Making Medicines Affordable

SUCCESS STORY of the EU Biosimilars Framework and Information Challenge

Bratislava, 3 June 2013

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Outlines

- **Communalities/differences-generics/biosimilars**
- **EU biosimilars framework**
- **Information challenge**
  - Terminology
  - «Misleading *mantra*: similar but not identical»
  - Extrapolation of indications-Biosimilarity
  - Immunogenicity
  - Pharmacovigilance; identification in case of ADRs
  - EU consensus definitions: interchange, substitution
  - Further reading list

Communalities/Differences-Generics/Biosimilars

Communalities Generics-Biosimilars

- **Both generics and biosimilars can only be authorised for use once the data exclusivity of the originator reference product has expired**
  - No patent linkage in the EU
- **Both generics and biosimilars can only be marketed once the respective patents of the originator product have expired**
  - They are off patent medicines

What is a Generic Medicine?
What is a Biosimilar Medicine?

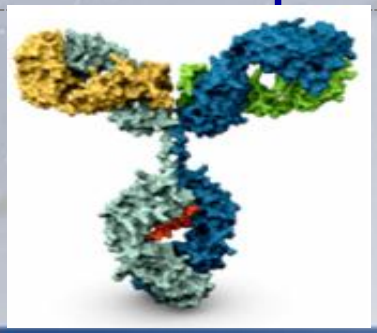
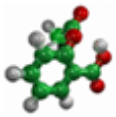
Directive 2001/83/EC (as amended)

- **Definition (Art. 10(2a))**: *"Generic medicinal product shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicine, …(…)"*

- **Legal basis for biosimilar applications (Art. 10(4))**

"Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided……(…)"

Differences Biosimilars-Generics

	Biosimilar Medicine	Generic Medicine
Nature	•Biological product made by or derived from a biological source •Complex molecule •Essentially the same biological substance as reference product	•Chemical product made by chemical synthesis •Small molecule •Same chemical active substance as reference product
Manufacture	• Costs: EUR 100-250 M • Development time: 7-8	•Costs: EUR 2-5 M •Development time: 2-4 years
Example	 *Monoclonal antibody (IgG)* *~25,000 atoms* *Molecular weight:* *150 000 Daltons* *1300 amino acids*	 *acetylsalicylic acid* *21 atoms* *Molecular weight:* *180 Daltons* *0 amino acids*

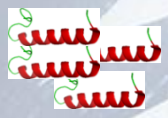
- Biologicals: Spectrum of Complexity
- Only Living Organisms are able to Reproduce such Complexity

Bacteria, Yeast → **Mammalian**

Peptide —

protein — Protein

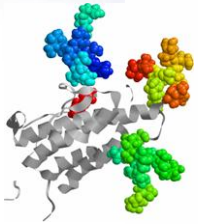
protein — Glycoprotein



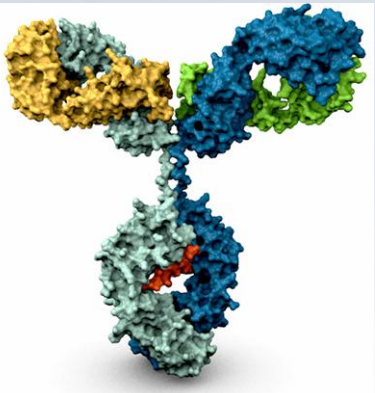
Calcitonin,
~3.5 kDa

filgrastim
~19 kDa

somatropin
~22 kDa



epoetin
~30 kDa

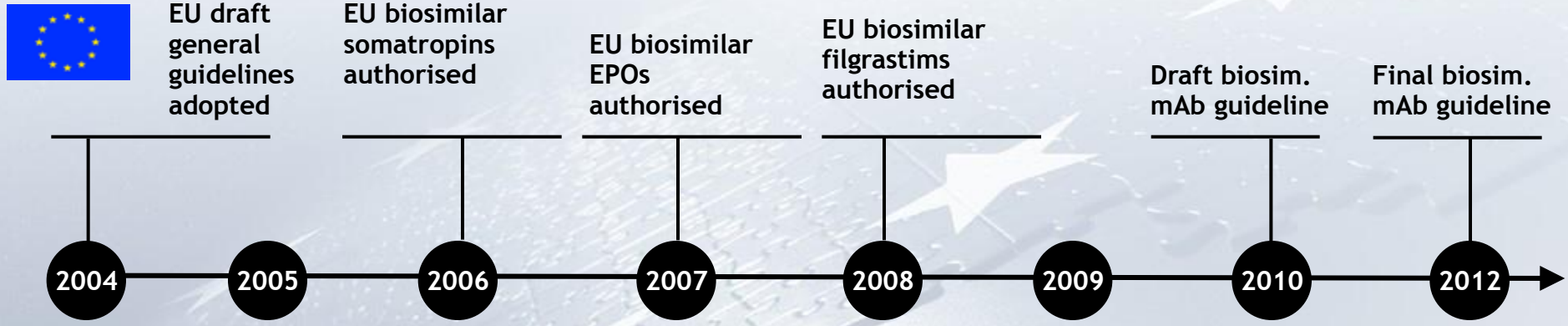


Monoclonal
Antibody,
~150 kDa

7

EU Biosimilars Framework

EU Biosimilars Scientific & Regulatory Framework Inspiring the World



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Guidelines for biosimilars

EMA slide as presented at EGA Biosimilars Conference April 2013

Overarching Guidelines:

Defines principles

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

Under Rev

General Guidelines on Q/S/E

Overarching non-clinical/clinical Guideline

Under Rev

Overarching Quality Guideline

Draft Rev

Class-specific Guidelines: non-clinical/clinical aspects

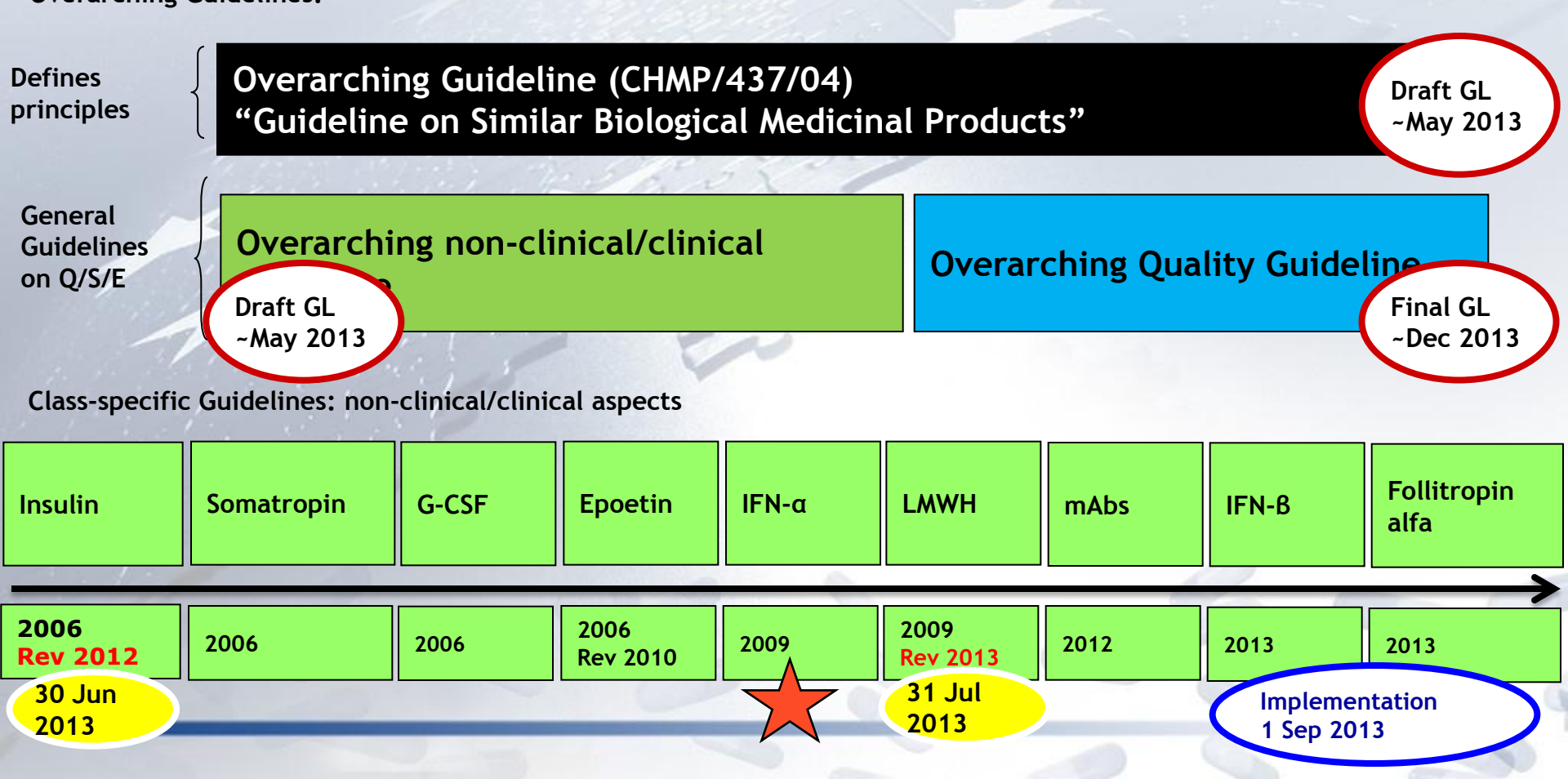
Insulin	Somatropin	G-CSF	Epoetin	IFN-α	LMWH	mAbs	IFN-β	Follitropin alfa
2006 Rev 2012	2006	2006	2006 Rev 2010	2009	2009 Rev 2013	2012	2013	2013

