Lääkealan turvallisuus- ja kehittämiskeskus | Säkerhets- och utvecklingscentret för läkemedelsområdet | Finnish Medicines Agency

Biosimilars from the perspective of an EU regulator

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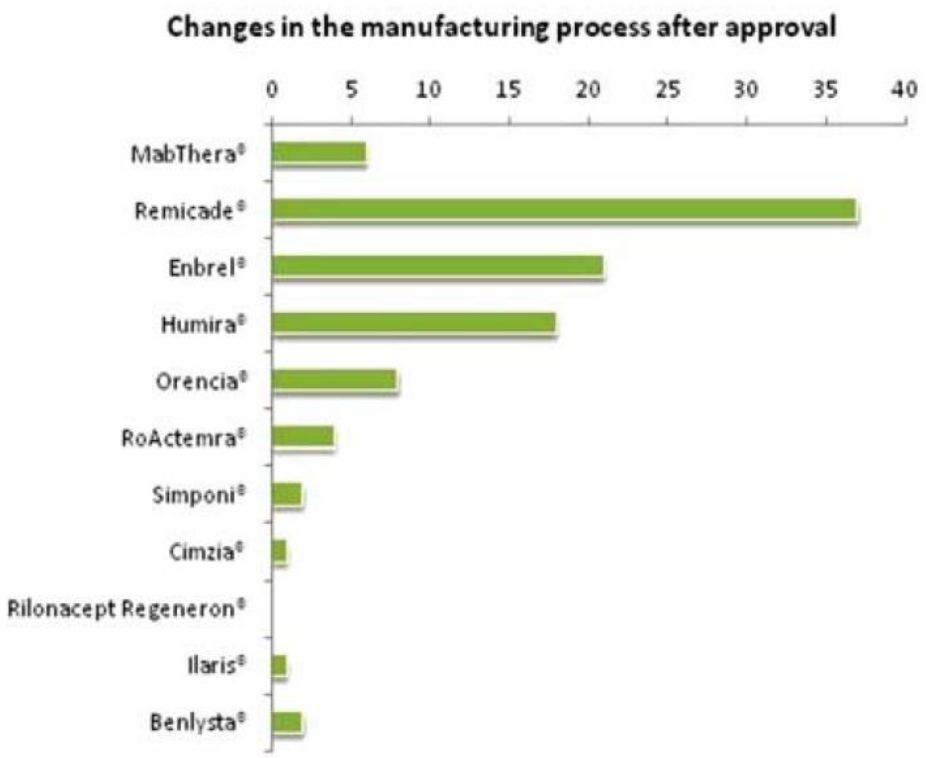
Content

1. **Main principles for developing and assessing biosimilars**
2. **Current and future EU biosimilars**
3. **The position of the Finnish Medicines Agency (FIMEA) on interchangeability of biosimilars**

Batch-to-batch variability for biologics



Schneider C., Ann Rheum Dis March 2013 Vol 72 No 3

- Batch-to-batch variability is inherent for biologics, no batch is fully identical to another
- Manufacturing process changes with the potential to alter the quality profile are frequently implemented
- The pre- and post-change version of the medicinal product needs to be demonstrated to be comparable through a comparability exercise
- Manufacturers and regulators are used to assess the impact of process changes – also in the case of complex biologics

What is a biosimilar?

Current EU regulatory definition of biosimilars

A biosimilar is a biological medicinal product that *contains a version of the active substance* of an already authorised original biological medicinal product (reference medicinal product).

A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a *comprehensive comparability exercise*

- ✓ *The scientific principles of a biosimilar comparability exercise are based on those applied for evaluation of the impact on changes in the manufacturing process of a biological medicinal product*

General principles for biosimilar development

- In principle, the concept of a biosimilar is applicable to any biological medicinal product
- The success of developing a biosimilar depends on;
  - The ability to *manufacture a close copy version* of the reference medicinal product in a consistent manner
  - The ability to *perform thorough physicochemical and biological characterization* and to *understand the clinical relevance* of any differences detected
  - The ability to demonstrate *bioequivalence*
  - The availability of *suitable clinical models*; sensitive endpoints, possibility to identify relevant comparability margins

Biosimilar vs Reference Medicinal Product - How close is close enough?

