Regulatory perspectives on biosimilars in Europe

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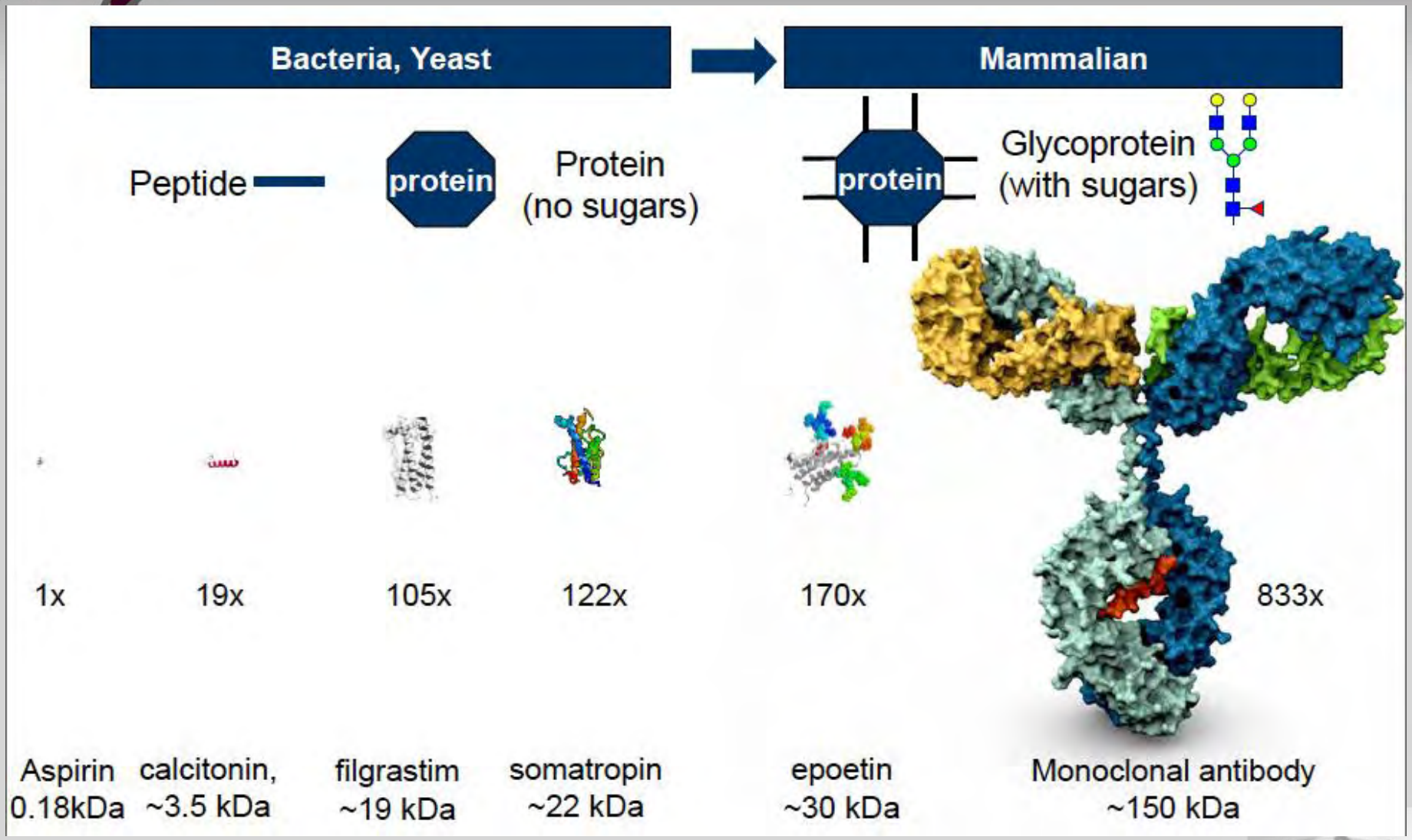
Biosimilars at the European Medicines Agency: a favourable environment for the first wave (growth factors)

