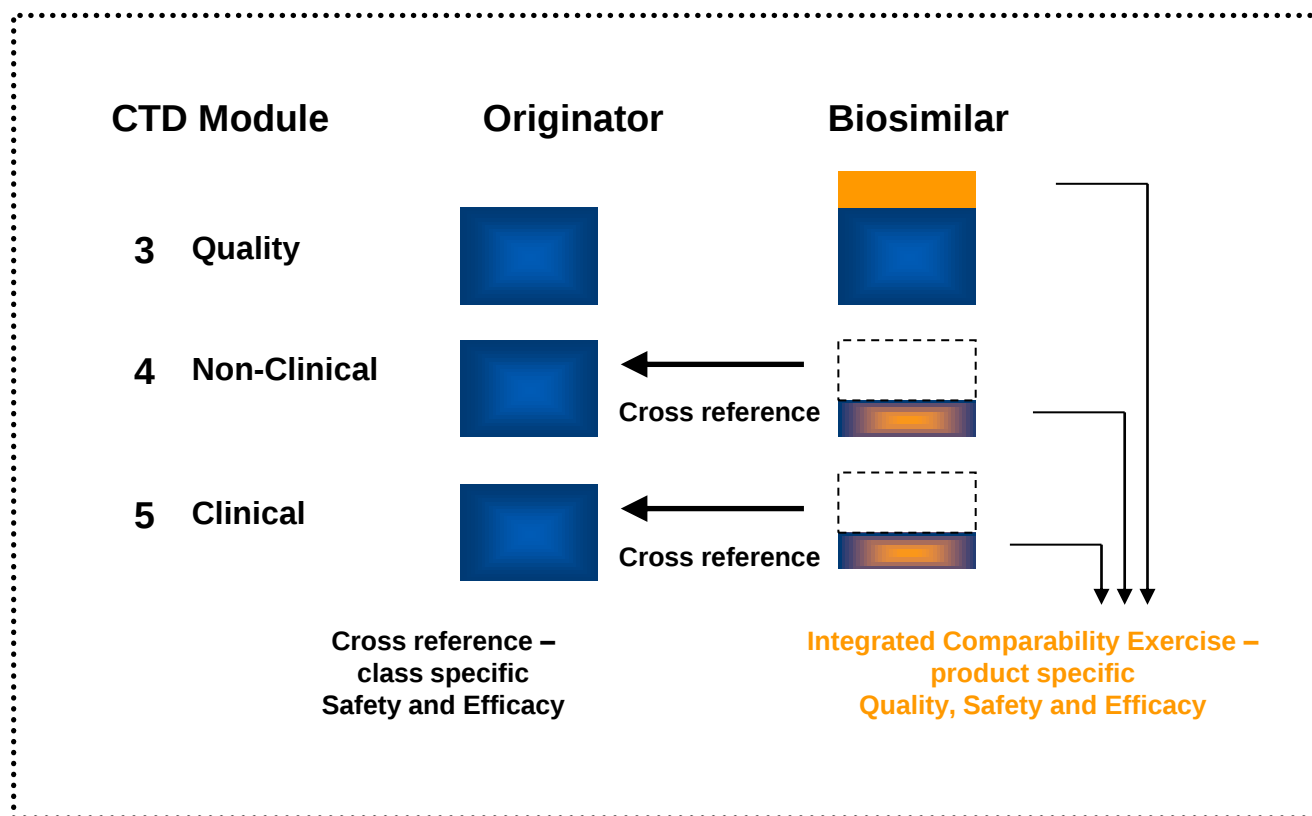
Article 10(4) of Directive 2001/83/EC, as amended

- Where there are differences, particularly relating to 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.
- The results of other tests and trials from the reference medicinal product's dossier shall not be provided.





Dossier requirements for Biosimilars





Comparability exercise

- Stepwise head-to-head comparison at the levels of quality, safety and efficacy to demonstrate that the biosimilar and the reference medicinal product have similar profiles in terms of quality, safety and efficacy.
- Depending on the similarity on the quality profile, the extent of the non-clinical and clinical testing may be reduced compared to a stand-alone development.
- Any differences in the quality attributes require a satisfactory justification of the potential implications with regard to the safety and efficacy of the product.