- Must be the same
  - The amino acid sequence
  - Posology and the route of administration
- Must be similar
  - The active substance in terms of molecular and biological characteristics
- Need to be justified
  - Differences in strength, pharmaceutical form, formulation, excipients or presentation
- Not allowed
  - Intended changes to improve efficacy (”biobetters”)

Analytical and functional characterisation of a typical monoclonal antibody

ATTRIBUTES OF THE VARIABLE REGION

- Deamidation
- Oxidation
- N-term Pyro-Glu
- Glycosylation
- Glycation
- Conformation changes

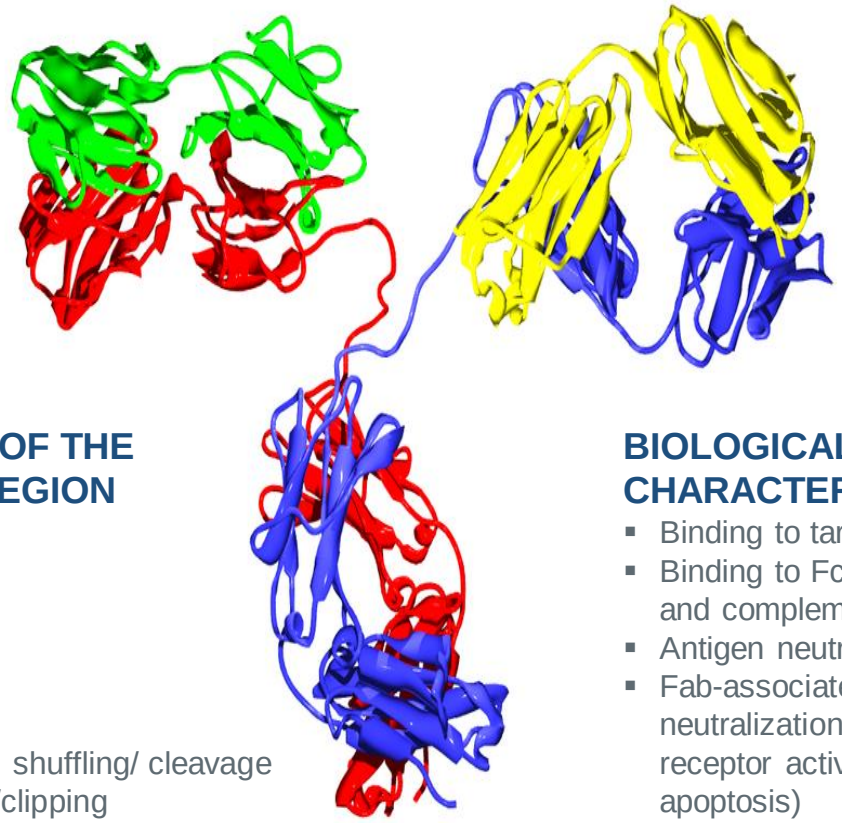


Figure from Wikipedia

PHYSICOCHEMICAL CHARACTERITICS

- Structure (primary, higher order structures)
- Molecular mass
- Purity/ impurity profiles
- Charge profile
- Hydrophobicity
- O- and N-glycans

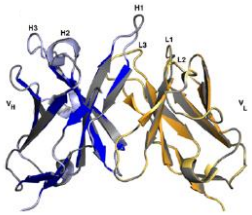
ATTRIBUTES OF THE CONSTANT REGION

- Deamidation
- Oxidation
- Acetylation
- Glycation
- Glycosylation
- C-term Lys
- Di-sulfide bond shuffling/ cleavage
- Fragmentation/clipping
- Conformation changes

