Biosimilars and Endocrinology

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Disclosure

(Potential) conflicts of interests	None
Relevant (for this meeting) relations to commercial companies	Names of companies
• Sponsorships or research funding • Honorary fee or other (financial) compensation • Shareholder • Other relations, namely ...	• • • •

Biosimilars and Endocrinology

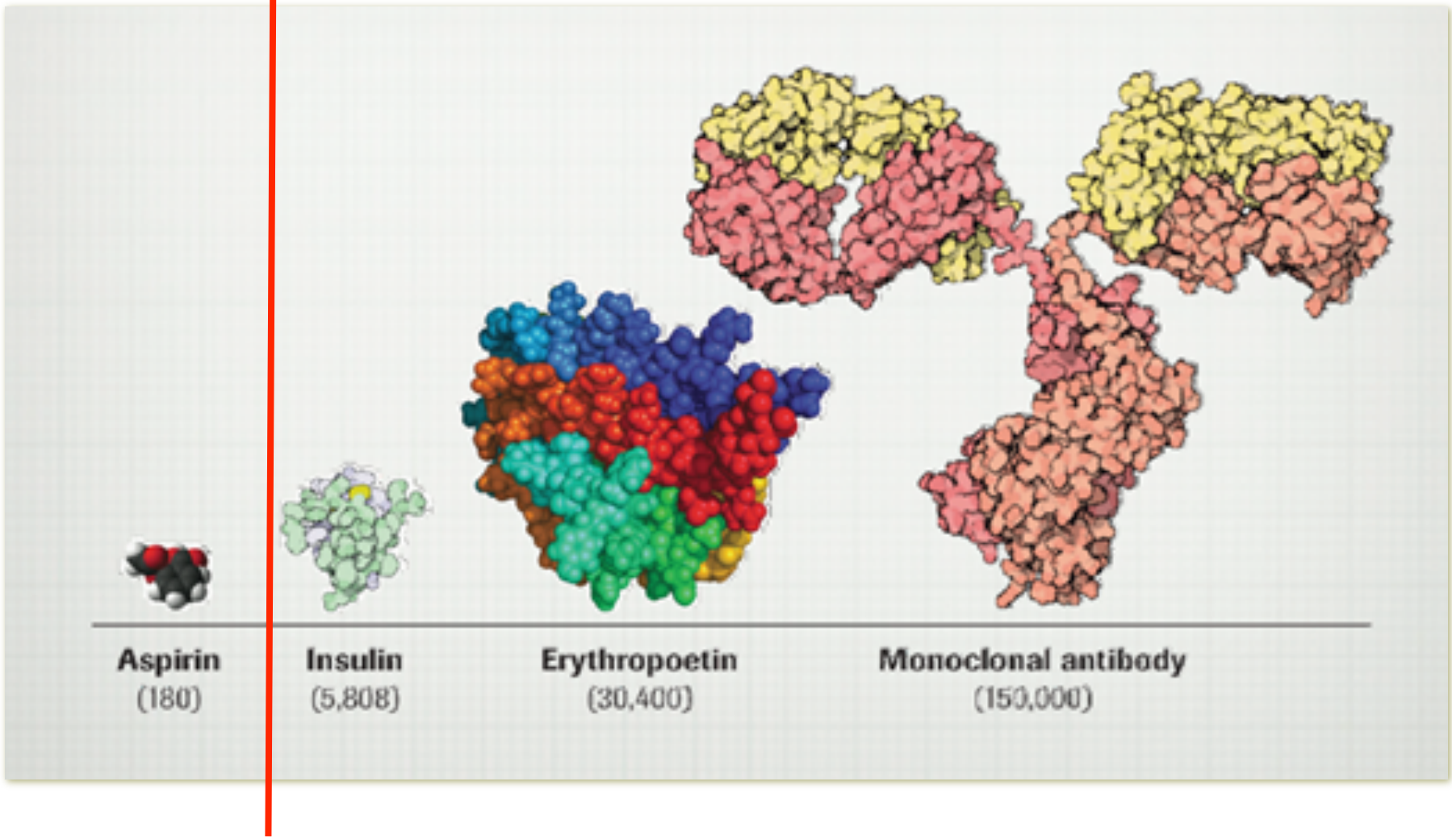
Agenda:

- Biological vs small drugs
- Generic drugs
- Biosimilars: definition and biosimilar pathway
- Regulatory requirements
- Switching/substitution
- Dutch guidelines (MEB/ FMS/NVR)
- Biosimilar growth hormone
- Biosimilar insulins
- Conclusion

Biopharmaceuticals

- Biologicals are produced by living entities, such as organisms, cells or tissues
- Complex recombinant proteins : insulin ,growth hormone, epo, monoclonal antibodies
- Complexity is determined by nature of drug molecule and by production process
- The process is the product .High process sensitivity
- Biosimilar is copy-product of biological