Public C.

Public C.

Guidelines for biosimilars

EMA slide as presented at EGA Biosimilars Conference April 2013



For updates: visit EMA Website

How Come that this Framework Became Possible?

- **Science and technology have evolved tremendously:** proteins can be well characterized (at least up to the complexity of monoclonal antibodies), which makes the comparability exercise possible
- "*Regulatory authorities have reviewed literally hundreds of applications where comparability data have been submitted. Thus, the **regulators are very experienced in assessing comparability**, probably more so than anyone else*". (Topra interview with Dr. Pekka Kurki, first Chair of the Biosimilar Medicinal Products Working Party, 2006)
- "*The **scientific principles** underlying the comparability exercise required for changes in the manufacturing process of a given biological product and for the development of a biosimilar product are the **same***" (Weise et al in Biosimilars-why terminology matters, Nature Biotechnology,2011; see also revised draft over-arching guideline)

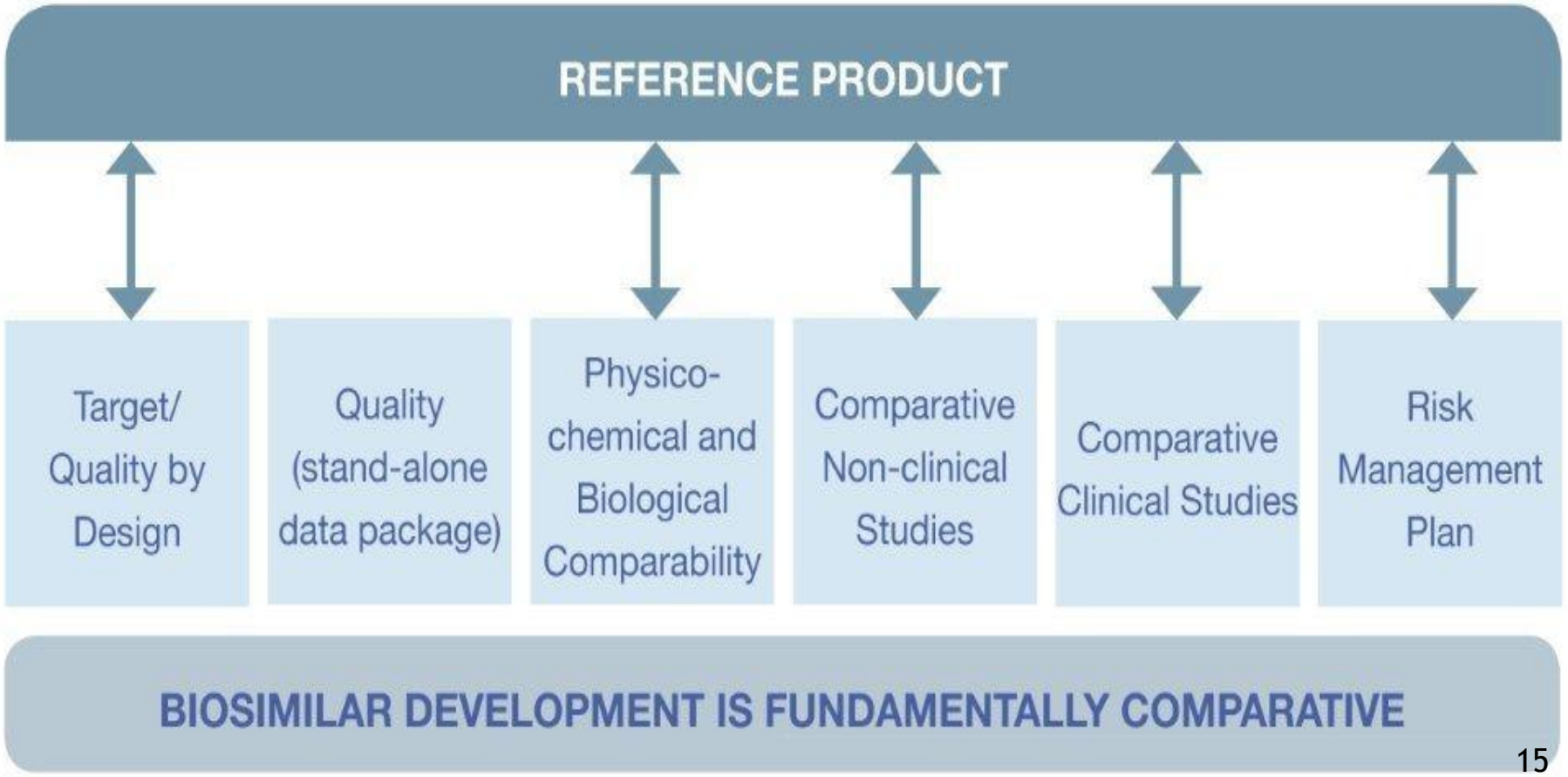
Comparability and Biosimilarity

- **Comparability of biotechnology-derived medicinal products after a change in the manufacturing process**
- ICH Q5E (2003)

"The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any difference s in quality attributes have no adverse impact upon safety or efficacy of the drug product"

- This is called "comparability exercise"