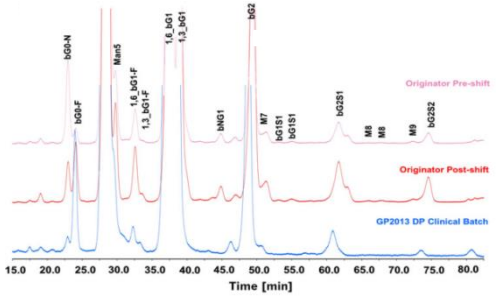
BIOLOGICAL/ FUNCTIONAL CHARACTERISTICS

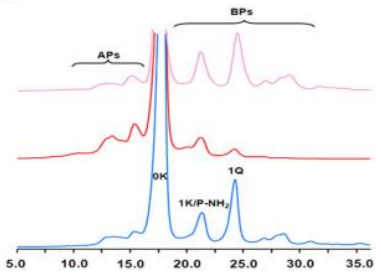
- Binding to target antigen(s)
- Binding to Fc γ receptors, FcRn and complement
- Antigen neutralisation (if relevant)
- Fab-associated functions (e.g. neutralization of a soluble ligand, receptor activation, induction of apoptosis)
- Fc-associated functions (ADCC and CDC)

Analytical tools commonly used in protein characterisation



- Amino acid sequence and modifications
  - MS, LC-MS, peptide mapping, N- and C-terminal sequencing, AA content
- Disulphide bridging, protein folding and higher-order structures
  - Peptide mapping, Ellman's assay, CD, FTIR, HDX-MS, NMR, DSC, X-ray crystallography
- Glycosylation and glycation
  - Anion exchange, enzymatic digestion, peptide mapping, CE, MS, BAC
- Size heterogeneity
  - SEC, AUC, AF4, MALDI-TOF, CD-SDS, SDS-PAGE
- Heterogeneity of charge and hydrophobicity
  - IEF, cIEF, IEX, RP-HPLC
- Functional characterisation and bioassays
  - Target and/or receptor binding; SPR, ELISA, cell-based assays
  - Bioassays; Signal transduction, ADCC, CDC, other cell-based assays





Figures from Visser J. et al. BioDrugs. 2013 Oct;27(5):495-507

The ”pivotal” evidence for analytical similarity

- An extensive, side-by-side (whenever feasible) comparability exercise is required to demonstrate high similarity
  - Composition, physical properties, primary and higher order structures, purity, product-related isoforms and impurities, and biological activity
  - Orthogonal methods should be used whenever possible
  - The aim is to show high similarity using material produced with the final (commercial) manufacturing process using sensitive analytical methods
- Quantitative comparability ranges should be established
  - Ranges should be primarily based on characterisation data obtained from analyses of a large number of reference product batches (forming the Quality Target Product Profile used to guide biosimilar product and process development)

The ”pivotal” evidence for analytical similarity

- Any differences detected in quality attributes must be justified in relation to safety and efficacy
  - It may be challenging to claim biosimilarity if relevant quality differences are confirmed, clinical data cannot be used to justify substantial differences in quality attributes
  - For justifying differences in low criticality attributes, previous knowledge might be sufficient
  - For medium to high criticality attributes, Structure Activity Relationship (SAR) studies are usually required
- Additional comparative stability studies under accelerated conditions can be useful to compare degradation pathways, i.e. to reveal “hidden” differences

Stepwise approach to establish biosimilarity

1. Comprehensive physicochemical and biological characterisation
2. Non-clinical studies
   - *In vitro* functional studies and if needed, *in vivo* studies
3. Pharmacokinetics and pharmacodynamic studies
   - Comparative PK study in a sensitive and homogeneous study population such as healthy volunteers (if possible/ feasible)
4. Confirmatory efficacy/safety studies
   - Adequately powered, randomised, parallel group, usually equivalence trial
   - Study population should be representative of approved indication(s) and be sensitive for detecting potential differences
   - Endpoints selected with the aim to investigate possible differences, not to demonstrate efficacy per se
   - Comparative safety data is always required pre-authorisation