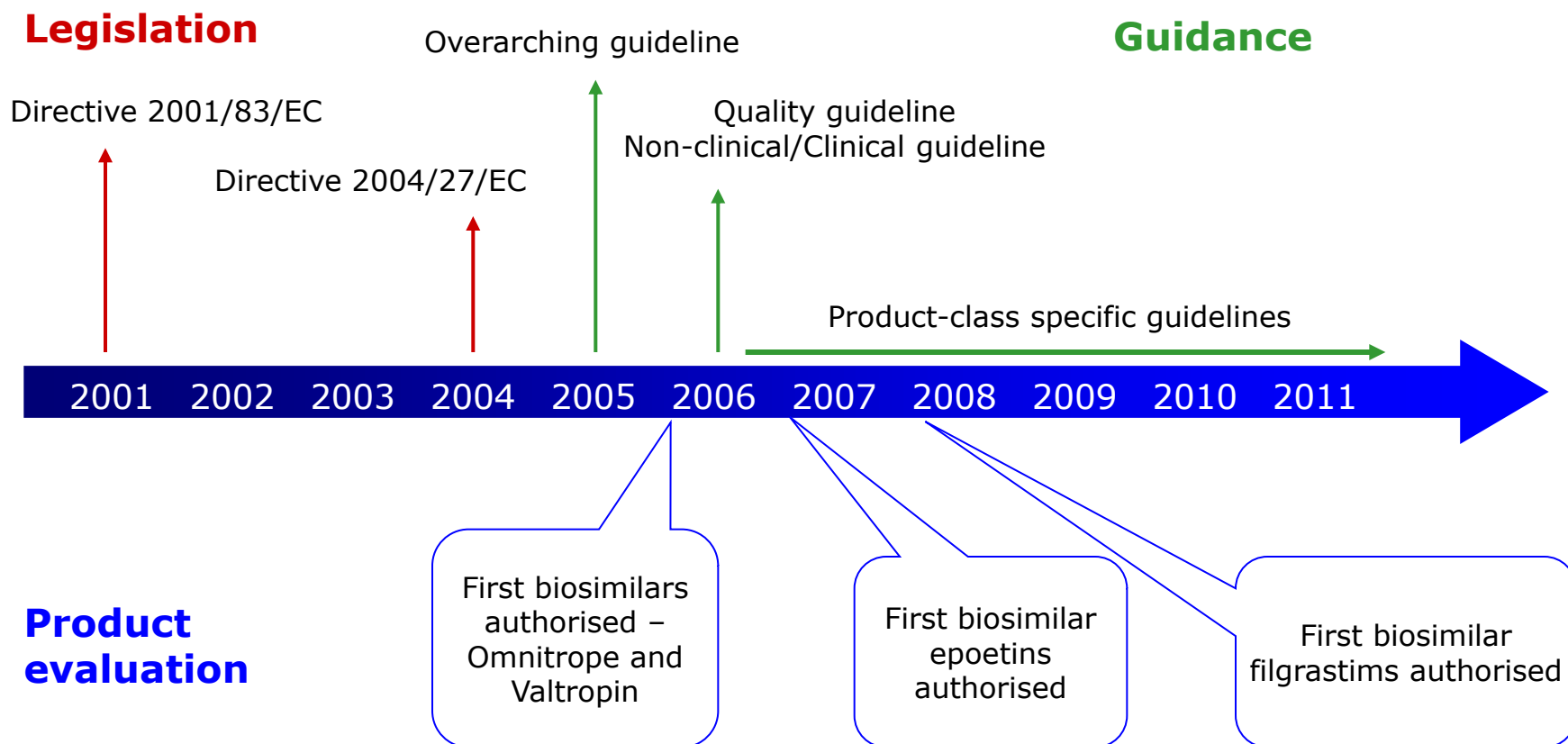


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Evolution of Biosimilars in the EU