2006	1 Omnitrope (somatropin)	Sandoz (Novartis)	Authorized	1
	2 Valtropin (somatropin) – [yeast]	Biopartners	Authorized	2- withdrawn
	3 Alpheon (interferon alfa)	BioPartners	Negative	
2007	4 Binocrit (epoetin alfa)	Sandoz (Novartis)	Authorized	3
	5 Epoetin alfa Hexal (epoetin alfa)	Hexal (Novartis)	Authorized	
	6 Abseamed (epoetin alfa)	Medice	Authorized	
2007	7 Silapo (epoetin zeta)	Stada	Authorized	4
	8 Retacrit (epoetin zeta)	Hospira	Authorized	
	9 Insulin Marvel Short (human insulin)	Marvel Life Sci	Negative	
	10 Insulin Marvel Intermediate (human insulin)	Marvel Life Sci	Negative	
	11 Insulin Marvel Long (human insulin)	Marvel Life Sci	Negative	
2008	12-13 Filgrastim Ratiopharm & Ratiog. (filgrastim)	Ratiopharm	Authorized	5
	14 Biograstim (filgrastim)	CT Arzneimittel	Authorized	
	15 Tevagrastim (filgrastim)	Teva	Authorized	
2009	16 Zarzio (filgrastim)	Sandoz (Novartis)	Authorized	6
	17 Filgrastim Hexal	Hexal (Novartis)	Authorized	
	16 Biferonex (interferon beta-1a)	BioPartners	Negative	
2010	17 Nivestim (filgrastim)	Hospira	Authorized	7

Biologics: complex molecules produced from living organisms



From Joerg Windisch, CSO Sandoz

Biosimilars in the European Union (EU)

The EU Directive and the EMA guidelines

Biosimilars in the EU: the European Directive

- Directive **2004/27/EC** of the European Parliament & Council amending Directive 2001/83/EC (medicinal products [MP] for human use) states (Art. 10(4)):

« When a biological MP does not meet all the conditions to be considered as a generic MP, the results of **appropriate tests** *should be provided in order to fulfill the requirements related to safety (pre-clinical tests) or to efficacy (clinical tests) or to both. »*

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0034:0057:EN:PDF. Accessed: 14 November 2012.

Biosimilars in EU: the CHMP 2005 guideline

EMA **CHMP document 437/04** ("Guideline on Similar Biological Products" = "**overarching guideline**"), **effective 10/2005**, states:

*« Due to the complexity of biological/biotechnology-derived products the generic approach (i.e. demonstration of bioequivalence with a reference medicinal product) is scientifically not appropriate for these products. The "**biosimilar**" approach, based on a **comparability exercise**, will then have to be followed. »*

www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Accessed: 14 November 2012.

Key points of the CHMP 2005 guideline

1. **Biosimilar is NOT "biogeneric"**
2. ***A* "comparability exercise" is required**

Biosimilarity should be established at <u>all levels</u> in a stepwise fashion (Quality → Non clinical → Clinical Efficacy & Safety)

The concept is similar to, but more exacting than, the comparisons of internal versions of a biotech product

3. **The Quality comparison may be more important than the clinical comparison**
4. ***A* Risk Management Plan (RMP) will be needed**

NB. Is it really part of the comparability exercise?

The principle of biosimilarity

To establish that, when used as a therapeutic product, there is **not likely** to be any **clinically significant difference** between the reference product and the test product.

- But the key concept to demonstrate biosimilarity is NOT a therapeutic equivalence trial because this would be insensitive to differences (rather, the concept is a comparability exercise)