Comparability Exercise: Cornerstone of Biosimilar Development



Example of an Biosimilar Filgrastim: Highly Similar to Reference Product

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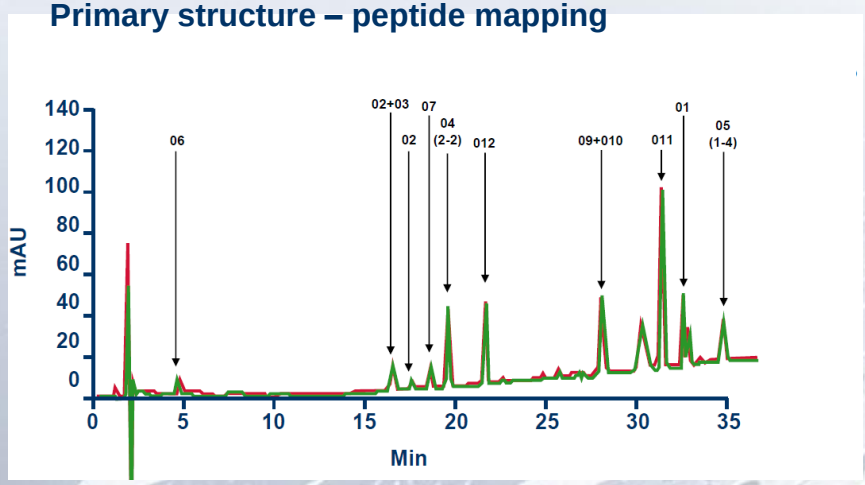
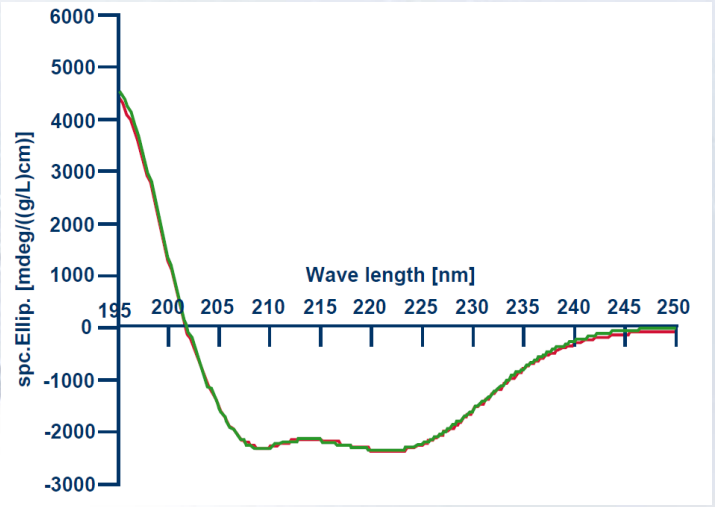
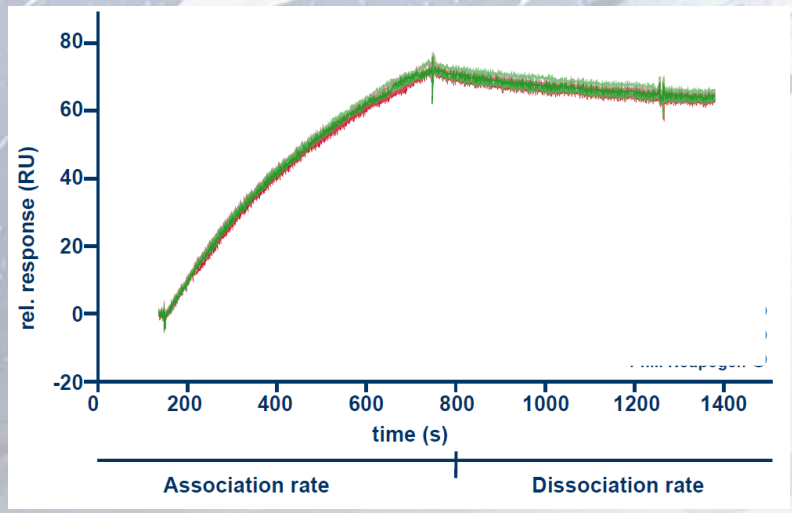
Primary structure – peptide mapping



Higher order structure – UV CD spectroscopy



Bioactivity – Surface plasmon resonance spectroscopy

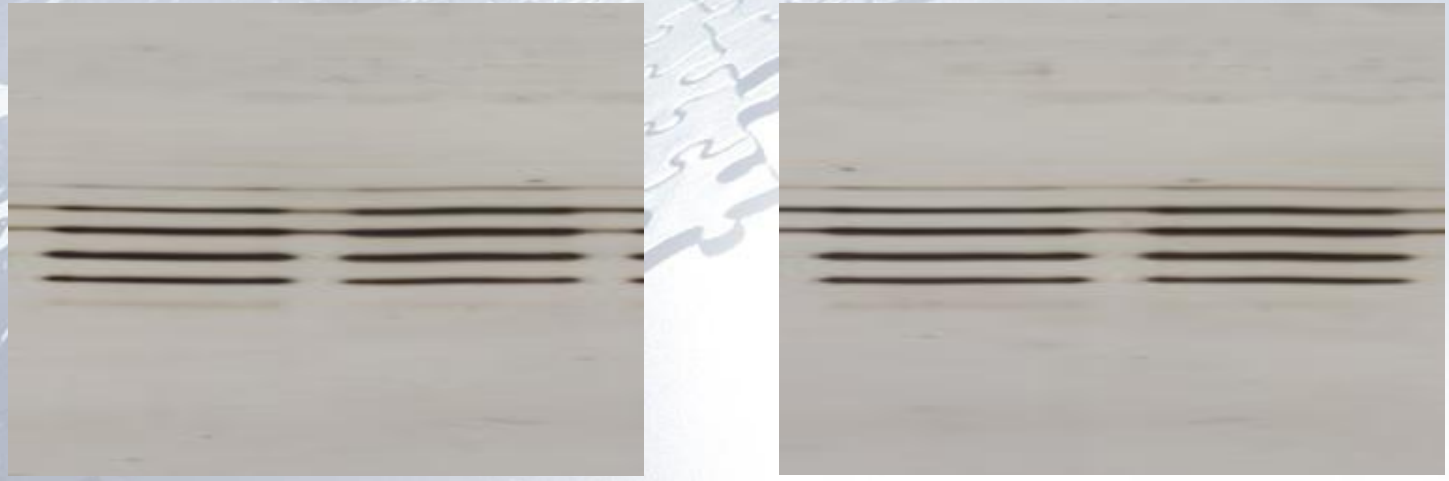


Comparability performed for EU Biosimilar application shows highly similar results with state of the art methods

Approved EU Biosimilar: Biosimilar and Reference Product Super Imposable Results

Gel A **Gel B**

Comparison of isoform pattern for epoetin alfa by isoelectric focusing gel electrophoresis



Sample

1(biosimilar) 2(reference) 3(biosimilar) 4(reference)

Brockmeyer C & Seidl A et al. *Eur J Hosp Pharm Pract* 2009;15:34-40

Information Challenge

- Terminology
- «Misleading *mantra*: similar but not identical»
- Extrapolation of indications-Biosimilarity
- Immunogenicity
- Pharmacovigilance; identification in case of ADRs
- Continued education

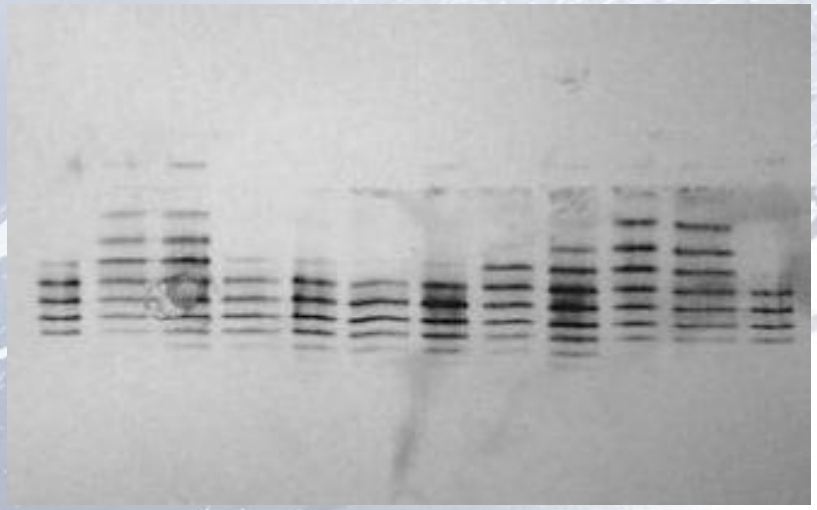
Terminology is important

- Inconsistency in nomenclature for biosimilars has caused confusion
- The term ‘biosimilar’ is often used as a blanket statement and used for poor quality of some non-comparable follow-biologicals not approved in the EU
  - Leading to fears about safety and efficacy of EU biosimilars
- “Biosimilar” is a regulatory term and stands for a biological product which has demonstrated high similarity with a reference product based on a comprehensive comparability exercise