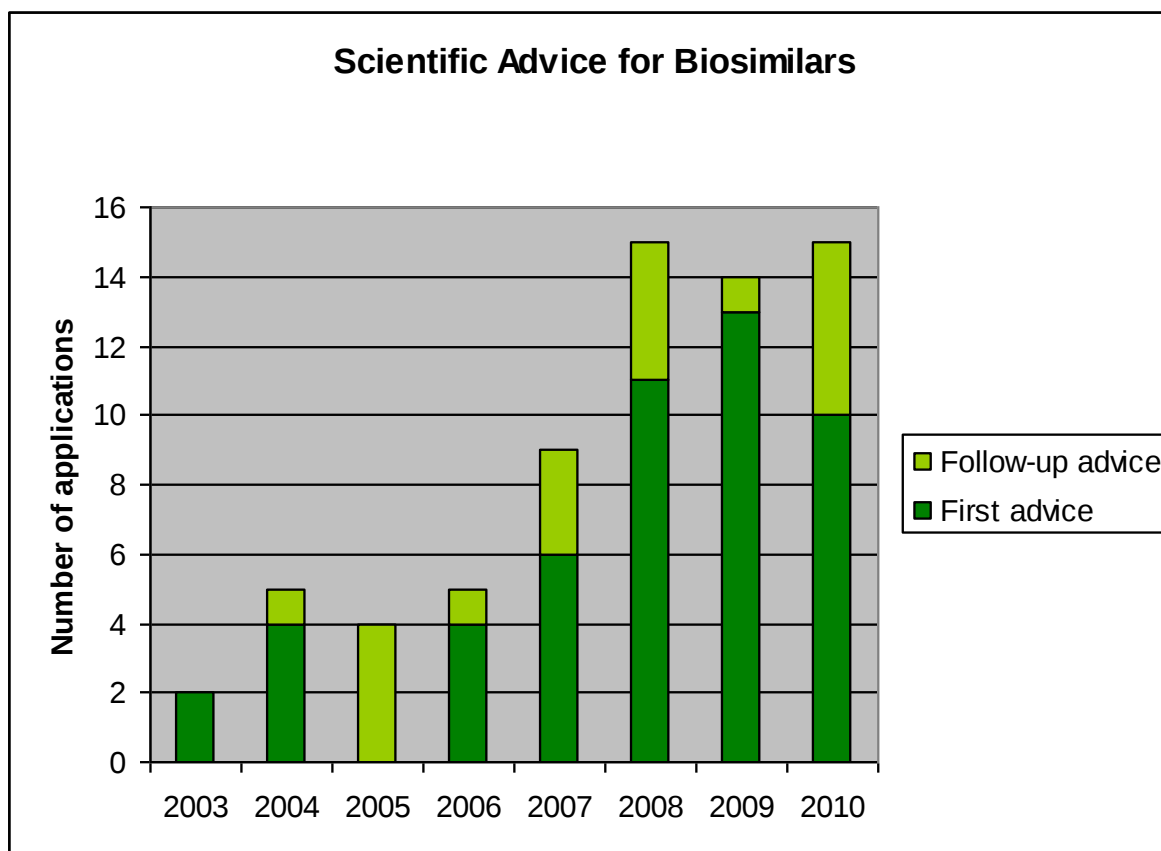
Biosimilar MAA Procedures

status May 2011

1	Omnitrope (somatropin)	Sandoz	Authorised
2	Valtropin (somatropin)	Biopartners	Authorised
3	Alpheon (interferon alfa)	Biopartners	Negative
4	Binocrit (epoetin alfa)	Sandoz	Authorised
5	Epoetin alfa Hexal (epoetin alfa)	Hexal	Authorised
6	Abseamed (epoetin alfa)	Medice	Authorised
7	Silapo (epoetin zeta)	Stada	Authorised
8	Retacrit (epoetin zeta)	Hospira	Authorised
9	Insulin Marvel Short (human insulin)	Marvel Life Sciences	Withdrawn
10	Insulin Marvel Intermediate (human insulin)	Marvel Life Sciences	Withdrawn
11	Insulin Marvel Long (human insulin)	Marvel Life Sciences	Withdrawn
12	Filgrastim Ratiopharm (filgrastim)	Ratiopharm	Authorised
13	Ratiograstim (filgrastim)	Ratiopharm	Authorised
14	Biograstim (filgrastim)	CT Arzneimittel	Authorised
15	Tevagrastim (filgrastim)	Teva	Authorised
16	Filgrastim Hexal (filgrastim)	Hexal	Authorised
17	Zarzio (filgrastim)	Sandoz	Authorised
18	Nivestim (filgrastim)	Hospira	Authorised
19	Epostim (epoetin alfa)	Reliance Genemedix	Withdrawn



Scientific Advice



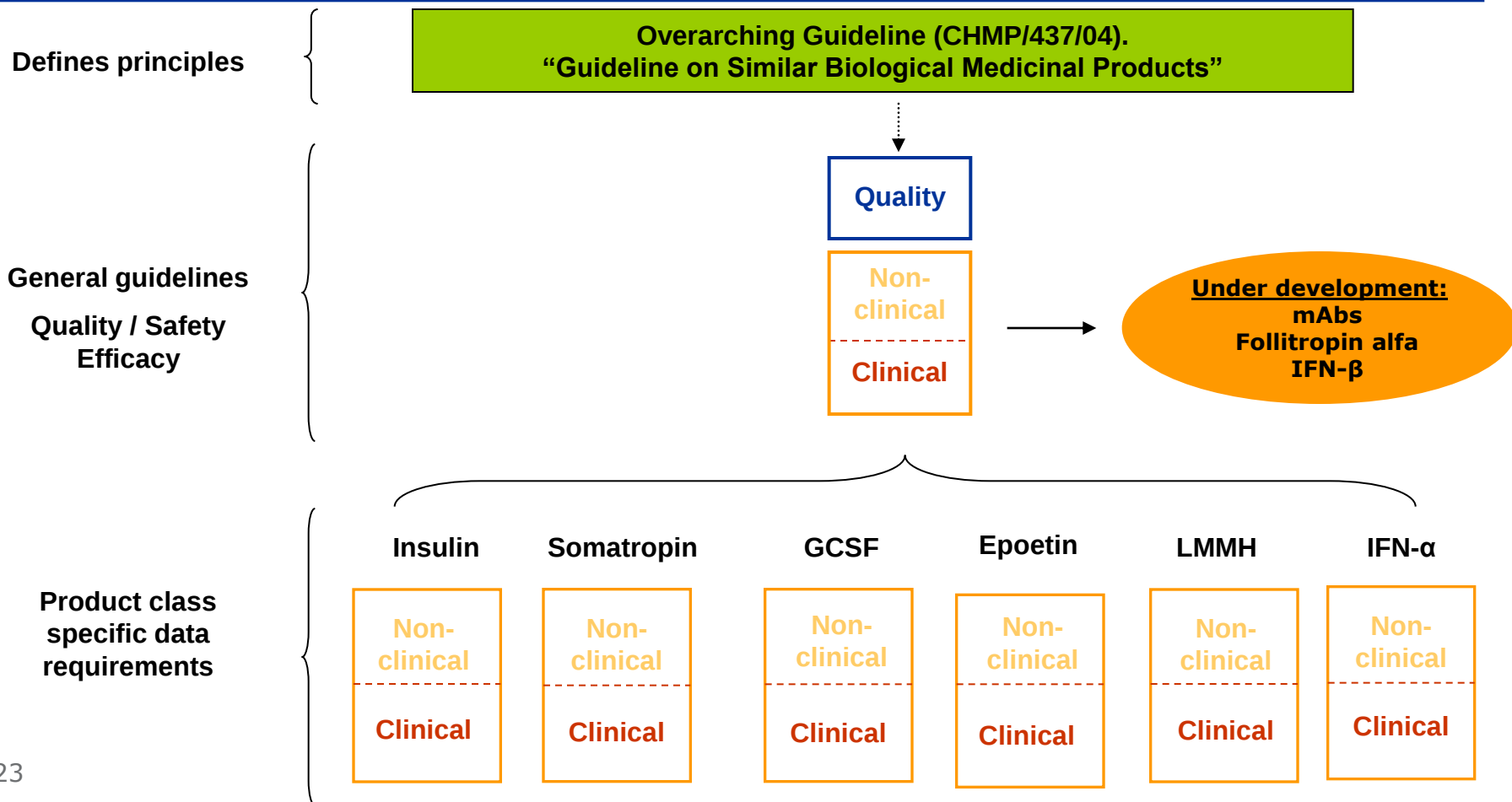


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Guidelines for biosimilars





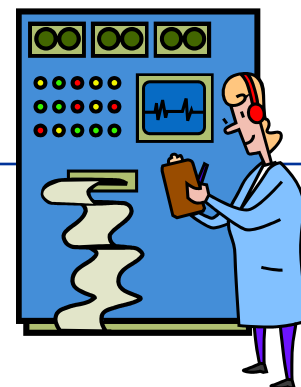
Overarching guideline

Guideline on similar biological medicinal products (CHMP/437/04)

- Scope
 - In principle: biosimilar concept applicable to any biological medicinal product.
 - In practice: Only for products that can be thoroughly characterised.
- Biosimilarity should be established at all levels (Q/S/E) using a reference medicinal product authorised in the Community on the basis of a complete dossier.
- Active substance should be similar to the reference medicinal product in molecular and biological terms.
- The pharmaceutical form, strength and route of administration should be the same as for the reference.
- The specific medicinal product given to the patient should be identified in order to support pharmacovigilance monitoring.