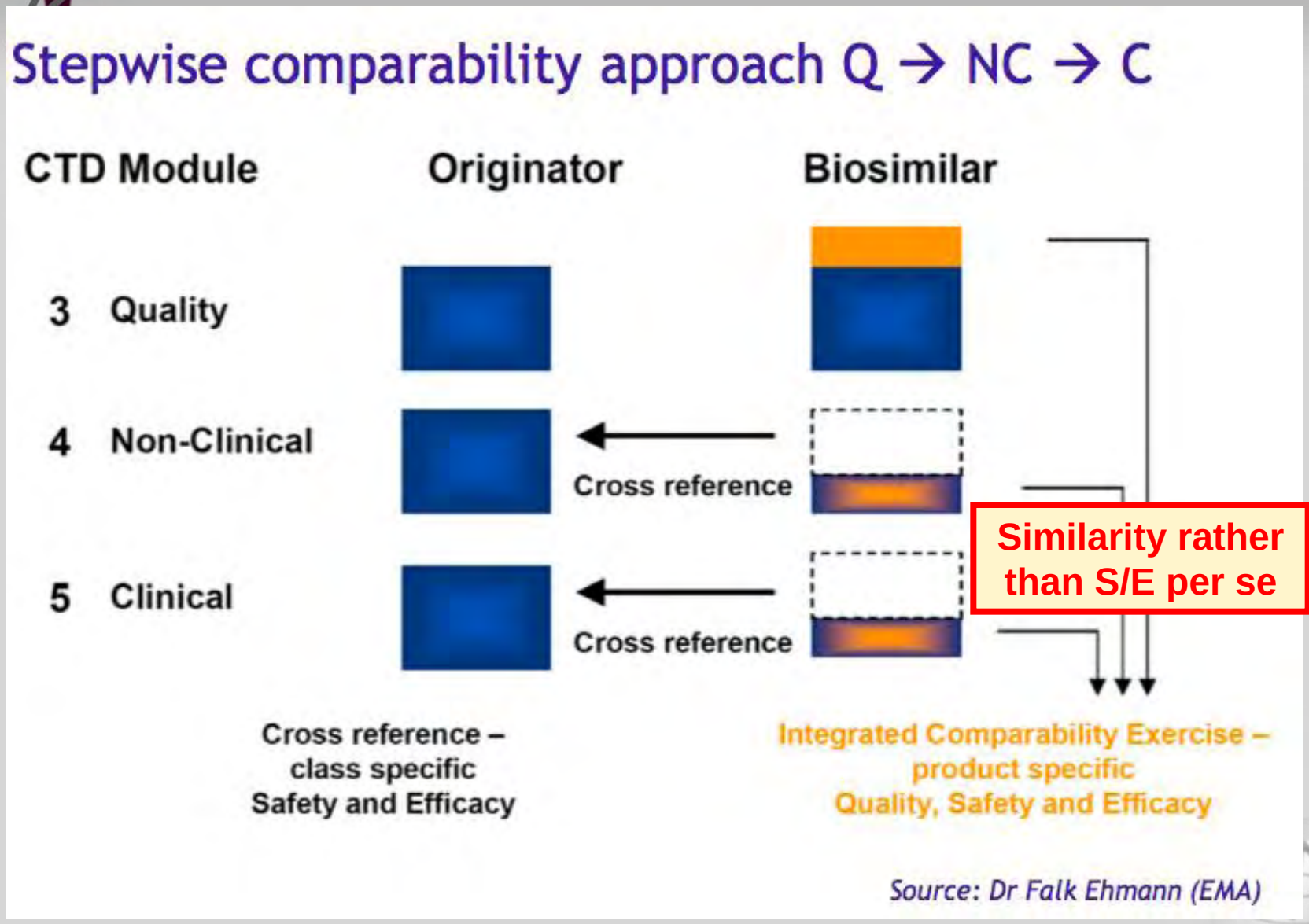
- Clinicians and regulators (*and big pharma industry…*) often view this issue differently

The comparability exercise

Comparability (change in manufacturing process)	**Biosimilarity**
▪ Extensive quality data ▪ Low need for clinical data	▪ Extensive quality data ▪ **High need for clinical data**
▪ Thorough internal knowledge by manufacturer	▪ No internal knowledge
▪ Noninferiority tests	▪ (Generally) **Therapeutic equivalence**

If the comparison **fails** at any stage, the products cannot be declared biosimilar

EMA dossier requirements for biosimilars



Some critical points in the dossier

Quality comparison

- *A key step – possibly the most critical step*
- Cell culture, impurities – product and process related, sterilisation methods, presence or absence of serum albumin, glycosylation pattern…

Non-clinical comparison

- *In vitro receptor binding & cell-based assays are fundamental*
- (where model allows) In vivo PK/PD/activity/toxicity

Clinical comparative studies

- *Most sensitive population and endpoints* (healthy volunteers and/or PK/PD/biomarker data may suffice) → **this was easily accepted for growth factors**
- "Equivalence" study with justified margins (δ) → **uncertainty !**
- 6-12 month safety data (incl. immunogenicity)
- ***Extrapolation of indications !!***