Non-EU
Non-Comparable Follow-on Biologicals
“Bio-questionables”

Isoelectric focusing gels

Non-comparable follow-on biologicals



Sample E IA IB IIA IIB IIIA IIIB IV V VII VIII E

They should not be named «biosimilars»

Schellekens H *et al*. *Eur J Hosp Pharm Pract* 2004;3:43–7

Official Journal of the
GENERICS AND BIOSIMILARS INITIATIVE
GaBi Journal
Building trust in cost-effective treatments

PERSPECTIVE

Biosimilars Educational Series

GaBiJournal
Generics and Biosimilars Initiative Journal

Terminology for biosimilars–a confusing minefield

Robin Thorpe, PhD, FRCPath; Meenu Wadhwa, PhD

Biosimilars are firmly established in the EU as copy biologicals with a clear and effective regulatory route for approval. Unfortunately, inconsistency in nomenclature for biosimilars has caused confusion. This problem of terminology has been the subject of a recent publication. The confusion is not just a potential concern for patient safety and efficacy, but also can lead to misconceptions in published reports. Several examples of this have occurred, some of which are discussed below. The definitions provided should be adopted for clarity in the future.

Keywords: Comparability, efficacy, guidelines, 'non-innovator biologic', quality, safety

Biosimilars are now firmly established in the EU as copy biologicals with a clear and effective regulatory route for approval, which allows marketing of safe and efficacious biological

approach to the EU for approval of biosimilars, e.g. Australia, Canada, Japan. In addition, the World Health Organization (WHO), with the aim of achieving harmony in regulations and increasing access to safe medicines globally

paper also recommends the use of more precise terminology for biosimilars (and non-biosimilars) to attempt to clarify the confusing situation.

The confusion over terminology is not just a potential concern for patient safety and efficacy, but also can lead to misconceptions which arise from misleading published reports on apparent problems with 'biosimilars'. Several examples of this have already occurred, some of which are discussed below.

A case of pure red cell aplasia (PRCA) in an end-stage renal disease patient associated with induction of antibodies to administered erythropoietin (EPO) was described in India [10]. The patient had received the EPO product Wepox (Wockhardt Limited, India) which is referred to as a 'follow-on' product. In the paper the authors state that 'in Europe, follow-on EPOs are also referred to as biosimilar EPOs'. However, there is no evidence that this product has been approved using the comparability approach required in the EU for biosimilarity and described in the WHO and other guidelines. This is in fact unlikely as the Indian regulatory process at that time did not include biosimilars (or follow-on products) and approved non-innovator

Vol 1, (2012) 132-134

Misleading '*Mantra*': «Similar but Non-Identical»

- **No biological can ever be identical to another, not even one batch to the other of the same product (inherent variability)**
- This inherent variability is a scientific fact that has been accepted by the scientific and regulatory community since the introduction of biotech medicines
- Furthermore, all originator biological products have undergone manufacturing changes after initial authorisation

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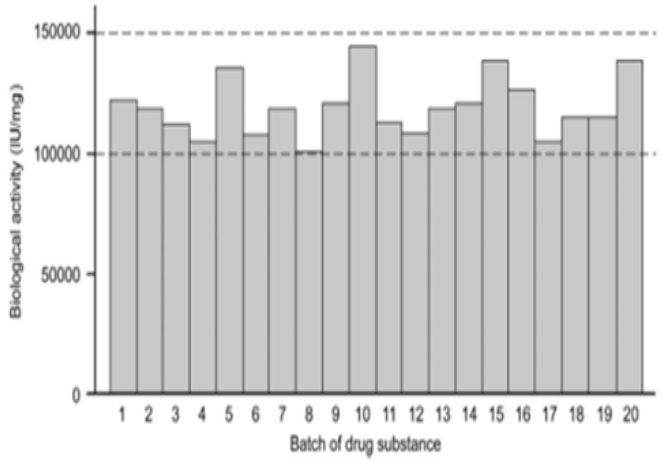
"Similar but not identical"

Biological products always vary

- in the human body
- from batch to batch
- after manufacturing changes
- between manufacturers

- „Non-identicality" is a normal principle in biotechnology.
- No batch of any biological is „identical" to the others



- The „art" is to demonstrate that the biosimilar is as close as possible to its reference product in all relevant functional and structural aspects, within current technical and scientific limitations (inherent variability)

© Christian Schneider

nature biotechnology

Biosimilars—why terminology matters

Martina Weise, Marie-Christine Bielsky, Karen De Smet, Falk Ehmann, Niklas Ekman, Gopalan Narayanan, Hans-Karl Heim, Esa Heinonen, Kowid Ho, Robin Thorpe, Camille Vleminckx, Meenu Wadhwa & Christian K Schneider

Affiliations | Corresponding author

Nature Biotechnology **29**, 690–693 (2011) | doi:10.1038/nbt.1936
Published online 05 August 2011

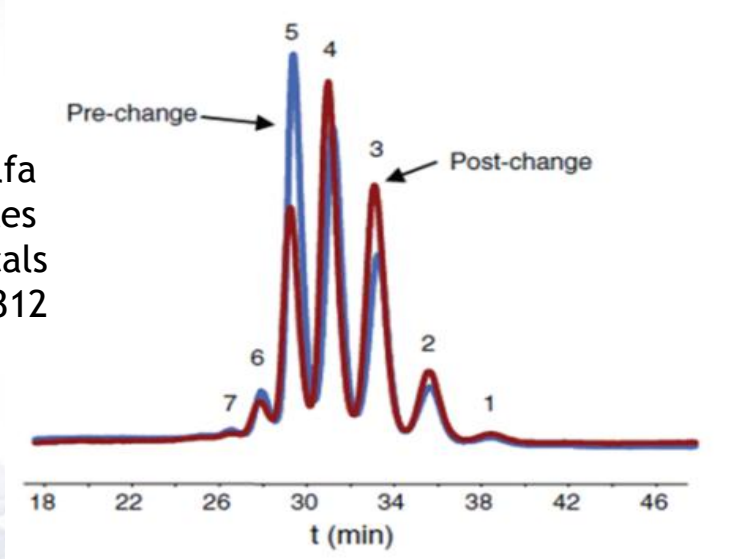
To the Editor:

As members of the Biosimilar Medicinal Products Working Party (BMWP) at the European Medicines Agency (EMA; London), we would like to draw readers' attention to problems arising from imprecise usage of the term biosimilar (similar biological medicinal product) in the literature. We have repeatedly noticed misinterpretations of the biosimilar concept as well as inconsistent use of terminology and are concerned about potential implications of this, such as negative perception and impaired acceptance of biosimilars among prescribing physicians and patients. Here we outline the scientific principles underlying the biosimilar concept in the European Union (EU; Brussels). We also address problems in terminology in the context of global emergence of copy biologicals (including 'true' biosimilars) and 'biobetters', and the potential for unjustified concerns about the efficacy and safety of biosimilars in their stricter sense.