Quality guideline



Scope:

- Applies to recombinant DNA derived proteins and peptides

Manufacturing process:

- Use state of the art process development
- Use material from final process for clinical trials (i.e. avoid additional comparability exercises)
- The suitability of the formulation should be demonstrated

Comparability exercise:

- Use state-of-art analytical methods for characterisation of both biosimilar and reference medicinal product
- Comparative characterisation studies should include assessment of composition, physical properties, primary and higher order structures, purity, product-related isoforms and impurities, and biological activity
- Comparability both at level of medicinal product and active substance



Non-clinical / Clinical guideline

Non-clinical studies:

- Comparative in nature; designed to detect differences
- *In vivo* studies should be conducted in relevant species
 - Pharmacodynamic study + at least one repeat dose toxicity study



Clinical studies:

- Comparative pharmacokinetics (PK) and pharmacodynamics (PD) studies are requested
- In certain cases, comparative PK/PD studies might be sufficient to demonstrate clinical comparability, but usually comparative efficacy trials are required
- Pre-licensing safety data in patients should be obtained
- One year follow-up data on immunogenicity usually required pre-licensing for long term treatment



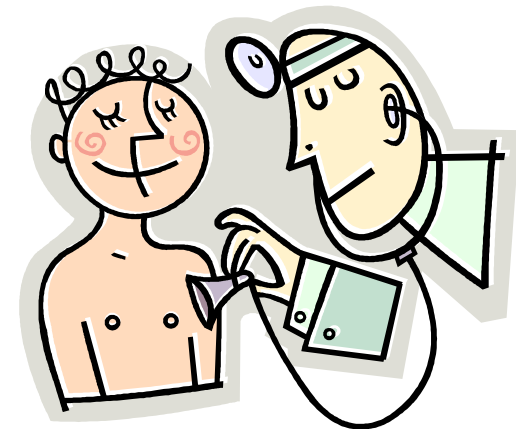
Non-clinical / Clinical guideline

Pharmacovigilance/Risk management:

- Risk Management Plan and Pharmacovigilance system must be in place, in accordance with EU legislation
- Any safety monitoring imposed on the reference product or product class should be considered in the RMP

Indication(s):

- Each claimed indication should be justified or demonstrated separately
- Extrapolation is possible, but depends on clinical experience, available literature data, same mechanisms of action or receptor(s) involved in all indications





Revision of guidelines

- In light of additional experience, guidelines are revised if necessary.
- Revision of epoetin guideline (2008-2010)
 - Amended to accept extrapolation of efficacy data from one route of administration to the other via bridging studies (PK/PD studies)
- Revision of quality guideline initiated (concept paper published for comments until 31 May)
 - Include considerations for product lifecycle (e.g. change in reference product during biosimilar development, post-authorisation activities)
- Need for revision of LMWHs guideline?
 - Potential revision to increase flexibility in clinical data requirements: consider extent of quality characterisation



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Increasing complexity

Current situation:

- Biosimilars currently licensed are “small biologicals”
- Biosimilar framework exists for more complex products

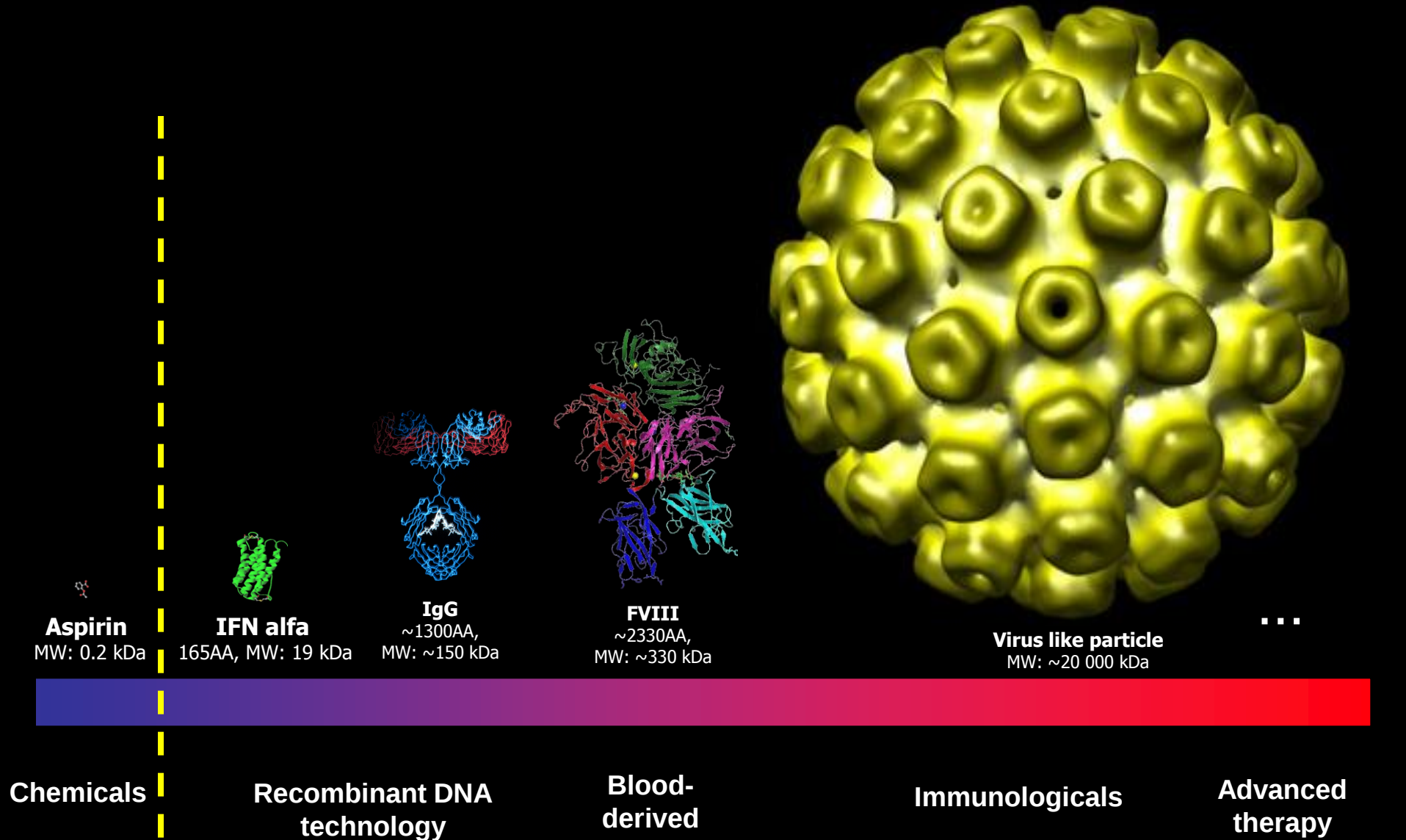
Ongoing:

- High interest in biosimilar monoclonal antibodies
 - Scientific advice
 - Workshop organised by the Agency in July 2009
 - Guideline under development

Future:

- In principle, the concept applies to any biological medicine
- Ability to characterise becomes critical
- **How far can we go?**

Spectrum of complexity



Source: Dr Kowid Ho (Afssaps, France)

Biosimilar Monoclonal Antibodies?

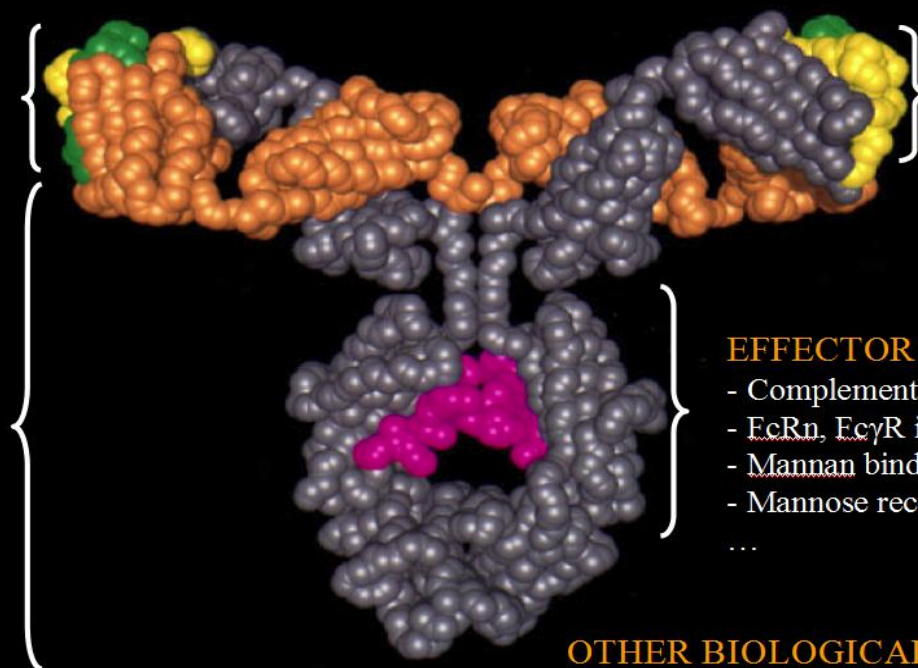
PHYSICOCHEMICAL CHARACTERISTICS

VARIABLE REGION

- Deamidation
- Oxidation
- N-term Pyro-Glu
- Glycosylation
- Glycation
- ...

CONSTANT REGION

- Deamidation
- Oxidation
- Acetylation
- Glycation
- Glycosylation (fucosylation, sialylation, galactosylation, mannosylation...)
- C-term Lys
- Di-sulfide bond shuffling/cleavage
- Fragmentation/clipping
- ...



BIOLOGICAL CHARACTERISTICS

BINDING

- Affinity
- Avidity
- Immunoreactivity / crossreactivity
- Unintentional reactivity
- ...

EFFECTOR FUNCTION

- Complement interaction
- FcRn, FcγR interaction
- Mannan binding ligand interaction
- Mannose receptor interaction
- ...

OTHER BIOLOGICAL PROPERTIES

- PK properties
- Epitope / Immunogenicity
- Modulatory region (Tregitope ...)
- ...