Biologicals Are More Complex Than Small Molecule drugs

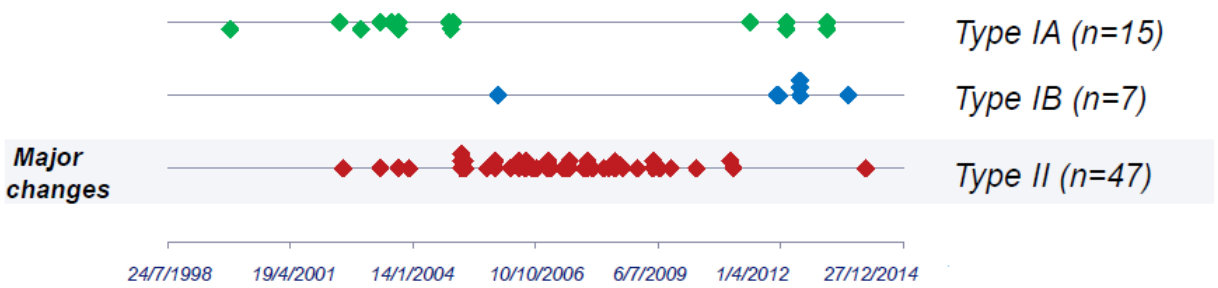


Micro-variability is in the nature of glycoproteins: no batch of any biologic is identical to the other batches. Variability is natural and usualy not problematic.

Manufacturing changes are made frequently and are controlled by EMA

Scale-up and post-approval changes of Remicade® production

Manufacturing Changes are a normal process in all biologics



Comparability protocols validated that these major (Type II) manufacturing changes did not impact the quality, safety and efficacy of the drug.

Type IA Variation
- Minimal or no impact on the quality, safety, or efficacy of the medicinal product concerned
- Notification procedure

Type IB Variation
- Variation which is neither Type IA nor Type II
- Notification procedure

Type II Variation
- A significant impact on the quality, safety, or efficacy of a medicinal product
- Prior approval procedure

European Medicines Agency. REMICADE™ procedural steps taken and scientific information after the authorisation. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000240/WC500050890.pdf. Accessed October 12, 2014.

Isala

Small Chemical Drugs vs Biologicals

	Small Chemical Drugs	Biopharamceuticals
Size	Small	Large
Structure	Simple	Complex
Stability	Stable	Unstable
Modification	Well defined	Many options
Manufacturing	• Predictable chemical process • Identical copy can be made	• Unique line of living cells • Impossible to ensure identical copy
Characterization	Easy to characterize fully	Difficult to characterize fully due to a mixture of related molecules
Immunogenicity	Nonimmunogenic	Immunogenic

Generic drugs

- Similar chemical substances
- Identical to the original drug (=exact copy)

- Limited registration requirements:

- Complete chemical-farmaceutical file
- Bioequivalence study

- Toxicology (animal) and clinical efficacy studies not required

- Cost-saving

What is a biosimilar?

Guideline on Similar Biological Medicinal Products (EMA 2005)

- 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

What is a biosimilar?

- A drug that is highly similar but not identical to the reference biological product.

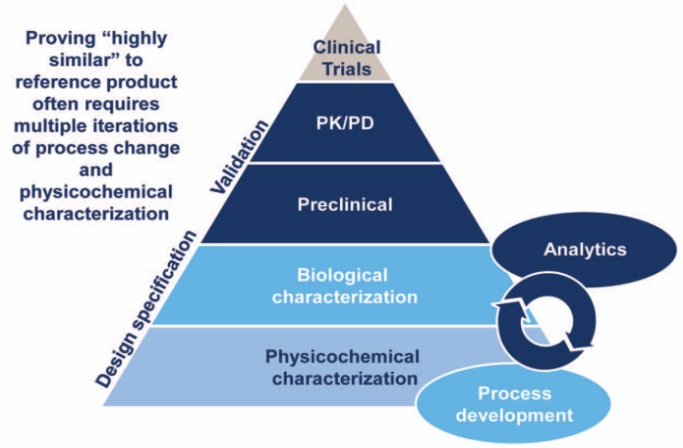
Development of a biosimilar

Biosimilar pathway

- Mainstay is an extensive physicochemical and biological characterisation:

Form and function of the molecule

  - Same primary, secondary and tertiary structure
  - Comparable post-translational profile



- Pre-clinical tests
  - Extensive *in vitro* characterization of biological activity
  - *In vivo* only in case of remaining uncertainties based on physicochemical and biological characterization and *in vitro* studies and animal studies should add valuable information (=exceptional)

Clinical efficacy

- The aim of a biosimilar development program is not to establish benefit of a treatment for the patient

  (this had been done before for the reference product (for 10-15 years)!

- The aim is to establish biosimilarity!

