EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Biologics/Biosimilars Evaluation model: Lessons learned and perspectives after biosimilars approvals

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The European Regulatory Network

- 500 million users of medicinal products
- 28 EU Member states
- > 45 national competent authorities
- > 4 500 European Experts
- EMA role: Pooling of best scientific expertise from across Europe for evaluation and supervision of medicines
- Decision on authorisation: European Commission

The European Regulatory Network

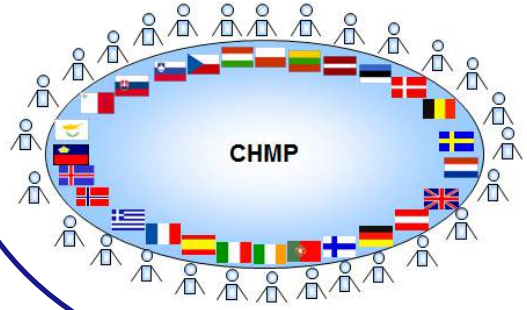
National Competent Authorities

Working Parties

e.g. **Biologics Working Party** (BWP)
Biosimilar Medicinal Products Working Party (BMWP)

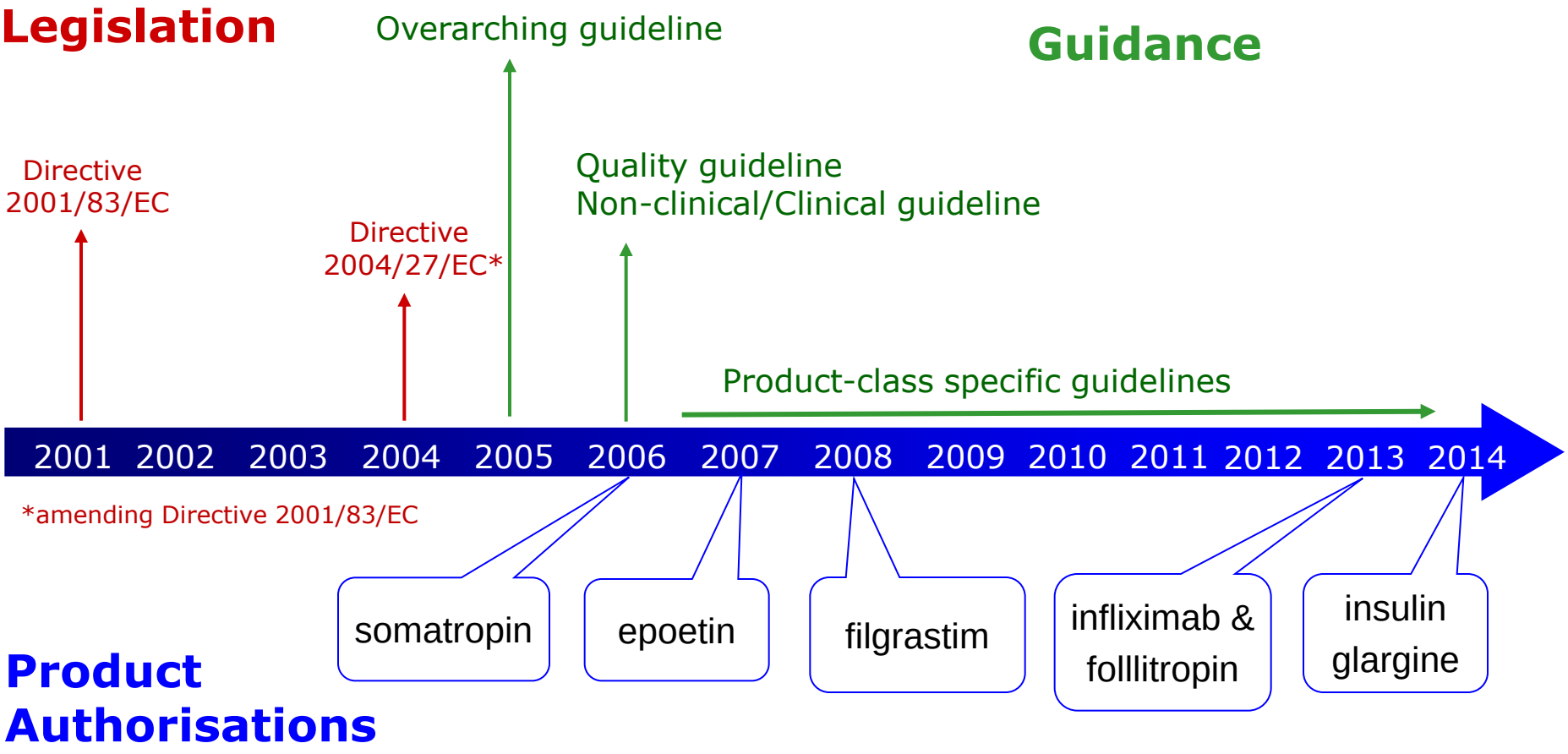
Committees

e.g. CHMP



EMA secretariat

Evolution of Biosimilars in the EU



Biosimilar product review

31 MAAs submitted

29 MAAs reviewed

2 MAAs under review

Etanercept (1)
Insulin (1)