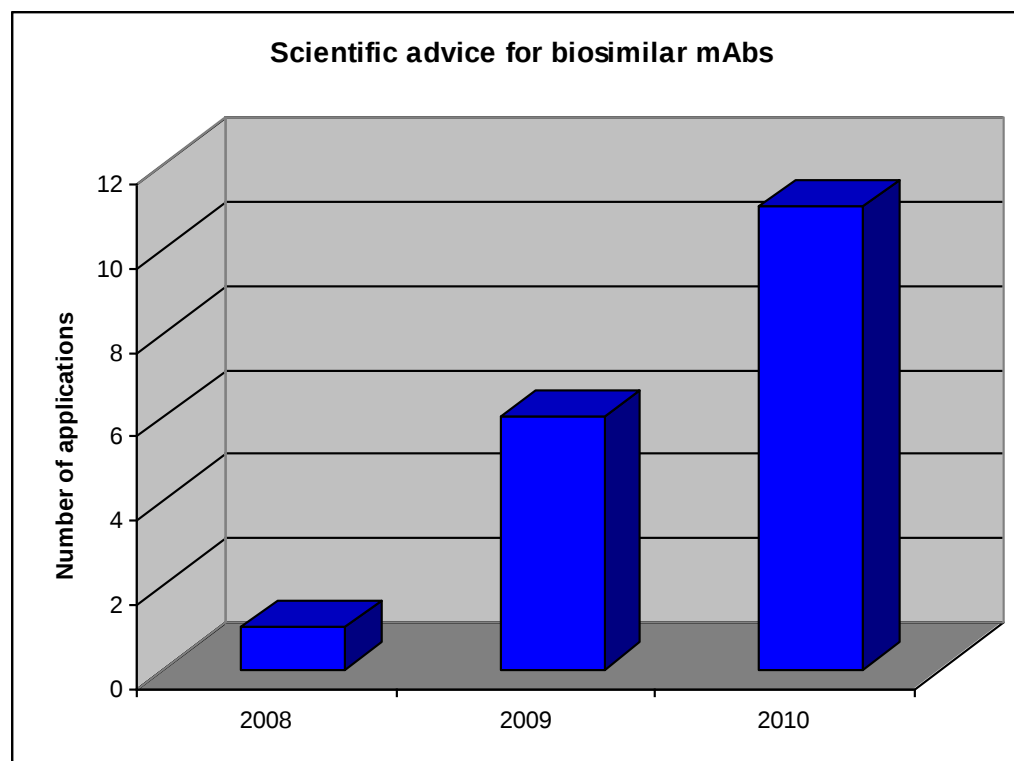


Biosimilar Monoclonal Antibodies?

- Monoclonal antibodies are complex molecules
 - High level of microheterogeneity, there will always be differences
 - The mode of action is complex and may involve contributions from multiple mechanisms
- The challenge: to demonstrate that differences between the biosimilar and the reference medicinal product do not have a significant impact on clinical efficacy and/or safety
 - Even small differences may have significant effects.
 - Need to combine physicochemical results with functional assays (e.g. antigen-antibody binding assays and cell-based assays) and the qualification in preclinical and clinical studies



Scientific Advice for biosimilar monoclonal antibodies





Draft guideline on biosimilar mAbs

(EMA/CHMP/BMWP/403543/2010)

- For public consultation until 31 May 2011 -

Scope:

- Non-clinical and clinical data requirements for biosimilar monoclonal antibodies. Principles may also apply to certain fusion proteins (-cept molecules).

Non-clinical:

- A risk-based approach to evaluate mAb on a case-by-case basis is recommended to decide on the choice and extent of *in vitro* and particularly *in vivo* studies.

PK/PD:

- Comparative pharmacokinetic study in a sufficiently sensitive and homogeneous study population (healthy volunteers or patients)
- Pharmacokinetic data can be helpful to extrapolate data on efficacy and safety between different clinical indications
- PD studies, if feasible, can provide strong support for biosimilarity



Draft guideline on biosimilar mAbs

(EMA/CHMP/BMWP/403543/2010)

Safety/Efficacy:

- Should normally be demonstrated through a phase III equivalence trial
- Trial designed to demonstrate similar efficacy and safety compared to the reference product, not patient benefit per se
- Choose most sensitive population
- Extrapolation of indications possible based on overall evidence of biosimilarity

RMP and PhVig plan:

- Required as for all biosimilars
- Post authorisation safety studies may be required



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Biosimilars - International Cooperation

The European Medicines Agency is liaising with international partners

- **Health Canada** (finalised Guidance on Subsequent Entry Biologics published in March 2010)
- **Japan** (Guideline on quality, safety and efficacy of follow-on biologics was published in March 2009)
- **WHO** (Guidelines on Evaluation of Similar Biotherapeutic Products adopted in October 2009)
- **FDA** (Abbreviated approval pathway for Biosimilars created via the Patient Protection and Affordable Care Act, signed on March 23, 2010) - ongoing liaison and exchange

CHMP guidance also adopted by, e.g.:

- Australia
- Malaysia

→ EU experience important reference for others



Global development of biosimilars?

- Directive 2001/83/EC states that the chosen reference medicinal product must be a medicinal product authorised in the Community.
- The set-up of the biosimilar development is not specified in the Directive. However, the implementing guidelines state that the reference medicinal product authorised in the Community should be used throughout the development.
- Can requirements for the sourcing of reference product evolve to allow for parts of the comparability exercise to be performed with reference medicinal product sourced outside the Community?





Traceability



- Trade name and batch number of biological products (including biosimilars) should be included in adverse reaction reporting
 - Notice to Applicants Vol.9 (2008)
 - Directive 2010/84/EU (December 2010)
- INN important factor, responsibility of WHO
- Interchangeability/substitution is not covered by EU pharmaceutical legislation – outside remit of EMA (responsibility of the individual member states)



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Case studies





Omnitrope (somatropin)

- Reference medicinal product: Genotropin
- Changes during development (active substance manufacturer). Increase in complexity of demonstration of comparability
- Additional steps introduced to reduce levels of Host Cell Protein
- Very high levels of (non-neutralising) antibodies, up to ~ 60% (for material used in clinical trials – manufactured according to old process)
- Additional liquid formulations added in the post-authorisation phase, posology unchanged



Valtropin (somatropin)

- Reference medicinal product: Humatrope
- Different expression system compared to reference medicinal product (*S. Cerevisiae* vs *E.coli*). Process specific HCP (yeast) assay required
- Changes during development subject to additional comparability
- Clinical trial:
 - initially calculated to demonstrate non-inferiority
 - US sourced reference product used (considered supportive)
- Indications differ from Omnitrope (Different reference medicinal product used)
 - Paediatric indications for Omnitrope only: Small Gestational Age (SGA), Prader-Willi Syndrome (PWS)