Extrapolation of indications

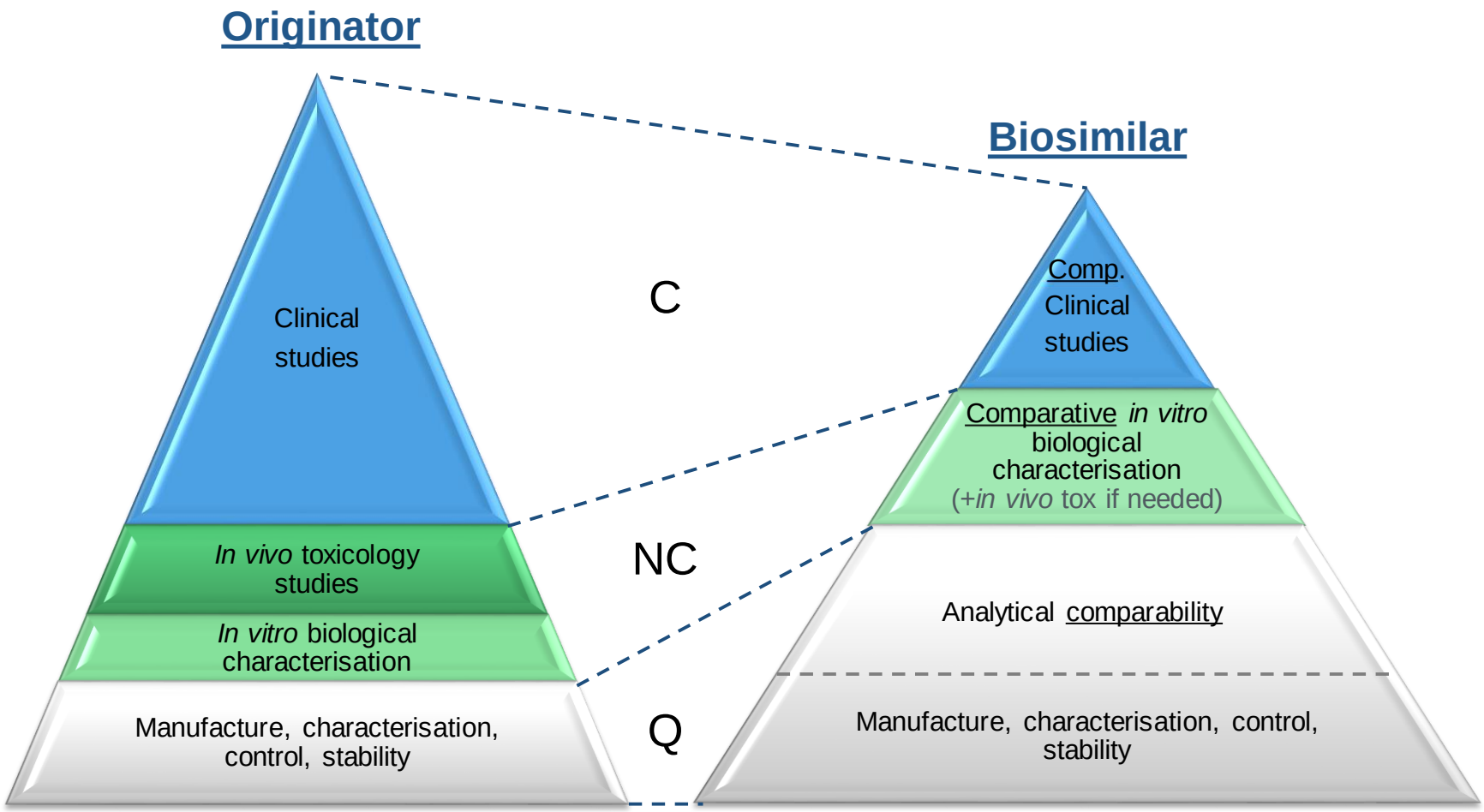
To leverage efficacy and safety data from clinical studies in one studied indication to support authorisation of other indications approved for the reference product

