The Dutch Medicines Board Opinion on Biosimilars

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- EU first region in the world estabilished a regulatory framework for biosimilar approval (2005)

- Marketing authorisation applications for biosimilar medicinal products, are by law reviewed centrally by the European Medicines Agency (EMA).

- Based on EMA/CHMP scientific opinion, according to the requirements included in the scientific guidelines ,the EC releases authorisation which is valid in all (28) EU Member States.

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EMA biosimilar guidelines (2005-2015)

GUIDELINES OF RELEVANCE FOR BIOSIMILAR MEDICINES

OVERARCHING BIOSIMILAR GUIDELINES

- GENERAL
- QUALITY ISSUES
- NON-CLINICAL AND CLINICAL ISSUES

PRODUCT-SPECIFIC BIOSIMILAR GUIDELINES

Insulin | Somatropin | G-CSF | EPO | LMWH | IFN-alpha | FSH | IFN-beta | mAbs

OTHER GUIDELINES RELEVANT FOR BIOSIMILARS

- COMPARABILITY – QUALITY ISSUES
- COMPARABILITY – NON-CLINICAL AND CLINICAL ISSUES
- IMMUNOGENICITY

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EMA approved 21 biosimilars (1/1/2015)

Molecule	Company	Approval Date	Reference Product	Brand Name
Somatropin	Sandoz	Apr-06	Genotropin [PFE]	Omnitrope
Somatropin	Biopartners	Apr-06	Humatrope [LLY]	Valtropin
EPO-alfa	Sandoz	Aug-07	Epogen [AMGN]	Binocrit
EPO-alfa	Hexal	Aug-07	Epogen [AMGN]	EPO-alfa Hexal
EPO-alfa	Medice	Aug-07	Epogen [AMGN]	Abseamed
EPO-zeta	Stada	Dec-07	Epogen [AMGN]	Silapo
EPO-zeta	Hospira	Dec-07	Epogen [AMGN]	Retacrit
Filgrastim	Ratiopharm	Sep-08	Neupogen [AMGN]	Filgrastim Ratiopharm
Filgrastim	Teva Pharma	Sep-08	Neupogen [AMGN]	TevaGrastim
Filgrastim	AbZ-Pharma GmbH	Sep-08	Neupogen [AMGN]	Biograstim
Filgrastim	Ratiopharm	Sep-08	Neupogen [AMGN]	Ratiograstim
Filgrastim	Hexal	Feb-09	Neupogen [AMGN]	Filgrastim Hexal
Filgrastim	Sandoz	Feb-09	Neupogen [AMGN]	Zarzio
Filgrastim	Hospira	Jun-10	Neupogen [AMGN]	Nivestim
Infliximab	Celltrion	Sep-13	Remicade [JNJ]	Remsima
Infliximab	Hospira	Sep-13	Remicade [JNJ]	Inflectra
FSH	Teva Pharma	Sep-13	Gonal-f [MRK-GR]	Ovaleap
Filgrastim	Apotex Europe BV	Oct-13	Neupogen [AMGN]	Grastofil
FSH	Finox AG	Mar-14	Gonal-f [MRK-GR]	Bemfola
Insulin glargine	Eli Lilly	Sep-14	Lantus [SNY]	Abasaglar
Filgrastim	Accord Healthcare	Sep-14	Neupogen [AMGN]	Accofil

- EMA issued no guidance on biosimilar interchangeability or substitution.
  - The responsibility of the EMA is restricted to the market authorisation of biosimilars and has no mandate concerning reimbursement issues like switching
  - Decisions on prescribing and dispencing are the province of the individual member states.

- In many member states automatic substitution is not allowed for biologicals including biosimilars

- **Switching**: Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.

- **Substitution**: Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.

- **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.

The Dutch Medicines Evaluation Board (MEB) has updated its opinion about biosimilar medicinal products (31st March 2015)

- The MEB adopted a stance about biosimilars in 2010. At the time, the MEB was of the opinion that patients should be kept on a biological medicinal product as much as possible if they exhibited a good clinical response.
- Based on a careful study of the most recent literature and experiences in the evaluation of biosimilars, the MEB deems that this strict condition is no longer valid. There is enough evidence to support the use of biosimilars in clinical practice, provided this occurs with caution and under certain conditions. However, these conditions are essential.

Switching – Review of Published Crossover Studies

Innovator and biosimilar switching studies
(including RCTs with run–in period)

Drug	Number of studies	Number of patients
hGH	12	401
ESA	35	11.249
GCSF	10	374
Total	**57**	**12.024**

1 study reported less injection site pain in Epoetin-β vs. darbepoetin

Others no safety concerns reported

Universiteit Utrecht

The safety of switching between therapeutic proteins
Ebbers et al. Expert Opin 2012

- Switching between innovator products and the biosimilars based on this reference medicine and between biosimilars based on the same reference medicine is possible, but only if adequate clinical monitoring is performed and the patient is well informed.

The Medicines Evaluation Board has therefore taken the following stance about biosimilars:

- New patients can always be treated with a biosimilar.

- Uncontrolled exchange between biological medicinal products (regardless of whether they are innovator products or biosimilar medicinal products) must be avoided. In other words, a patient must receive adequate clinical monitoring and clear instructions.

- If a patient is treated with a biological medicinal product, detailed product and batch information must be recorded in the patient file to guarantee the traceability of the product in the event of problems.

- **Shared decision making**: treating physician, pharmacist and patient. Doctor in the lead.