1 Negative

Interferon alfa

21 Positive

7 Withdrawn

Insulin (6)
Epoetin (1)

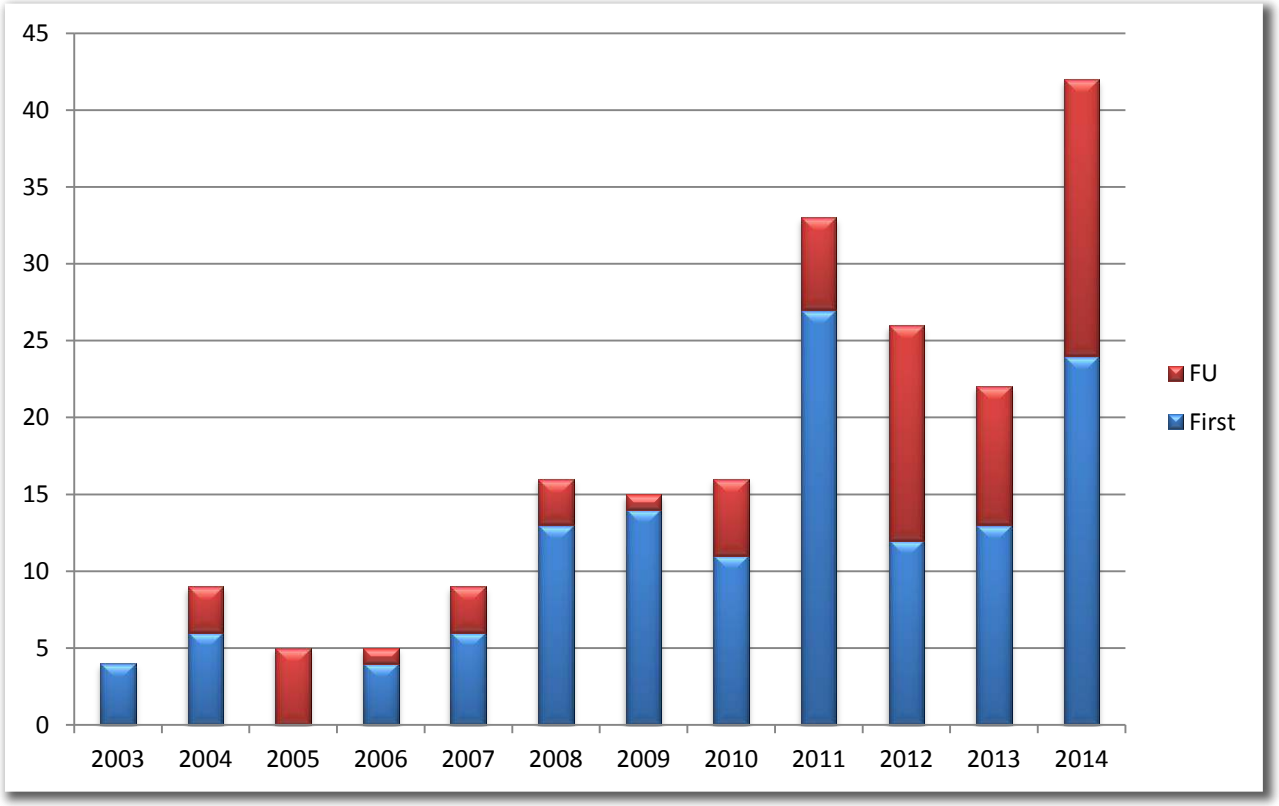
19 Valid MAs

Somatropin (1)
Epoetin (5)
Filgrastim (8)
Infliximab (2)
Follitropin (2)
Insulin glargine (1)

2 Withdrawn

Filgrastim (1)
Somatropin (1)