- This means:
  - The clinical study is focussed on confimation of similarity and not on proof of efficacy
  - The clinical study is selected to represent the most sensitive model to study differences

  Extrapolation of indications is a key aspect in the approval of biosimilars
  Additional data needed if:

  - Different receptors in different indications
  - Differences in immunogenicity
  - Differences in co-medication

Clinical safety

- Safety profile should be comparable
- Immunogenicity should specifically be studied
- Higher immunogenicity would question biosimilarity
- However, lower immunogenicity might be acceptable
- Pharmacovigilance (risk management plan (RMP), post-approval studies)

Immunogenicity

Not all Antibodies Lead to Clinically Relevant ADRs. Some Can be Assessed Before Authorization

Product	Antibody formation (%)	Consequence
Erythropoeitin	<1	PRCA
Factor VIII	15-52	Loss of efficacy
Factor IX	1-2	Loss of efficacy, anaphylaxis
Interferon α	44	Loss of efficacy
Interferon ß	<5	Loss of efficacy
IL1 Ra	2	Loss of efficacy
Growth hormone	1-2	No significant effects
Infliximab	17-60	Loss of efficacy, infusion reactions, anaphylaxis

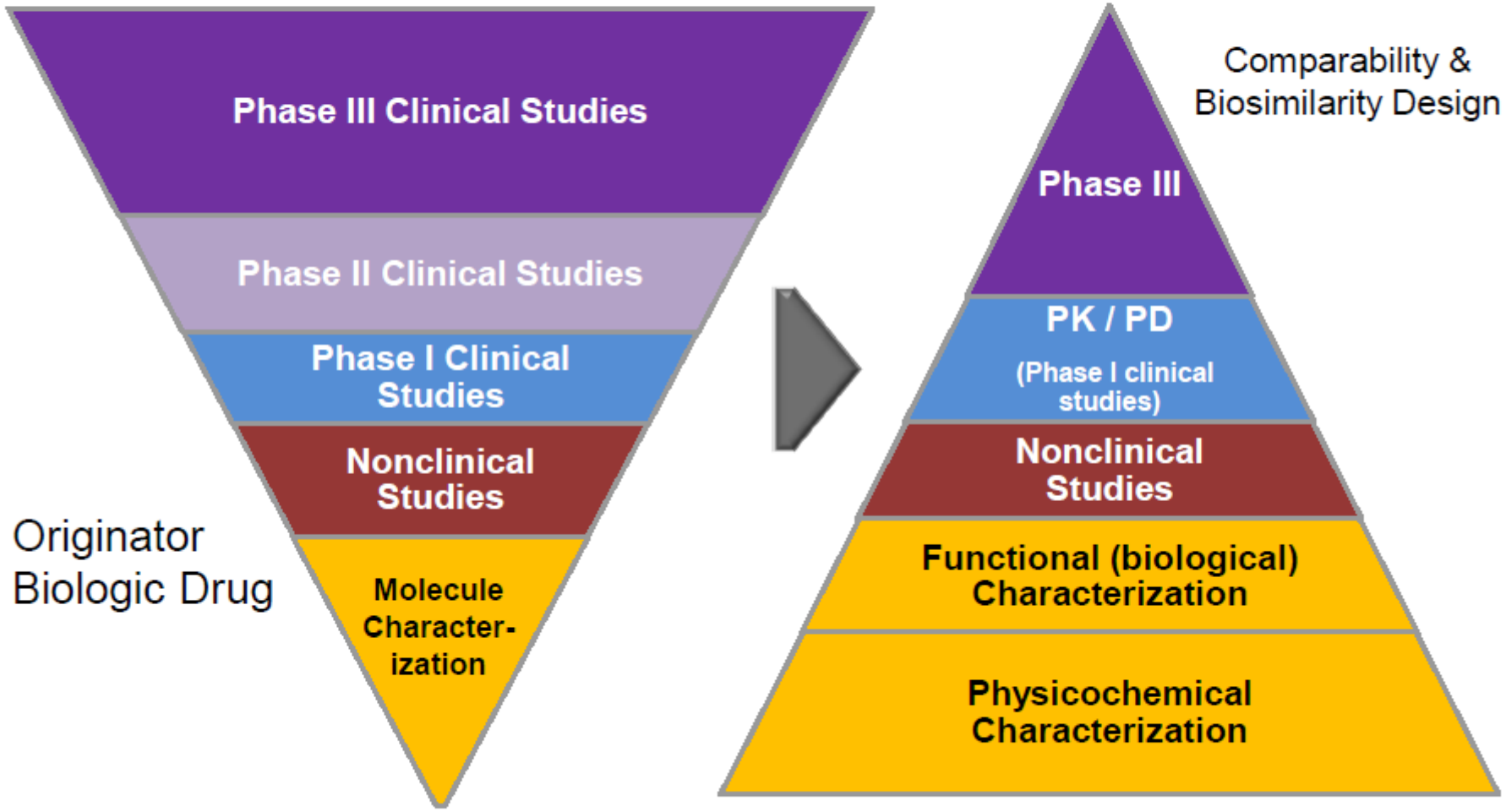
Most monoclonal Antibodies: Loss of efficacy & Hypersensitivity reactions

G-CSF or FSH isolated cases; limited effect on safety
Insulin, no clinical consequences

Universiteit Utrecht

Purcell J Investig Allergol Clin Immunol 2008; Vol. 18(5): 335-342
Abraham I Expert Opin. Drug Saf. (2013) 12(2):235-246

Totality of scientific evidence to characterize the biologic biosimilar antibody



Three generations of biosimilars

1st generation:

- Substitution products; immediate effect
- Epoetin, growth hormone, filgastrin, insulin

2nd generation:

- Short to intermediate effect ;distinct pharmacological effect, visible in weeks, but not in every patient
- TNF-alfa antagonist in reumatoid arthritis and inflammatory bowel disease

3rd generation:

- Remote clinical effect, longterm (oncology)
- -bevacizumab, trastuzumab

- 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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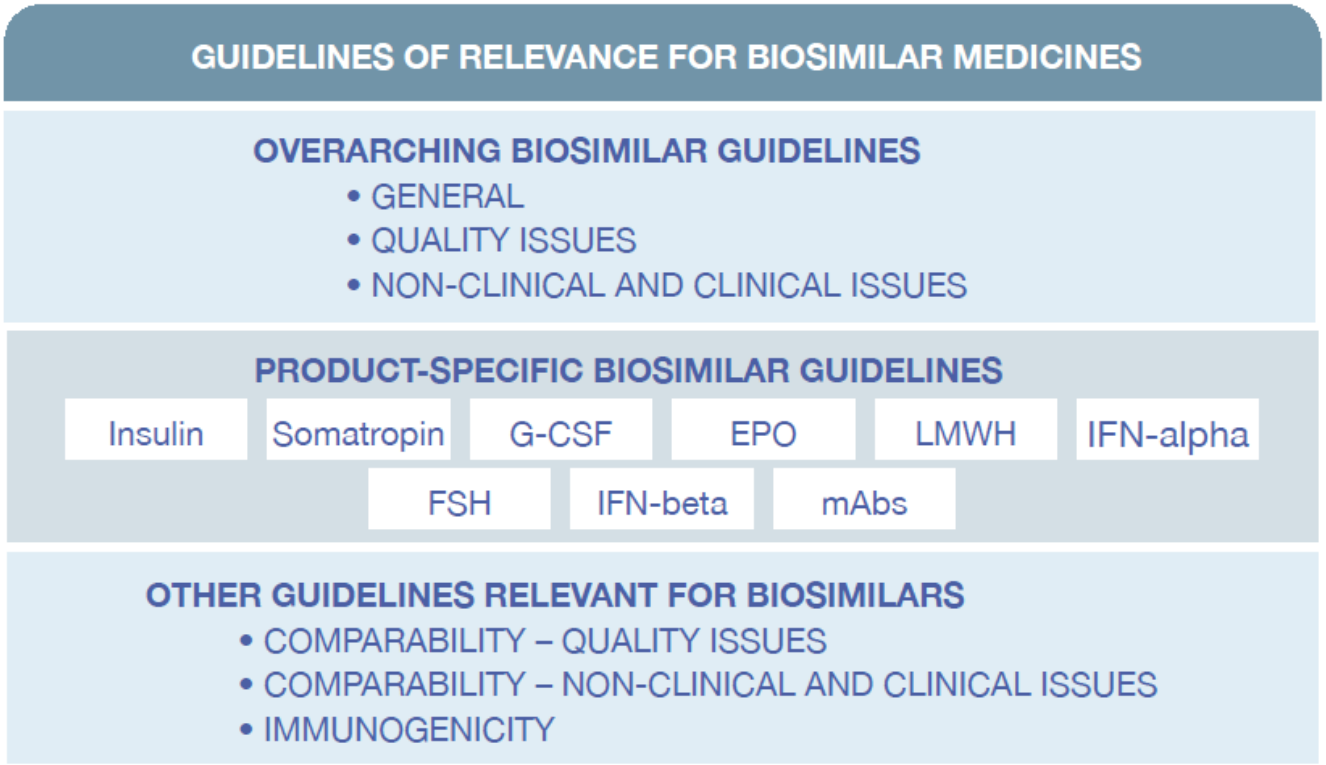
EMA biosimilar guidelines (2005-2015)



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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

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- 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/not advised for biologicals including biosimilars (Austria, Belgium, Ireland, Norway, Slovakia, Sweden, Greece