- Similar physicochemical and structural characteristics, similar biological function in *in vitro* models
- Similar human PK, PD, efficacy, safety, and immunogenicity at least in one therapeutic indication[1]
- Sound scientific justification
  - Clinical experience and available literature data
  - Mechanism of action of the active substance in each indications
  - Evidence that the lead indication is representative for the other therapeutic indications, both with regard to safety and efficacy

➢Extrapolation of indication(s) is always a case-by-case decision and will depend on the totality of evidence presented

[1] For simple biologics, safety and/or efficacy studies may not always be necessary

Summary - Marketing Authorisation Application



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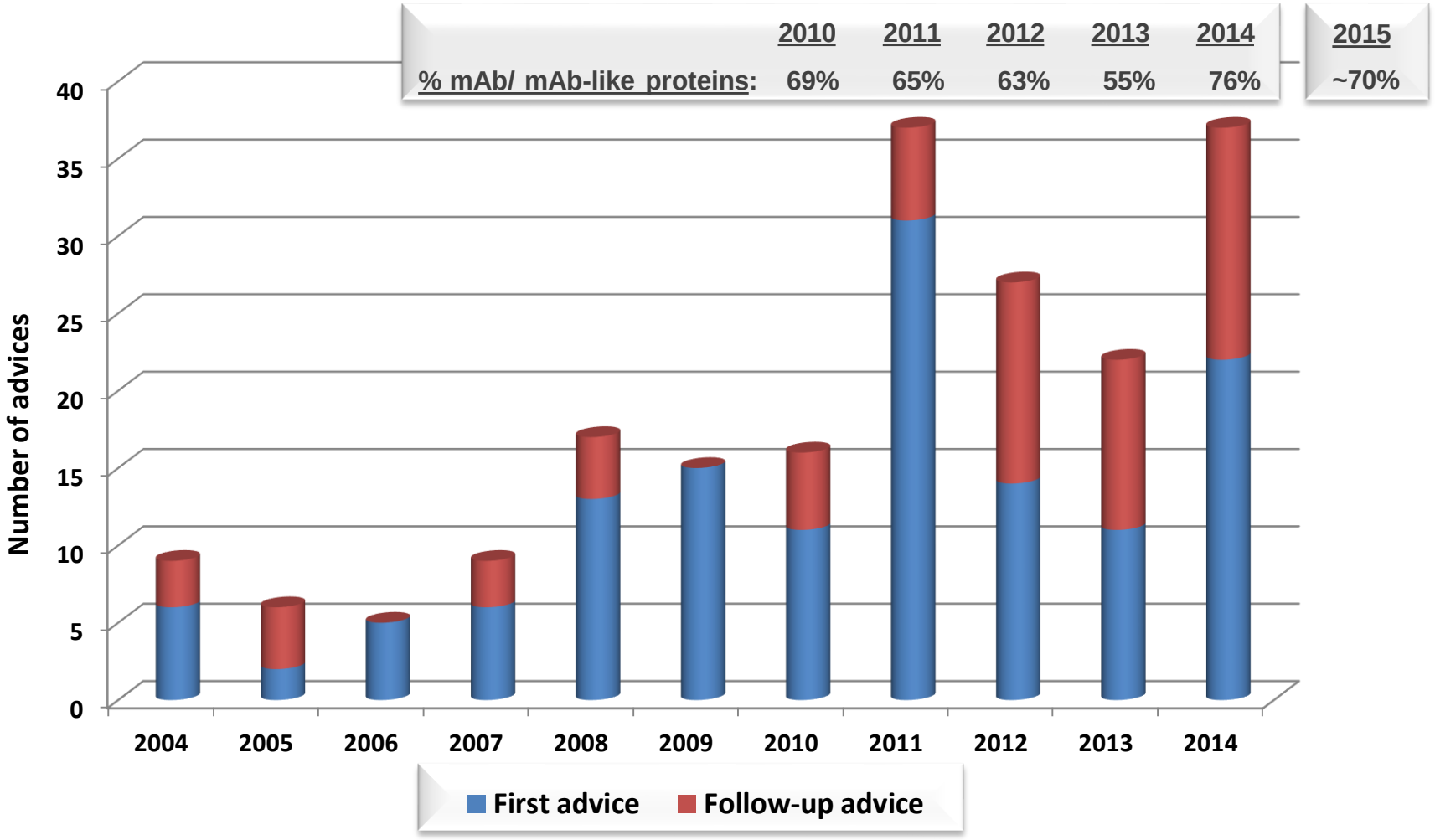
Marketing authorisation experience in EU