Variability of Reference Product, from Batch to Batch and After Manufacturing Changes

- **Glycoproteins are not single structures, but mixtures of closely related substances**
  - Even for a single manufacturer, these mixtures vary from batch to batch and after manufacturing changes

Example: Darbepoetin alfa
Ref.: Acceptable changes in quality attributes of glycosylated biopharmaceuticals
Schiestl *et al*. Nat. Biotechnol. 2011; 29: 310-312



Microheterogeneity: a «Normal» Feature of Any Biological Medicine

- *…» no batch of any reference product is 'identical' to the previous one-'non-identicality' is a normal feature of biotechnolgy that has to be controlled by tight specifications of critical product attributes, within current technical and scientific limitations (inherent variability).*
- *The 'art' for a biosimilar is to demonstrate that the biosimilar is as close as possible to its reference product in all relevant functional and structural aspects, again within current technical and scientific possibilities and its inherent variability'…*

Schneider K Christian – **Biosimilars in rheumatology: the wind of change**

Annals of the Rheumatic Diseases 2013

Similarity-Same Safety & Efficacy

Revised EMA Questions and Answers on biosimilar medicines
27 September 2012

- *"A biosimilar medicine is a biological medicine that is developed to be similar to an existing biological medicine (the 'reference medicine')…..*
- *The active substance of a biosimilar and its reference medicine is essentially the same biological substance, though there may be minor differences due to their complex nature and production methods. Like the reference medicine, the biosimilar has a degree of natural variability. When approved, its variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness."…….*

Extrapolation of Indications-Biosimilarity

- The primary purpose of biosimilar development is not to re-establish safety and efficacy of a known biological substance (this has been done for the reference product before);
- The aim of a biosimilar development is to establish biosimilarity and proving biosimilarity is different than proving efficacy *de-novo*

Proving Efficacy of New Product versus Clinical Biosimilarity

- Proving efficacy of a new medicine requires testing in each indication sought in 'real life' patient populations
- Clinical study performed with the biosimilar is to confirm biosimilarity with the reference product
  - *«The clinical study is selected to represent the most sensitive model to study differences*
  - *Thus, trial design might be (entirely) different from the normal guideline principles!»*
    - Dr. Med. Christian Schneider; What are biological medicinal products and biosimilars – an introduction; Meeting of the Project group on Access and Uptake of Biosimilars; Copenhagen 18 April 2012

All Approved Indications are Based on Science

- Every indication granted for licensed biosimilars has been 'actively' granted based on data or solid scientific justification (i.e. has not been granted automatically)
- *"Every word in the Summary of Product Characteristics (SmPC) that informs the prescriber has been assessed and approved including the indications granted for a biosimilar"….*

Schneider K Christian – Biosimilars in rheumatology: the wind of change
Annals of the Rheumatic Diseases 2013

Immunogenicity

- A concern for all biolgicals
- Usually cannot be predicted from analytical or non-clinical comparison alone
  - therefore immunogenicity data requested pre-approval
- Applicable to all biologicals: *"When filing a Marketing Authorisation Application, it is recommended that applicants present an integrated summary of their strategy on risk identification, characterisation, monitoring, minimization and mitigation"*

Pharmacovigilance (PV)
Same for all Biologicals

- EU PV legislation requires that approved name + batch number be of ADR reports

- Importance of brand name (i.e. unique identifier) for all biologicals, including biosimilars
- Necessity to record detailed exposure information (including batch number) for all biopharmaceuticals

"Vermeer study" on Traceability of Biopharmaceuticals in EU and US Spontaneous Reporting Systems

- **Study shows that product identification of biosimilars was well ensured in Europe:**
  - 96.2% across 3 product classes.
  - For epoetins, the product identification was as high as 98/9%.
    - This study was presented in July 2012 at an EMA stakeholder meeting by Sabine Strauss/MEB, Member of the EMA Pharmacovigilance Risk Assessment Committee
    - Study covered the period 2004-2010 i.e. before the new EU PV legislation came into effect

EU Consensus Definitions

Interchange/eability

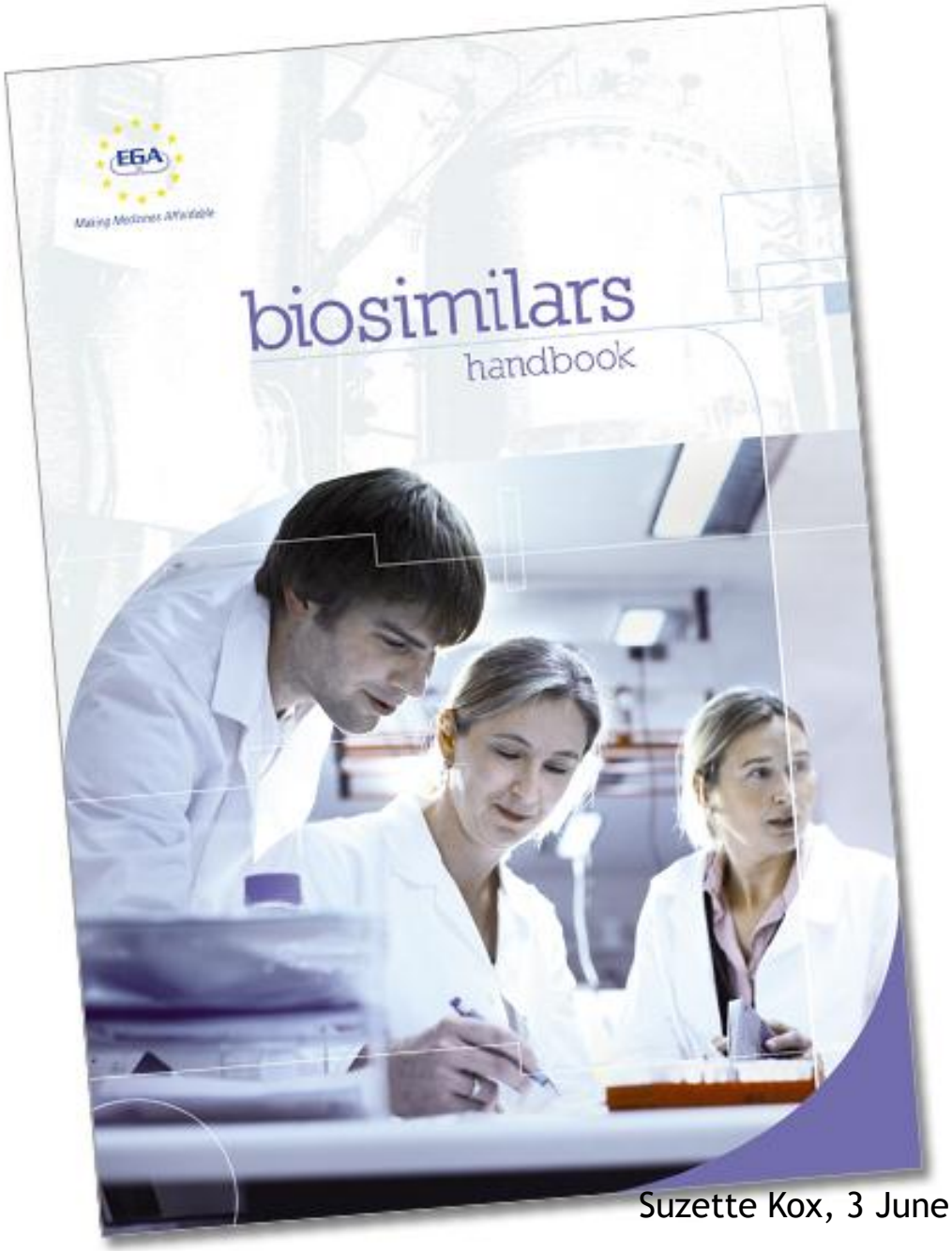
- The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber

Substitution

- practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber

Continued Education of All Stakeholders Needed

- EC-DG Enterprise Project Group on Market Access and Uptake of Biosimilars
  - Consensus information document prepared by all EU key stakeholders **published since 22 April**



2nd Edition of the EGA *BIOSIMILARS HANDBOOK*

EGA
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The EMA Regulatory Guidance for Biosimilars!

- EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications
- Updated March 2013-EMA/940451/201

- It provides an overview of the EMA position on issues, which are typically addressed during the course of Pre-Submission Meetings

Further Reading List

- Weise Martina et al - Biosimilars – why terminology matters, published in Nature Biotechnology, Volume 29, Number 8, Aug. 2011, page 690
- Schneider K Christian et al - Setting the stage for biosimilar monoclonal antibodies, published in Nature Biotechnology, Volume 30, Number 12, December 2012; 1179-85
- Schneider K Christian et al - In support of the European Union biosimilar framework, published in Nature Biotechnology, Volume 30, Number 8, August 2012
- Thorpe Robin and Wadhwa Meenu - Terminology for biosimilars-a confusing minefield, published in Generics and Biosimilars Initiative (GABI) Journal, Volume 1, 2012, Issue 3-4
- Weise Martina et al - **Biosimilars: what clinicians should know**
  pre-published online in blood, October 23, 2012, doi:10.1182/blood- 2012-04-425744
- Schneider K Christian – **Biosimilars in rheumatology: the wind of change**
  Annals of the Rheumatic Diseases 2013; 72:315-318

Concluding Message

- ..»*Regulators evaluate biosimilars cautiously, and a biosimilar is only registered if the applicant has demonstrated in sufficient detail that the biosimilar is of good quality and equivalent in efficacy and safety to its reference medicinal product. Authorised biosimilars are as good, safe and efficacious as originator biologicals.*»

  Schneider K Christian - Biosimilars in rheumatology: the wind of change
  Annals of the Rheumatic Diseases 2013

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Thank you

Acronyms

- ADR-Adverse Drug Reaction
- EMA-European Medicines Agency
- EPAR-European Public Assessment Report
- EU-European Union
- PV- pharmacovigilance
- SmPC-Summary of Product Characteristics

Life in the Red Zone
Annual Deficit by Country

Life in the Red Zone

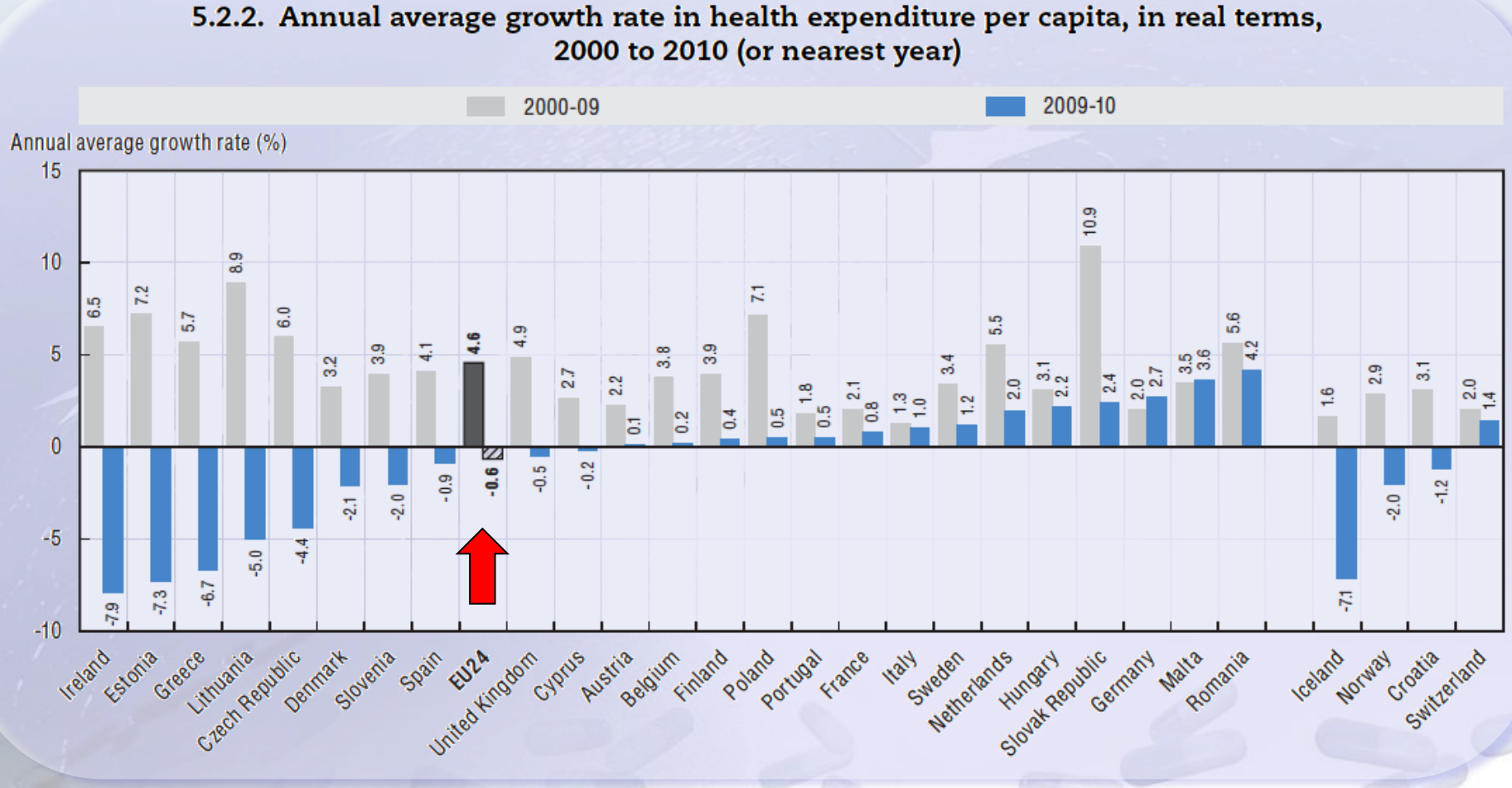
Euro-zone governments have increasingly broken their self-imposed limit of annual budget deficits of no more than 3% of gross domestic product.