Terminology

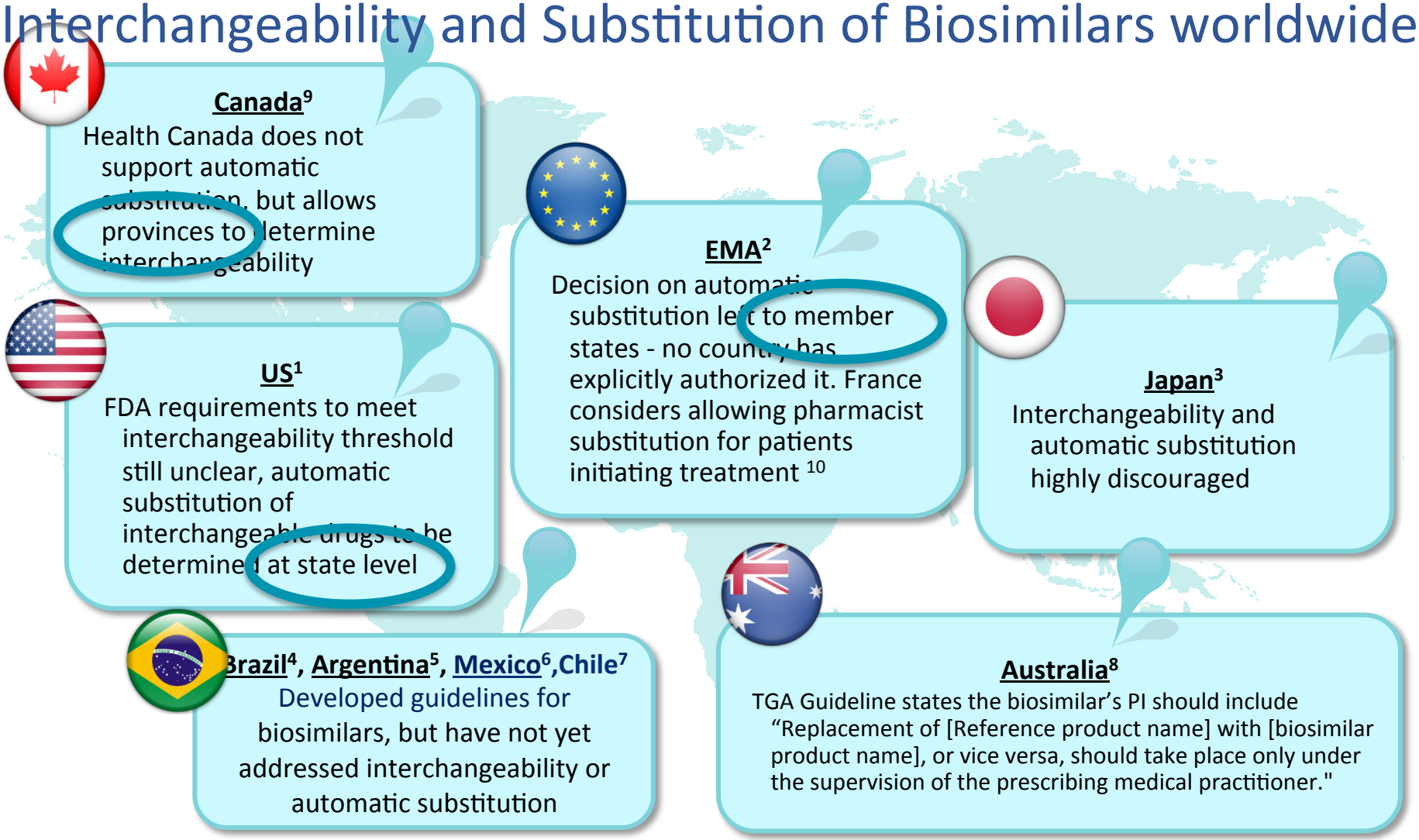
- **Switching**: Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.

- **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.

- Consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products. European Commission

Interchangeability and Substitution of Biosimilars worldwide



1: FDA Biosimilar Guidance Webinar, February 15, 2012; 2: EMA, Questions and Answers on biosimilar medicines; European Biopharmaceutical Enterprises (EBE) Survey on Biosimilars, May 2011; 3: MHLW Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products, March 2009 ; 4: ANVISA: Resolucao RDC N° 55, de 16 de Deem bro de 2010; Diario Oficial da Uniao-Secao 1; N° 241; 5: ANMAT, Disposición N° 7729/2011 (publicado el 21 de Noviembre de 2011); 6: Proyecto de PROY-NOM-257-SSA1-2013; 7.*Norma Técnica Nº 170 Sobre Registro Sanitario de Productos Biotecnológicos Derivados de Técnicas ADN Recombinantes; Diario Oficial de la República de Chile, 6 de Septiembre de 2014*)8: TGA Biosimilar Guidance; 30 July 2013; 9:; Health Canada Interchangeability and Substitutability of Subsequent Entry Biologics, July 2010 http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/seb-pbu/01-2010-seb-pbu-qa-qr-eng.php#q15 10: GaBiOnline.net France to allow biosimilars substitution Accessed 2/24/2014 http://www.gabionline.net/Policies-Legislation/France-to-allow-biosimilars-substitution

- 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.

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

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.

Use of biosimilars

- **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)

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

Federation of Medical Specialists

- Biosimilars are as efficacious and safe as the innovator product

New patients

- For new patients the most cost-effective (biosimilar) product is preferred
- Traceability needs to be guaranteed

Switching

- Switching should be avoided in well-responding patients
- Switching should only occur under well-controlled circumstances, e.g. as part of a scientific study. Besides regular pharmacovigilance, efficacy should should be monitored, according to guidelines for the therapeutic area.
- An adequate monitoring system should be in place

Dutch Society for Rheumatology

- Previously (2014): Switching in well-responding patients should be avoided.
- Revised view (end of 2015): Switching is possible if:
  - There are no signals related to a negative impact on efficacy and safety
  - Patient has been informed
  - Efficacy and safety is monitored
  - In case of diminished efficacy or safety issues the patient must be offered to switch back
  - Traceability is important
  - Frequent switching is not recommended

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.