- **Focus on clinical monitoring:**
  - tracebility
  - practise-based research for safety and efficacy
  - import role learned clinical societies (FMS, NHG)
  - collaboration with Dutch Center for pharmacovigilance (LAREB)

Switching From Originator to Biosimilar Human Growth Hormone Using Dialogue Teamwork: Single-Center Experience From Sweden

- 102 children who were offered the switch to biosimilar rGH, 98 decided to accept. Switching had no impact on the children's growth. No serious or unexpected ADRs were reported.

- Dialoque teamwork:
  - providing patients/parents clear information about reason for change
  - allowing individual patients sufficient opportunities to discuss the change with different HCP
  - a joint team approach that avoids mixed messages from different HCP
  - personal support throughout the change

flodmark et al Biol Ther 2013

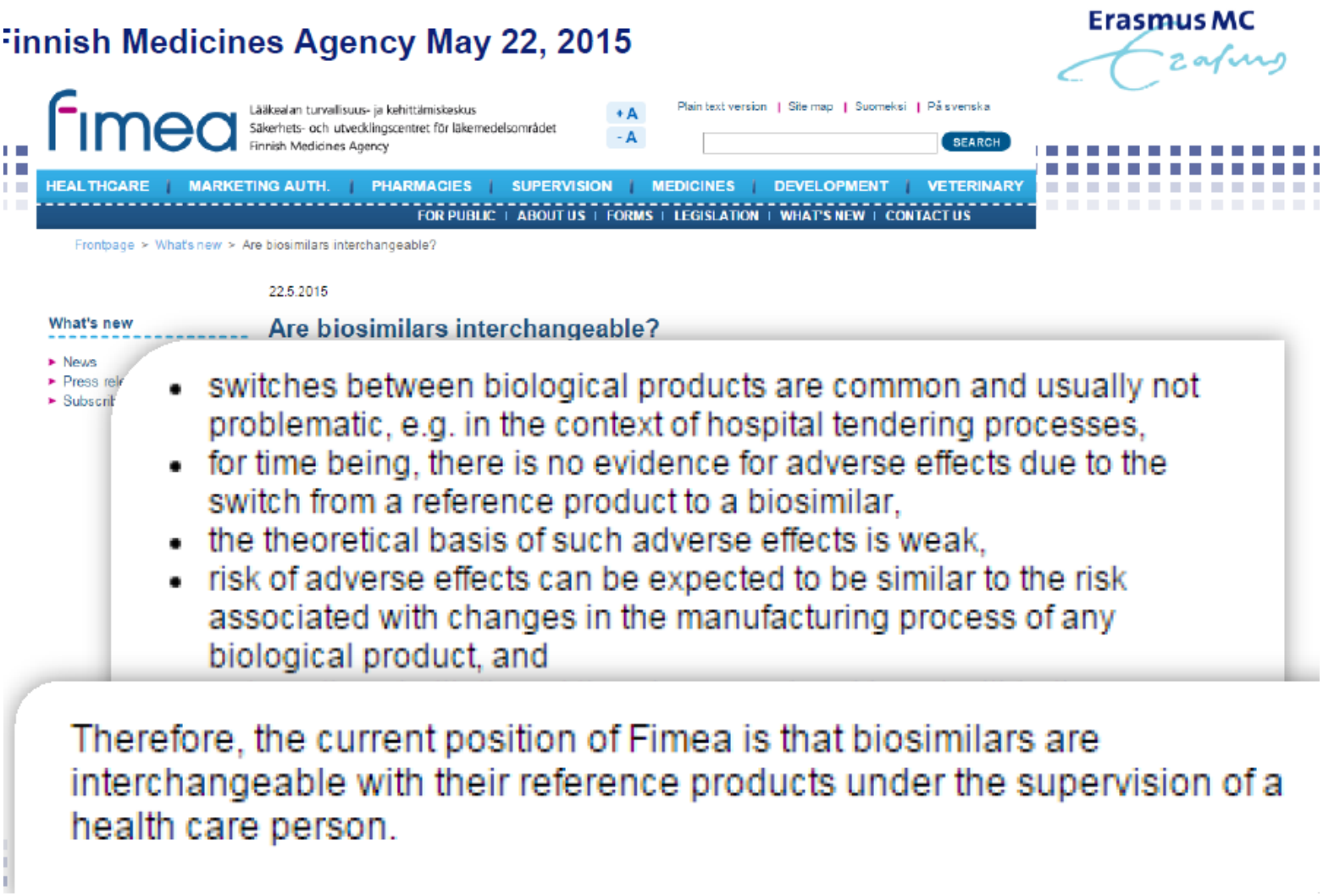
Creating support by education

- Education is required on the **scientific concept of biosimilar medicines**, their approval process, and their safety and efficacy

- need for **clear** information from **unbiased** sources, that is non-promotional, targeting doctors, other healthcare professionals, payers and patients

- Interaction between CBG-MEB and some stakeholders:
  - Centre for pharmacovigilance (Lareb)
  - learned clinical societies (FMS, NHG)
  - patient organisations
  - pharmacist organisations (KNMP, NVZA)
  - zonMw (health research and development)
  - Ministry of health (VWS)

Finnish Medicines Agency May 22, 2015



Conclusion

- Biosimilars have been proven to have no relevant differences compared to innovator biological medicines as far as quality, safety and efficacy are concerned.

- Switching between biological medicines is possible, but only if adequate clinical monitoring is performed and the patient is well informed.

BIOSIMILARS NEDERLAND

CBG MEB