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011 estimate
Euro area	-1.5	-0.1	-2.0	-2.7	-3.1	-2.9	-2.5	-1.4	-0.7	-2.1	-6.4	-6.2	-4.1
Austria	-2.3	-1.7	0	-0.7	-1.5	-4.4	-1.7	-1.5	-0.9	-0.9	-4.1	-4.4	-3.4
Belgium	-0.6	0	0.4	-0.1	-0.1	-0.3	-2.7	0.1	-0.3	-1.3	-5.8	-4.1	-3.6
Cyprus	-4.3	-2.3	-2.2	-4.4	-6.6	-4.1	-2.4	-1.2	3.5	0.9	-6.1	-5.3	-6.7
Estonia	-3.5	-0.2	-0.1	0.3	1.7	1.6	1.6	2.5	2.4	-2.9	-2.0	0.2	0.8
Finland	1.6	6.8	5.0	4.0	2.4	2.3	2.7	4.0	5.3	4.3	-2.5	-2.5	-1.0
France	-1.8	-1.5	-1.6	-3.3	-4.1	-3.6	-2.9	-2.3	-2.7	-3.3	-7.5	-7.1	-5.8
Germany	-1.6	1.1	-3.1	-3.8	-4.2	-3.8	-3.3	-1.6	0.2	-0.1	-3.2	-4.3	-1.3
Greece	-3.1	-3.7	-4.5	-4.8	-5.7	-7.6	-5.5	-5.7	-6.5	-9.8	-15.8	-10.6	-8.9
Ireland	2.7	4.7	0.9	-0.4	0.4	1.4	1.7	2.9	0.1	-7.3	-14.2	-31.3	-10.3
Italy	-2.0	-0.8	-3.1	-3.1	-3.6	-3.5	-4.4	-3.4	-1.6	-2.7	-5.4	-4.6	-4.0
Luxembourg	3.4	6.0	6.1	2.1	0.5	-1.1	0	1.4	3.7	3.0	-0.9	-1.1	-0.6
Malta	-7.7	-5.8	-6.4	-5.8	-9.2	-4.7	-2.9	-2.8	-2.4	-4.6	-3.7	-3.6	-3.0
Netherlands	0.4	2.0	-0.2	-2.1	-3.1	-1.7	-0.3	0.5	0.2	0.5	-5.6	-5.1	-4.3
Portugal	-2.7	-2.9	-4.3	-2.9	-3.0	-3.4	-5.9	-4.1	-3.1	-3.6	-10.1	-9.8	-5.8
Slovakia	-7.4	-12.3	-6.5	-8.2	-2.8	-2.4	-2.8	-3.2	-1.8	-2.1	-8.0	-7.7	-5.8
Slovenia	-3.0	-3.7	-4.0	-2.4	-2.7	-2.3	-1.5	-1.4	0	-1.9	-6.1	-5.8	-5.7
Spain	-1.2	-0.9	-0.5	-0.2	-0.3	-0.1	1.3	2.4	1.9	-4.5	-11.2	-9.3	-6.6

Note: Data include debt ratios for Greece, Slovenia, Cyprus, Malta, Slovakia and Estonia since 1999, even though they joined the euro zone later.

Source: European Commission

First Time Health Spending has Fallen in Europe since 1975

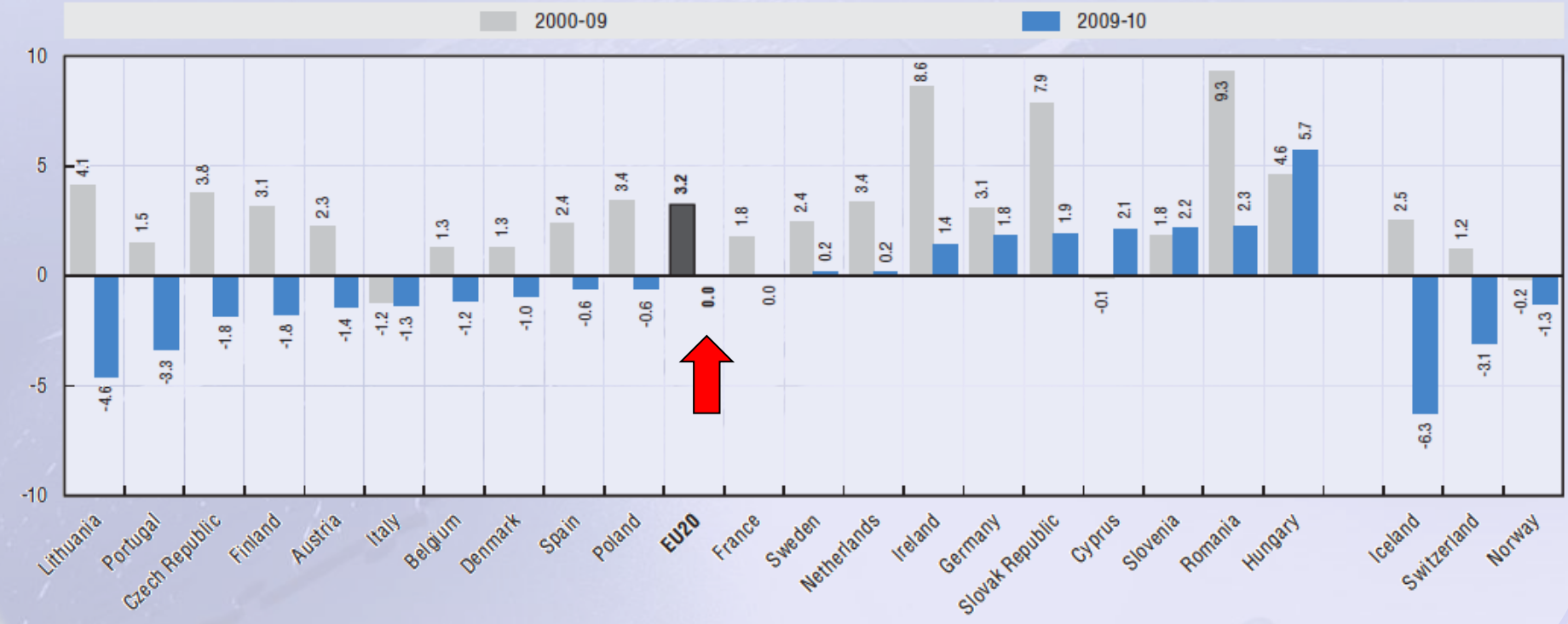


Source: OECD Health Data 2012; Eurostat Statistics Database; WHO Global Health Expenditure Database.

Pharmaceutical Expenditure Growth Rate Turned Negative in Several Countries (2010)