Top-10 biologicals Nederland naar omzet (2013 bron NZA)

	biological	Kosten (M€)	Exp jaar	biosimilar
1	Adalimumab	208	2018	2018 ?
2	Etanercept	156	2015	2016
3	Infliximab	143	2015	**2015**
4	Trastuzumab	73	2014	2017 ?
5	Rituximab	60	2013	2017 ?
6	Alglucosidase	51	2014(?)	??
7	Somatropine	48	2005	**2006**
8	bevacizumab	42	2018/2022	??
9	Ustekinumab	21	2024	> 2024
10	eculizumab	20	2020 (?)	> 2020

Biosimilar growth hormone

- 2006 EMA approved somatropin biosimilar: omnitrope; referenceproduct genotropin (1995)

- adopted according EMA product specific guideline:
  - clinical comparability efficacy study: a randomized, double-blind, parallel group clinical trial in the most sensitive model: prepubertal children with GHD
  - Clinical safety: comparative 12-month immunogenicity data
  - pharmacovigilance post-approval data (PATRO)

- Therapeutic indications : 1.growth disturbances in children
  - GHD
  - Chronic renal insufficiency
  - Small for gestational age (SGA)
  - Turner syndrome
  - Prader-Willi
  - (SHOX) 2. adult patients with pronounced GHD

P2-413

Results up to 3 years from PATRO Children, a multi-centre, non-interventional study of the long-term safety and efficacy of Omnitrope® in children requiring growth hormone treatment

Pfäffle R,[1] Kanumakala S,[2] Höybye C,[3] Kriström B,[4] Schuck E,[5] Zabransky M,[5] Battelino T,[6] Colle M[7]

[1]Department of Paediatric Endocrinology, University of Leipzig Medical School, Leipzig, Germany; [2]Department of Paediatrics, Royal Alexandra Children's Hospital, Brighton, UK; [3]Department of Endocrinology, Metabolism and Diabetology, Karolinska University Hospital, Stockholm, Sweden; [4]Department of Clinical Science/Paediatrics, Umeå University, Umeå, Sweden; [5]Sandoz International GmbH, Holzkirchen, Germany; [6]Department of Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, Ljubljana, Slovenia; [7]25 rue Boudet, Bordeaux, France

ESPE Barcelona 2015 (abstract P-2-413)

Table 1. Patient characteristics at baseline

Indication	Total (n)	Male/female (n)	Naïve/ pre-treated[a] (n)	Mean age, years (SD)	Mean BMI (SD)	Mean HSDS (SD)	Mean HV, cm year (SD)	Mean HVSDS (PC)
GHD	2511	1676/835	2056/434	9.9 (3.8)	17.0 (3.3)	−2.3 (1.1)	4.1 (2.2)	−2.1 (3.2)
SGA	1127	581/546	912/191	8.2 (3.4)	15.4 (2.4)	−2.7 (1.1)	4.3 (2.1)	−2.0 (2.8)
TS	199	0/199	146/48	9.4 (4.3)	18.2 (3.7)	−2.7 (1.2)	3.8 (2.2)	−1.8 (2.9)
PWS	141	67/74	112/25	4.2 (4.3)	18.1 (4.1)	−1.3 (1.5)	7.6 (4.2)	−2.0 (3.2)
CRI	32	19/13	27/3	6.9 (4.5)	16.5 (3.3)	−2.8 (1.3)	3.6 (2.6)	−5.4 (2.6)
ISS	47	34/13	24/23	10.1 (3.6)	17.4 (2.4)	−1.8 (1.1)	4.9 (3.8)	−0.8 (5.3)
Other	291	178/113	238/51	9.8 (3.7)	16.6 (3.0)	−2.6 (1.3)	4.0 (2.4)	−2.6 (3.0)
Unknown	49	31/18	8/0	9.2 (3.5)	18.1 (2.9)	−2.8 (0.4)	2.9 (0.7)	−4.3 (2.4)
Total	4397	2586/1811	3523/775	9.2 (3.9)	16.6 (3.2)	−2.4 (1.1)	4.2 (2.4)	−2.1 (3.1)

[a]Pre-treatment information was unavailable for 99 patients; BMI, body mass index; CRI, chronic renal insufficiency; GHD, growth hormone deficiency; HV, height velocity; HSDS, height standard deviation score; ISS, idiopathic short stature; PWS, Prader-Willi syndrome; SD, standard deviation; HVSDS, HV standard deviation score; SGA, born small for gestational age; TS, Turner syndrome

The PATRO Adults study of Omnitrope® for the treatment of adult patients with growth hormone deficiency: latest results

EP-665

Paolo Beck-Peccoz[1], Charlotte Höybye[2], Robert D. Murray[3], Suat Simsek[4], Alfonso Leal-Cerro[5], Markus Zabransky[6], Günter Stalla[7]

[1]Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Department of Endocrinology, Metabolism and Diabetology, Karolinska University Hospital, Stockholm, Sweden; [3]Department of Endocrinology, Leeds Centre for Diabetes and Endocrinology, St.James's University Hospital, Leeds, UK; [4]Medisch Centrum Alkmaar, The Netherlands; [5]Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío, Seville, Spain; [6]Sandoz International GmbH, Holzkirchen, Germany; [7]Max Planck Institute of Psychiatry, Department of Internal Medicine, Endocrinology and Clinical Chemistry, Munich, Germany