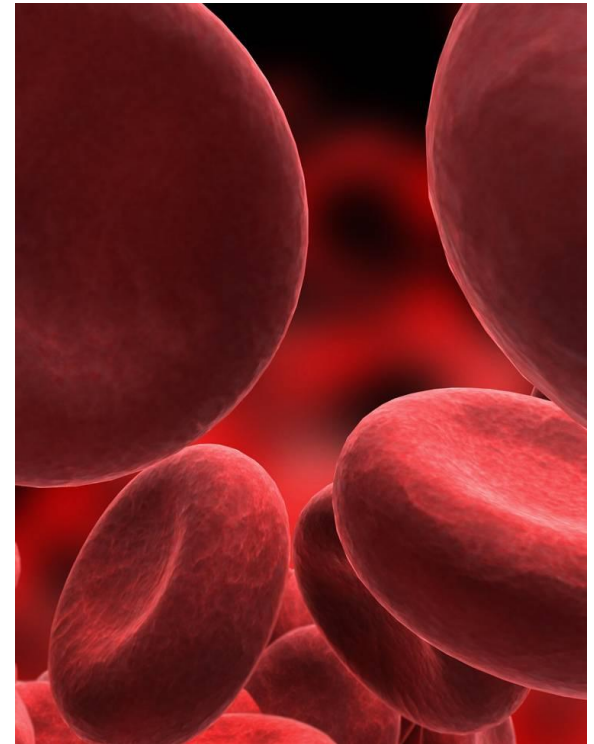


Binocrit (epoetin alfa)

- Reference medicinal product: Erypo/Eprex (epoetin alfa)
- Extensive characterisation and quality comparability exercise
- Structural comparisons
 - Qualitatively similar
 - Quantitative differences seen (Increase in high mannose-6-phosphate, Decrease in N-glycolyl-neuraminic acid)
 - Differences were justified
- PRCA (Pure Red Cell Aplasia) issue with Reference medicinal product
 - Subcutaneous (SC) route contraindicated (chronic kidney disease, CKD patients) until May 2006
 - SC route most sensitive for potential immunogenicity
 - Consequence: No comparative SC studies (CKD)
 - SC route in immunocompetent individuals contraindicated for biosimilar (further studies needed)
 - Risk minimisation required to avoid off-label SC use

Silapo (epoetin zeta)

- Reference medicinal product: Erypo/Eprex (epoetin alfa)
- Extensive characterisation and quality comparability exercise
- Structural comparisons
 - Qualitatively similar
 - Quantitative differences seen (Increase in des o-glycan forms, Decrease in N-glycolyl-neuraminic acid)
 - Differences were justified
- SC route initially contraindicated as for Binocrit. SC indications added post-authorisation upon availability of data





Tevagrastim (filgrastim)

- Reference medicinal product: Neupogen
- Extensive characterisation and quality comparability exercise
- Partial use of reference medicinal product sourced in Lithuania before EU accession – could only be considered supportive data
- Clinical data
 - Phase I: Comparative PK/PD studies in healthy volunteers
 - Phase III: Comparative Safety & Efficacy trials in cancer patients undergoing chemotherapy. Efficacy endpoint: duration of severe neutropenia



Zarzio (filgrastim)

- Reference medicinal product: Neupogen
- Extensive characterisation and quality comparability exercise
- Clinical data
 - Phase I: Comparative PK/PD studies in healthy volunteers. Efficacy endpoints: neutrophil and CD34+ cell counts
 - Phase III: Non-comparative (single arm) clinical trial in cancer patients undergoing chemotherapy. Safety focus. Only supportive
- The G-CSF Guideline states:
 - *“The recommended clinical model for the demonstration of comparability of the test and the reference medicinal product is the prophylaxis of severe neutropenia after cytotoxic chemotherapy in a homogenous patient group (...). Alternative models, including pharmacodynamic studies in healthy volunteers, may be pursued for the demonstration of comparability if justified.”*



Withdrawn applications - **Insulin Marvel**

- Reference medicinal product: Humulin S
- Three presentations: Short, intermediate (30/70), long acting
- Quality issues
 - Incomplete comparability exercise, particularly for drug product
 - Inadequate validation of manufacturing process
 - Batch traceability missing
 - More data required for extended release forms
- Clinical issues
 - Comparative PK & PD : euglycaemic clamp – most sensitive model
 - Similar PK parameters, 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 sufficiently sensitive
 - Limited immunogenicity data



Negative opinion – **Alpheon** (rhIFN α -2a)

- Reference medicinal product: Roferon-A
- Quality issues
 - Concerns regarding stability and impurities for drug substance and drug product. Profiles also not matching reference medicinal product
 - Drug product manufacturing process inadequately validated
 - Comparability between batches used for clinical trial batches and commercial batches not shown
- Non-clinical studies were inadequate and indicated differences
- Clinical issues
 - Difference in virological relapse rates
 - Inconclusive data in the response rate for the “difficult-to-treat” genotype 1 patients
 - Different rate of adverse events
 - Inadequate immunogenicity documentation



Risk management plan

- Risk Management Plan (RMP) and Pharmacovigilance system must be in place, in accordance with EU legislation
- The RMP should include:
 - **Safety specification** (*identify safety concerns*)
 - **Pharmacovigilance plan** (*planned PhVig actions for all identified safety concerns*)
 - **Evaluation of the need for risk minimisation activities** (*routine vs additional risk minimisation activities*)
 - **Risk Minimisation Plan** (*if additional risk minimisation activities are required*)
 - **Summary of the EU-RMP**
 - **Contact person details**
- Any safety monitoring imposed on the reference product or product class should be considered in the RMP