- 30 Marketing authorisation applications for biosimilars reviewed by the CHMP
  - 21 positive (12 active substances), 7 withdrawn during evaluation, 2 negative (interferon alfa-2a (2006), insulin human (2015))
- 19 biosimilar medicinal products currently holding a valid marketing authoriation
  - 1 somatropin, 5 epoetin (two active substances), 8 filgrastim (5 active substances), 2 infliximab (one active substance), 2 follitropin alfa (two active substances), 1 insulin glargine
  - 2 authorisations withdrawn by the MA holder post-approval
- 8 biosimilar MA applications currently under review (Feb 2016)
  - Adalimumab, enoxaparin sodium, etanercept, infliximab, insulin glargine, pegfilgrastim, rituximab, teriparatide

EMA biosimilar scientific advices 2004-2014



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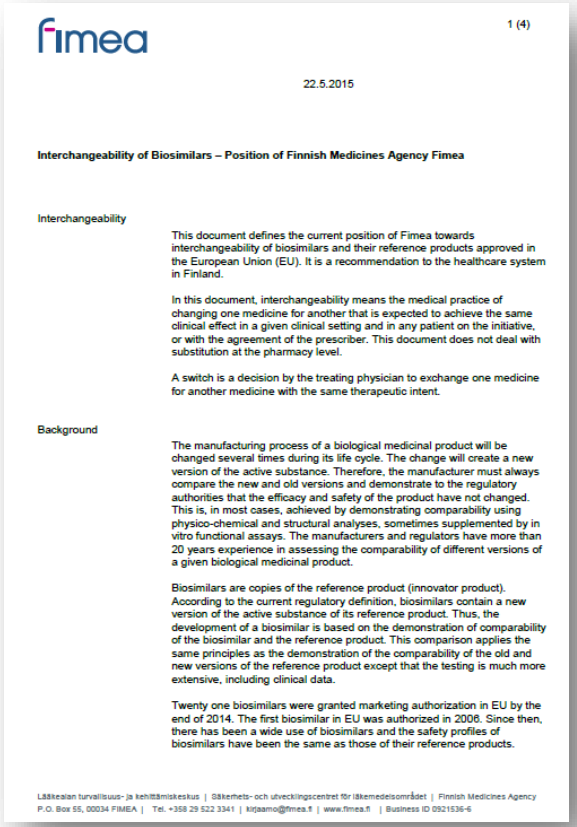
Funding of medicines in Finland

- Medicines administered in public hospitals
  - Costs beared by the communities
- Prescription medicines delivered by pharmacies
  - Costs are covered by the Social Insurance Institution (state)
  - A patient will pay annually maximally 610€ for reimbursed medicines
  - Three levels of reimbursement; 40%, 64%, and 100%
  - A biosimilar enjoys the same reimbursement level as its reference
  - Reimbursement is a prerequisite for the use of any biologicals outside hospitals
- Hospitals are leading the adoption of biosimilars (economical incentives)
- Prescribers and patients (on treatment) have no special interest in biosimilars because of the lack of incentives

Interchangeability of Biosimilars – Position of Finnish Medicines Agency (FIMEA)



fimea

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22.5.2015

Interchangeability of Biosimilars – Position of Finnish Medicines Agency Fimea

Interchangeability

This document defines the current position of Fimea towards interchangeability of biosimilars and their reference products approved in the European Union (EU). It is a recommendation to the healthcare system in Finland.