Table 2. Patient characteristics at enrollment

Variable	Isolated GHD	Combined GHD	Other	N/A
Gender				
Male, n (%)	44 (5.1)	396 (46.3)	3 (0.4)	8 (0.9)
Female, n (%)	53 (6.2)	343 (40.1)	4 (0.5)	4 (0.5)
Total (%)	97 (11.3)	739 (86.4)	7 (0.8)	12 (1.4)
Mean (SD) age, years	45.8 (15.8)	51.0 (15.1)	34.7 (13.2)	42.4 (16.2)
Mean (SD) BMI, kg/m²	30.2 (7.5)	29.5 (6.2)	26.3 (5.5)	39.0 (n/a)

Table 3. Summary of AEs

	No. of subjects (%) n=855	No. of AEs
Any AE	363 (42.5)	1179
Relationship to study drug		
Not suspected	335 (39.2)	1062
Suspected	66 (7.7)	107
Missing	5 (0.6)	10
Intensity		
Mild	293 (34.3)	784
Moderate	154 (18.0)	295
Severe	36 (4.2)	61
Missing	18 (2.1)	39
Outcome		
Resolved completely	187 (21.9)	381
Resolved with sequelae	47 (5.5)	68
Ongoing	264 (30.9)	688
Fatal	3 (0.4)	3
Missing	24 (2.8)	39
Changes to Omnitrope® treatment		
Not changed	318 (37.2)	985
Increased	19 (2.2)	28
Reduced	46 (5.4)	71
Interrupted	28 (3.3)	51
Permanently discontinued	21 (2.5)	34
Missing	7 (0.8)	10
Serious AEs		
No	343 (40.1)	1063
Yes	68 (8.0)	109
Missing	5 (0.6)	7

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

- 18 patients reported pain at injection site (6 pts switched back)

flodmark et al
Biol Ther 2013

Use of Biosimilar growth hormone in clinical practise

- Not only the growth hormone itself matters but also:

- Delivery system
  - device (pen system, needle free device)
  - storage conditions (outside refrigerator)
  -

- Supportive package by manufacturer (education)

- Patient choice important (adherence tot therapy)

- Doctor and patient (parents) in the lead

- Impact of biosimilar competiton on price

The impact of biosimilar competition

- Competition drives down the price, not only the direct comparable drug but also the whole product class
- The correlation between biosimilars market share and price reduction is weak
- Competition can also influence the originator's behaviour
- Lower prices has the most impact on usage (patient access) in countries with low initial usage