RMP summary example - Binocrit

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Pure Red Cell Aplasia (PRCA)	• Routine pharmacovigilance • Post-authorisation safety study INJ-14 • Phase 3 study INJ-17	• Contraindication in section 4.3 of the SPC for use in patients who have previously experience PRCA following treatment with erythropoetins • Warning in section 4.4 of the SPC regarding PRCA • Mention in section 4.8 of the SPC
Increased risk of PRCA with off-label subcutaneous administration in renal failure patients	• Routine pharmacovigilance • Phase III study INJ-17 • Market survey to monitor potential off-label s.c. use in renal anaemia patients	• Advice to use i.v. route only in treatment of renal anaemia, in Section 4.2 of the SPC. • Warning in section 4,4 of the SPC that iv route only should be used in chronic renal anaemia patients due to lack of immunogenicity data Additional measures to avoid s.c. use in renal anaemia patients • Educational leaflet • Cool boxes with visual label



RMP summary example - Binocrit

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Thrombotic vascular events (TVE)	• Routine pharmacovigilance • Post-authorisation safety study INJ-14 • Phase 3 study INJ-17	• Risk of thrombotic vascular events (TVE) including serious and life threatening cardio-vascular complications including the dose recommendation that the target haemoglobin not exceed 12 g/dl are mentioned in Sections 4.1, 4.2, 4.3, 4.4 and 4.8 of the SPC.
Tumour Growth Potential	• Routine pharmacovigilance • Post-authorisation safety study INJ-14 • Phase 3 study INJ-17	• Risk of tumour growth potential are mentioned in Sections 4.4 and 5.1 of the SPC.



Any class-effect applies across all products!

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European Medicines Agency to review the safety of somatropin-containing medicines

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Press release

European Medicines Agency to review the safety of somatropin-containing medicines

The European Medicines Agency is starting a review of the safety of somatropin-containing medicines authorised centrally or by national procedures in the European Union (EU). The review will look into all available data on somatropin to reassess the benefit-risk balance of these medicines.

This review is being initiated further to information received from the French medicines agency on a long-term epidemiological study in patients treated during childhood with somatropin-containing medicines. The study results suggest an increased risk of mortality with somatropin therapy compared to the general population. The risk appears to be particularly increased when high doses are used (beyond doses as recommended in the Summary of Product Characteristics). The study looked at patients treated during childhood for growth hormone deficiency or short stature of unknown cause. Based on this observational study alone, the risk

Related information

- ▶ [NutropinAq: EPAR](#)
- ▶ [Omnitrope: EPAR](#)
- ▶ [Valtropin: EPAR](#)

Contact point:

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E-mail: press@ema.europa.eu



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Conclusions

- EU biosimilar portfolio and related guidelines continue to grow
- EU experience important reference for others
- Challenges for the future:
 - Moving towards more complex biosimilars, such as mAbs
 - Consider the possibility of a global development of biosimilars





EMA website:

The screenshot shows the EMA website interface. The top navigation bar includes links for Home, Find medicine, Regulatory, **Special topics** (highlighted with a red dashed circle), Document library, News & events, Partners & networks, and About us. A search bar is located on the right. The left sidebar contains a list of topics, with 'Regulatory science' and 'Biosimilar medicines' (highlighted with a red dashed circle) visible. The main content area is titled 'Biosimilar medicines' and provides information about biological medicines, their authorization, and the Agency's role. It includes links to scientific guidelines and draft guidelines on biosimilar monoclonal antibodies and immunogenicity. A table of documents of interest is at the bottom.

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Biosimilar medicines

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A similar biological or 'biosimilar' medicine is a biological medicine that is similar to another biological medicine (the 'biological reference medicine') that has already been authorised for use. Biological medicines are made by a living organism, such as a bacterium or yeast, and can consist of relatively small molecules such as human insulin or erythropoietin or complex molecules such as monoclonal antibodies.

Biosimilars can only be authorised for use once the period of data exclusivity on the biological reference medicine has expired. In general, this means that the biological reference medicine must have been authorised for at least 10 years before a similar biological medicine can be made available by another company.

Role of the Agency

The Agency is responsible for assessing applications from companies to market biological medicines for use in the European Union (EU), including biosimilar medicines.

For biosimilar medicines, the company needs to carry out studies to show that the biosimilar is similar to the reference medicine and does not have any meaningful differences in terms of quality, safety or efficacy. As information on the reference medicine is already available, the amount of information on safety and efficacy needed in order to recommend a biosimilar for authorisation is usually less than the amount needed to authorise an original biological medicine.

As with all medicines, the Agency continues to monitor the safety of biosimilar medicines once they are on the market.

For more information, see the [scientific guidelines on biosimilar medicines](#).

Draft guidelines on biosimilar monoclonal antibodies and immunogenicity

On 26 November 2010, the Agency published a draft guideline on similar biological medicinal products containing monoclonal antibodies for public consultation until 31 May 2011. The guideline lays down the requirements for medicines containing monoclonal antibodies that claim to be similar to another such medicine that is already marketed.

For more information, see the [draft guideline on similar biological medicinal products containing monoclonal antibodies](#).

A [draft guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use](#) has also been released for public consultation until 31 May 2011.

Documents of interest

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Document(s)	Language	Status	First published	Last updated	Effective Date
Questions and answers on biosimilar medicines (similar biological medicinal products)	EN = English		30/10/2008		



Further reading

EMA Website:

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

- European Public Assessment Reports (EPARs):
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125
- Biosimilar Guidelines:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002958c
- Directive 2001/83/EC, as amended:
http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_cons/dir2001_83_cons_20081230_en.pdf



Thank you for your attention

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