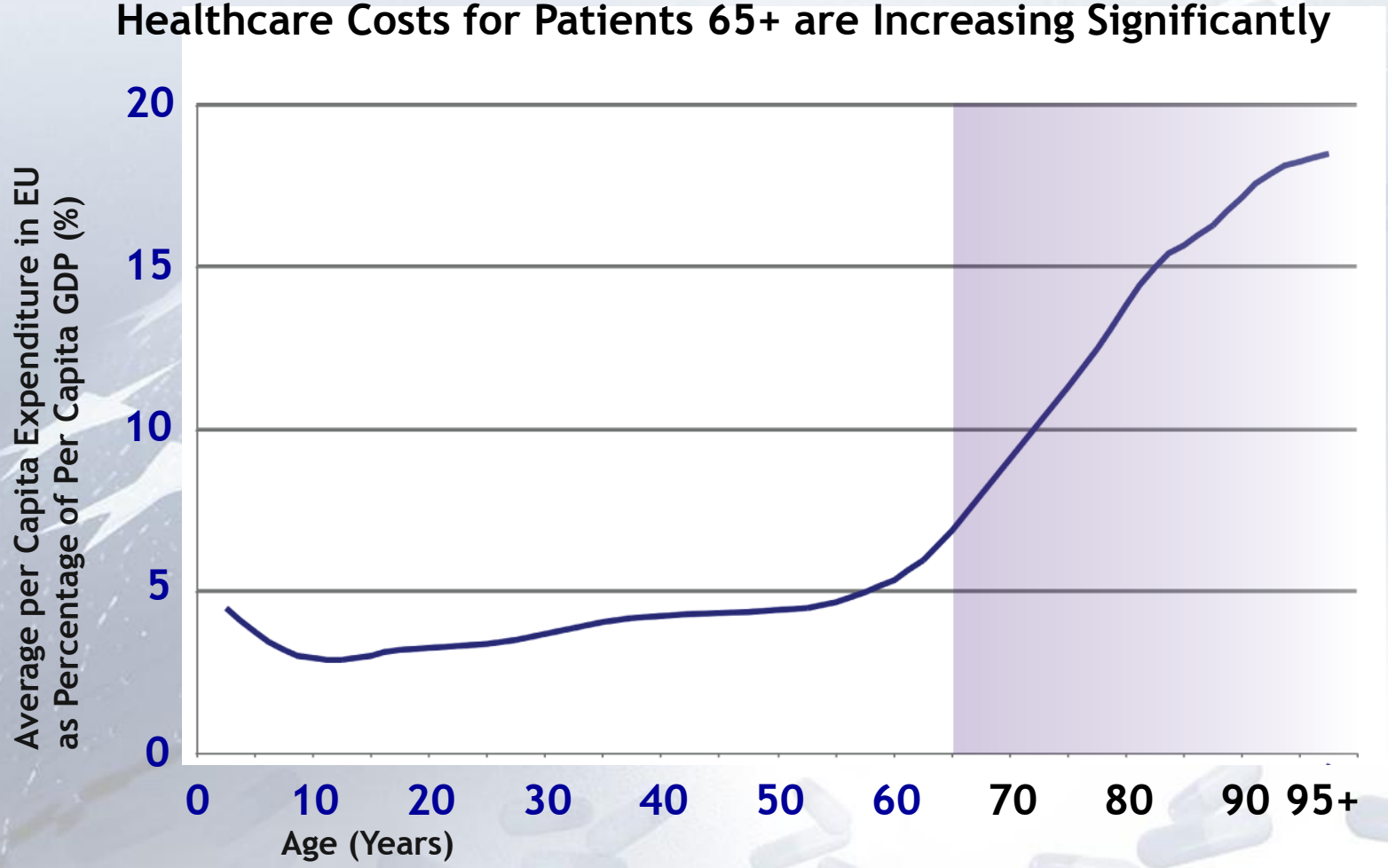
Making Medicines Affordable

5.5.2. Average annual growth in pharmaceutical expenditure per capita, in real terms, 2000 to 2010 (or nearest year)



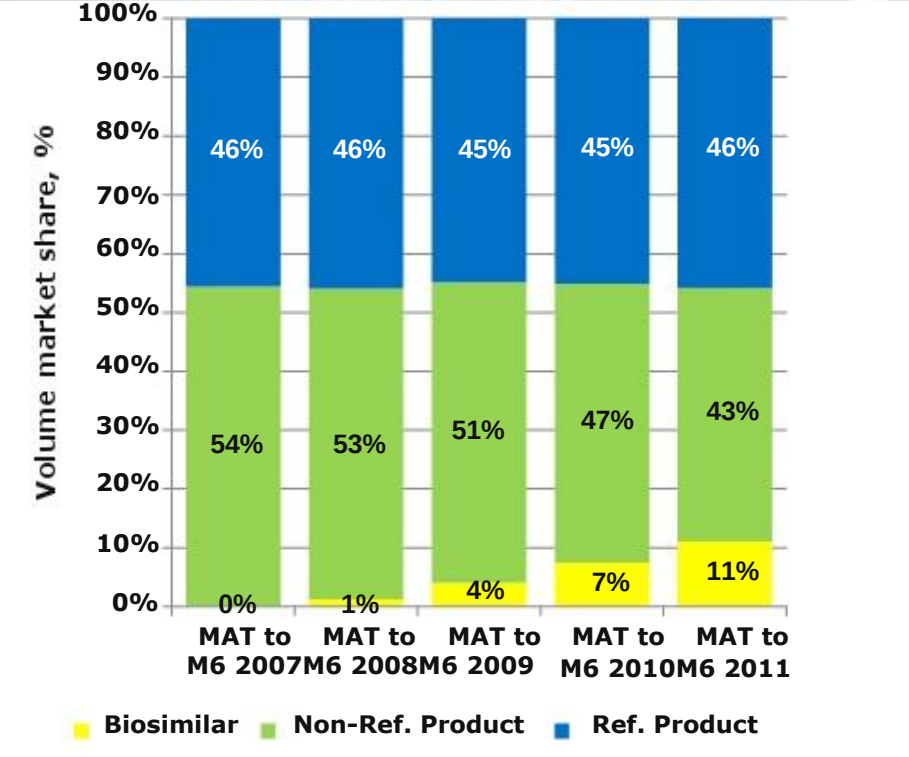
Source: OECD Health Data 2012; Eurostat Statistics Database.

Ageing Population will Drive Future Healthcare Costs across the EU



Biosimilars:11% Share of the Accessible European Market

EU + NO, CH share of biosimilar accessible market by product type, % of DDD, Mat to M6 2011

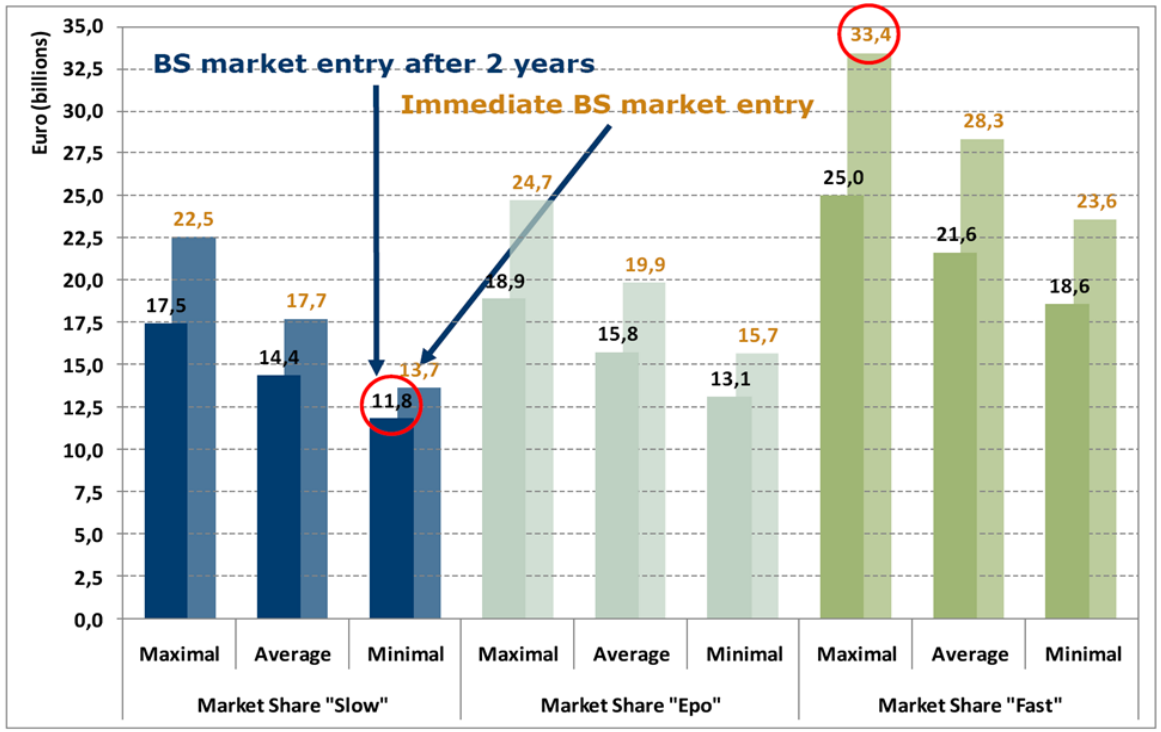


In the 12 month period, biosimilar products represent 19 million, of a total market estimate of 175 million DDD (11%)

Source: IMS MAIDAS Q6 2011.

EU8: Cumulative Savings, 2007-2020: between €11.8 to 33.4 bn (IGES Study)

EU8: Cumulative savings by biosimilars (all compounds included, 2007 to 2020)



IGES 2012

Source: EGA International Symposium London, April 19th, 2012 / Bertram Häussler IGES Institut, Berlin Germany

- EU8 = Germany, France, the UK, Italy, Spain, Sweden, Poland and Romania
- All compounds = Epoetin, Filgrastim, mAbs
- BS = biosimilar
- Market entry: immediate at IP expiry or 2 years later