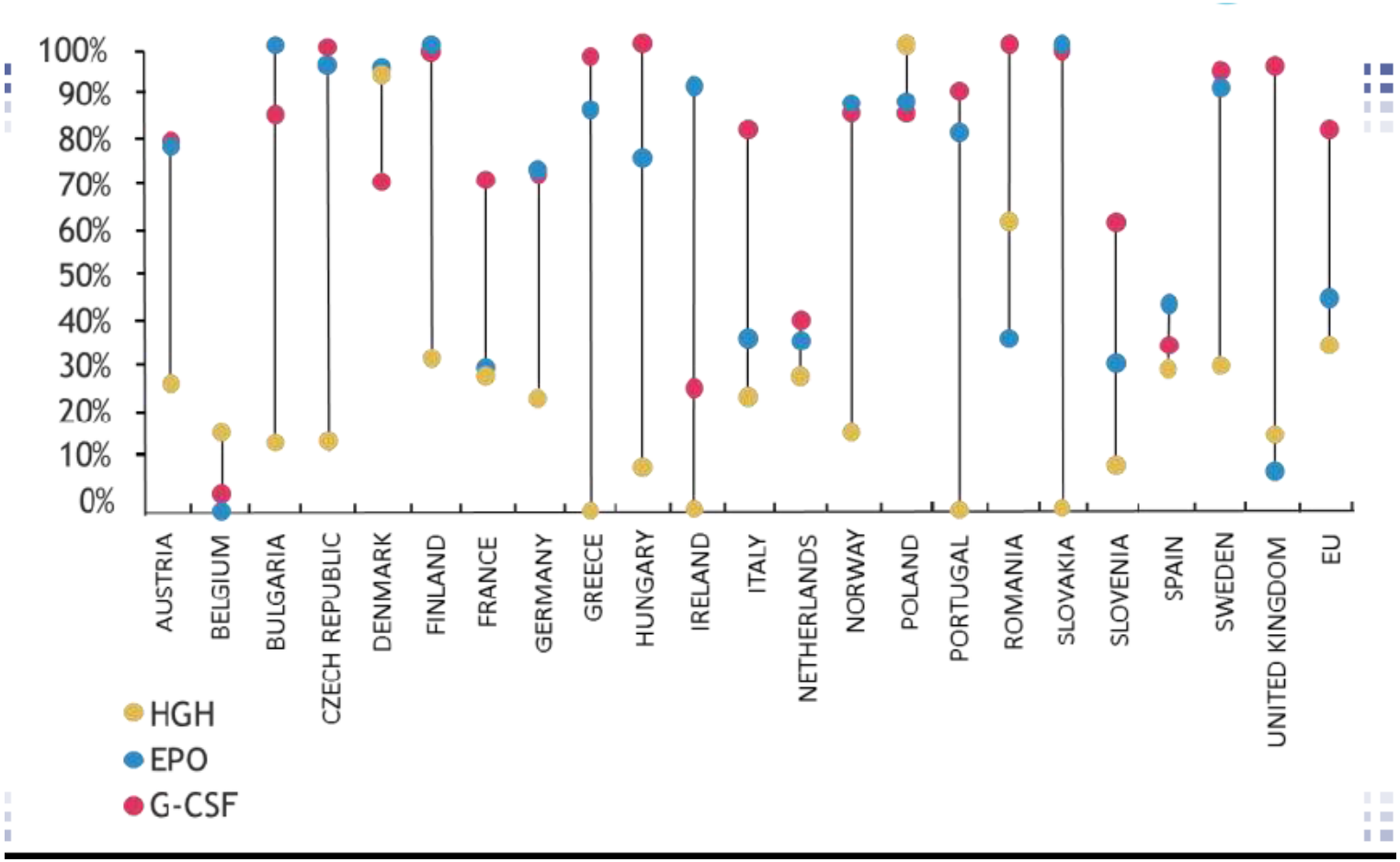
Table 1

	Price per TD (2014/Year before biosimilar entrance)		
	Biosimilar and Reference product	Accessible market	Total market
EPO	-28%	-33%	-27%
G-CSF	-19%	-10%	-28%
GH	-7%	-7%	-13%

Table 2

	Price per TD (2014/Year before biosimilar entrance)
	Total Market
Epoetins	
Slovakia	-61%
Portugal	-51%
Bulgaria	-51%
HGH	
Bulgaria	-72%
Slovakia	-71%
Romania	-59%
G-CSF	
Finland	-49%
Slovenia	-48%
Slovakia	-39%

Biosimilar penetration EU market 2014



Volume share of omnitrope counting units at end 2015 is 18%, norditropin/zomacton/genotropin: each about 25 %

Regulatory requirements for biosimilar insulins

- Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (2014)

- non-clinical: pharmacotoxicological and in vitro PD studies, in vitro affinity assays for insulin and IGF1 receptor binding

- Clinical:
  - 1.PK/PD cross-over glucose clamp studies in healthy volunteers and patients with type 1 diabetes.
  - 2.no clinical efficacy studies needed (HbA1c is not sensitive enough for the purpose of showing biosimilarity of two insulins
  - 3. clinical safety study: safety ,immunogenicity in type 1 and 2 DM (12 month duration
  - 4. RMP: post-approval pharmacovigilance plan (detection potential rare adverse events

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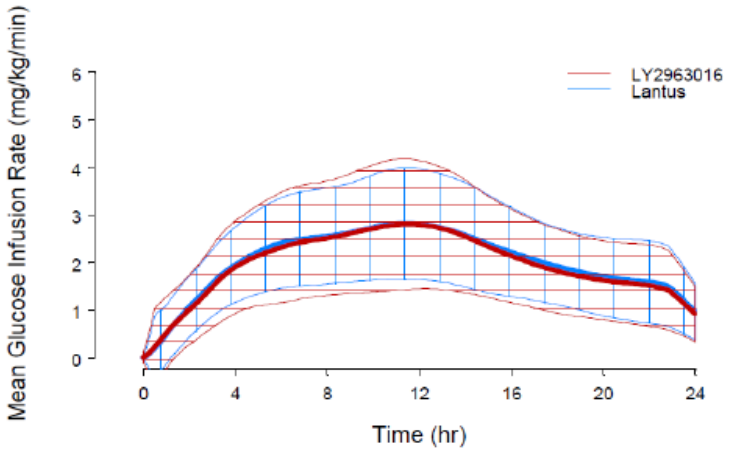
Biosimilar insulin

- 2014: insulin glargin: abasaglar
- PK/PD equivalence in 5 glucose-clamp studies in healthy volunteers and type 1 patients



- 2 safety clinical studies (ABEB (type 1 n= 536, ABEC (type 2 n= 759):
  - Safety profile lantus and abasaglar comparable: AEs, hypoglycaemic events, allergic or injection site reactions
  - No difference in antibody levels between lantus and abasaglar; no relation between antiobodies and efficacy or safety

Biosimilar insulin: clinical aspects

- No relevant differences in quality, efficacy and safety (short term) between Lantus and Abasaglar

- The role Insulin delivery device: insulin pen (prefilled, re-usable)
  - Difference between insulin pen systems (convenience features)
  - Patient preference for given type of pen
  - Each company has its own system: interchangeability
  - Patient-nurse- doctor

- Interchangeability between Lantus and Abasaglar
  - Switching: new patients, stable patients, repeated switching
  - Substitution: pharmacy level, role of insurance companies (preference policy

- What is the incentive for doctor and patient?

- NDF stance 01-12-2015

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 lead to reduced costs for the healthcare system, increased patient access to treatment, increased range of treatment options, choice of delivery systems and patient support programs
- Biosimilars are a natural part of the life-cycle of a biological drug