In this document, interchangeability means the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber. This document does not deal with substitution at the pharmacy level.

A switch is a decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent.

Background

The manufacturing process of a biological medicinal product will be changed several times during its life cycle. The change will create a new version of the active substance. Therefore, the manufacturer must always compare the new and old versions and demonstrate to the regulatory authorities that the efficacy and safety of the product have not changed. This is, in most cases, achieved by demonstrating comparability using physico-chemical and structural analyses, sometimes supplemented by in vitro functional assays. The manufacturers and regulators have more than 20 years experience in assessing the comparability of different versions of a given biological medicinal product.

Biosimilars are copies of the reference product (innovator product). According to the current regulatory definition, biosimilars contain a new version of the active substance of its reference product. Thus, the development of a biosimilar is based on the demonstration of comparability of the biosimilar and the reference product. This comparison applies the same principles as the demonstration of the comparability of the old and new versions of the reference product except that the testing is much more extensive, including clinical data.

Twenty one biosimilars were granted marketing authorization in EU by the end of 2014. The first biosimilar in EU was authorized in 2006. Since then, there has been a wide use of biosimilars and the safety profiles of biosimilars have been the same as those of their reference products.

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- Defines the current position of FIMEA towards interchangeability of EU biosimilars and their reference products
- Interchangeability; the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber
- Automatic substitution at the pharmacy level is not considered by the current recommendation

http://www.fimea.fi/download/29197_Biosimilaarien_vaihtokelpoisuus_EN.pdf

Main conclusions from the position paper

- Switches between (non-similar) biological products, for example in the context of hospital tendering processes, are common and usually not problematic
- The clinical crossover studies conducted have given no evidence of adverse effects due to a switch from a reference product to a biosimilar (somatropin, epoetin alfa, filgrastim, insulin glargine, infliximab)
- Also the theoretical basis of such adverse effects is weak
- Risk of adverse effects can be expected to be similar to the risk associated with changes in the manufacturing process of any biological products

➢ The position of FIMEA is that EU biosimilars are interchangeable with their reference products under the supervision of a health care person. As with any biological products, the switch should be documented (including brand name and batch number)

Similar positions adopted by other EU national authorities

Medicines Evaluation Board – MEB (The Netherlands) [1]

Exchange between biological medicines (regardless of whether they are innovator products or biosimilar medicinal products) is permitted, but only if adequate clinical monitoring is performed and the patient is properly informed

Paul Ehrlich Institute – PEI (Germany) [2]

Biosimilars can be used in the same way as the reference products to which they have shown equivalence. This implicitly covers both patients who have not yet received biological therapy as well as patients who previously received the originator molecule

Health Products Regulatory Authority – HPRA (Ireland) [3]

If it is planned to change the medicine a patient receives from a reference to a biosimilar medicine or vice versa, the treating physician should be involved; this should involve discussion between the prescriber/ patient, and prescriber /dispensing pharmacist

[1] http://english.cbg-meb.nl/human/for-healthcare-providers/contents/biosimilar-medicines
[2] http://www.pei.de/DE/arzneimittel/immunglobuline-monoklonale-antikoerper/monoklonale-antikoerper/zusatz/position-pei-interchangebility-biosimilars-inhalt.html
[3] http://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/guide-to-biosimilars-for-healthcare-professionals-and-patients-v1.pdf?sfvrsn=6

Thank you for your attention!

EMA Website
http://www.ema.europa.eu/ema/

Biosimilar guidelines
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c

Interchangeability of Biosimilars – Position of Fimea
http://www.fimea.fi/download/29197_Biosimilaarien_vaihtokelpoisuus_EN.pdf

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