Scientific advice for biosimilars



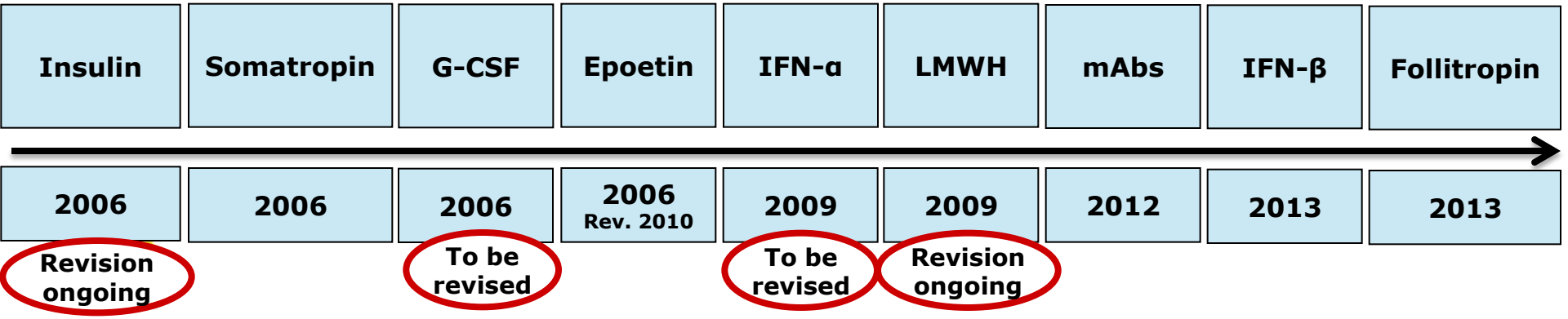
Guidelines for biosimilars

General Guidelines:

Overarching Guideline (CHMP/437/04 Rev. 1)
"Guideline on Similar Biological Medicinal Products"

Non-clinical/clinical Guideline	Quality Guideline

Class-specific Guidelines: non-clinical/clinical aspects:



Overarching Guideline (1/2)

Revision finalised in October 2014

Main changes

- Definition of biosimilar and scope of biologicals covered
- Choice of reference medicinal product
- Principles of establishing biosimilarity (use of sensitive methods, risk-based step-wise approach)
- Possibility of authorisation based on a PK comparative study +/- supportive PD data (no comparative efficacy study)

Overarching Guideline (2/2)

- Facilitate global development
- Reference product must be authorised in the EEA
- Comparability exercise: Non-EEA authorised comparator can be acceptable for certain clinical studies and in vivo non-clinical studies, provided it is:
  - Authorised by regulatory authority with similar scientific/regulatory standards
  - Representative of the reference medicinal product (to be demonstrated by the applicant – bridging data required)

Non-clinical/Clinical Guideline (1/2)

Revision finalised in January 2015

Main changes

Risk-based approach: extent and nature of studies dependent on

- product complexity and ability to characterise at quality level
- differences at quality level (active substance and formulation)
- Mode of action across indications
- Immunogenicity

Non-clinical/Clinical Guideline (2/2)

Non-clinical

- Step-wise approach (in vitro, need for in vivo, in vivo)

Clinical

- PK comparability, study design, SC vs IV route, endpoints
- PD fingerprinting
- Efficacy trials with non-inferiority design, surrogate endpoints
- Safety: immunogenicity
- Extrapolation of indication: totality of data (consider mechanism of action, relevance of studied indication)
- Pharmacovigilance monitoring and switching

Quality Guideline (1/2)

Revision finalised in June 2014

Main changes

- Quality target product profile (QTPP) to be used as development tool
- Choice of expression system (atypical glycosylation, higher variability, different impurities)
- Comparison of amino acid sequence, immunological functions
- Comparability at the level of the finished product

Quality Guideline (2/2)

- Differences with potential clinical relevance may require additional non-clinical and/or clinical studies unless conferring safety advantage
- Acknowledgement that the quality of both biosimilar and reference product may evolve through their life-cycles
- Global development aspects covered by overarching guideline

Case study – Remsima/Inflectra

First approval of biosimilar mAb

- Remsima (duplicate Inflectra): first biosimilar monoclonal antibody to be approved in Europe
- European Commission Decision – 10 September 2013
- Active substance: infliximab
- Reference product: Remicade (authorised 1999)
- Data provided: Extensive quality and non-clinical (in-vitro) comparability exercise + PK study in ankylosing spondylitis + Pivotal efficacy and safety study in rheumatoid arthritis

Extrapolation of indications

- Extrapolation to IBD indications (Crohn's disease and ulcerative colitis) was considered acceptable

Remsima EPAR executive summary: "...small difference in the amount of afucosylated infliximab translated into a lower binding affinity towards specific Fc receptors and a lower *ex vivo* antibody-dependent cellular cytotoxicity (ADCC) activity in the most sensitive ADCC assay. This difference was, however, not considered clinically meaningful, as it did not affect the activities of Remsima in experimental models regarded as more relevant to the pathophysiological conditions in patients."

Further details – see comprehensive EPAR:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002576/WC500151486.pdf

Biosimilars working party: Ongoing/planned activities

- Revision of guidelines: insulin, LMWH, interferon alfa, G-CSF, immunogenicity guideline
- Workshops:
  - Stakeholder meeting on immunogenicity
  - Meeting with patients', consumers' and healthcare professionals' organisations
- Assessor training
- International cooperation (e.g. Biosimilar cluster EMA/FDA/HC/PMDA)

EMA Website - Biosimilar landing page

URL:http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jsp&mid=WC0b01ac0580281bf0

Links to:

- ✓Q and A for biosimilars
- ✓Biosimilar guidelines
- ✓BMWP mandate & work plan
- ✓Procedural guidance for biosimilars
- ✓Public assessment reports (EPARs) for biosimilars

Thank you for your attention!

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