BMWP Proposal for Using Precise Terminology

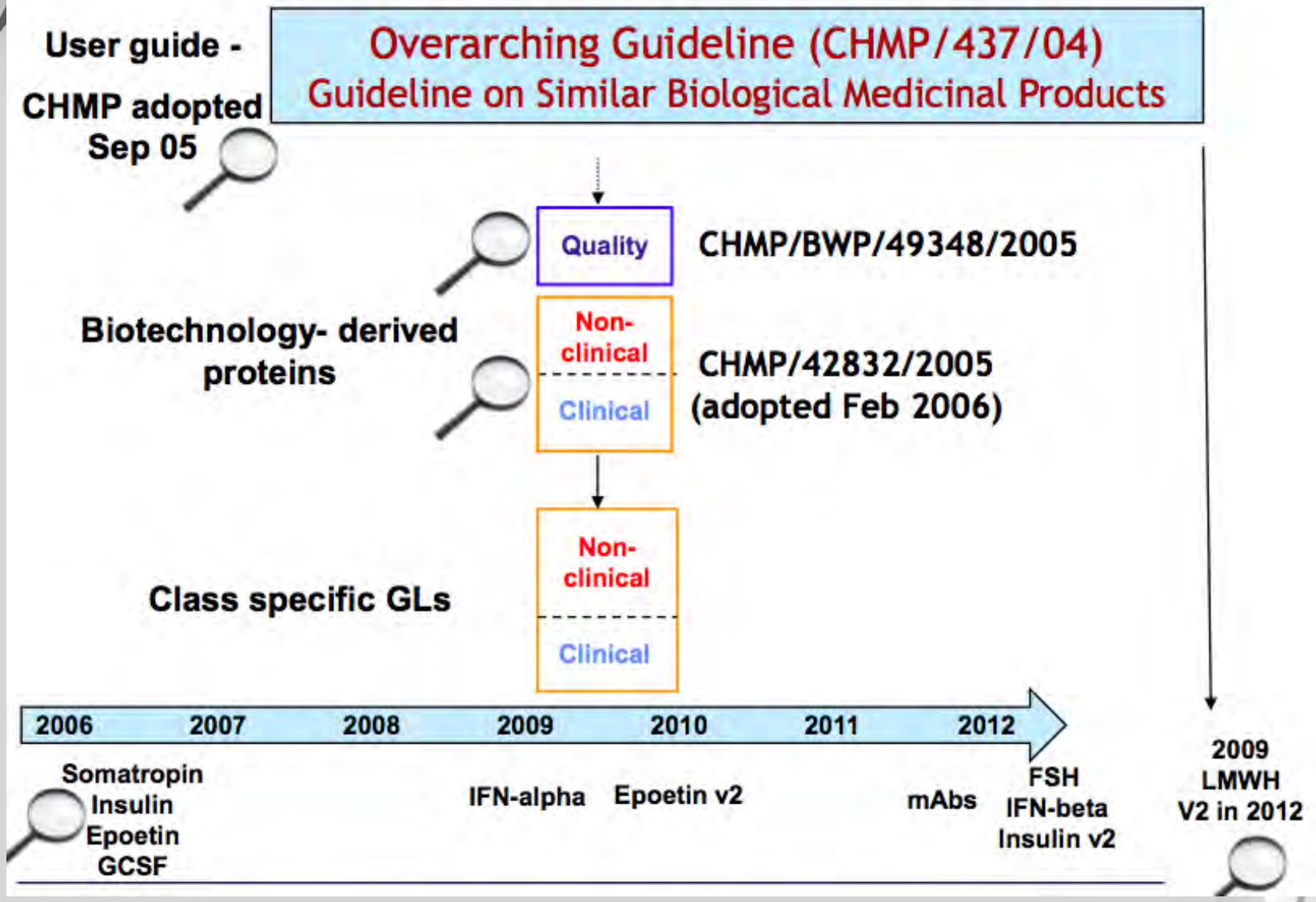
Term(s)	Definition	Implications
Biosimilar[a]	Copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy, and safety, based on a comprehensive comparability exercise.	Only very small differences between biosimilar and reference with reassurance that these are of no clinical relevance. Extrapolation of clinical indications acceptable if scientifically justified.
Me-too biological/biologic **Noninnovator biological/biologic**	Biologic medicinal product developed on its own and not directly compared and analyzed against a licensed reference biologic. May or may not have been compared clinically.	Unknown whether and which physicochemical differences exist compared to other biologics of the same product class. Clinical comparison alone usually not sensitive enough to pick up differences of potential relevance. Therefore, extrapolation of clinical indications problematic.
Second-generation (next-generation) biological/biologic **Biobetter**	Biologic that has been structurally and/or functionally altered to achieve an improved or different clinical performance.	Usually stand-alone developments with a full development program. Clear (and intended) differences in the structure of the active substance, and most probably different clinical behavior due to, for example, different potency or immunogenicity. From a regulatory perspective, a claim for 'better' would have to be substantiated by data showing a clinically relevant advantage over a first- or previous-generation product.

BMWP-Biosimilar Medicinal Products Working Pary at EMA

Weise M, et al. *Nat Biotechnol*. 2011;29(8):690-693.

[a]Comparable terms defined by the same/similar scientific principles include the WHO's 'similar biotherapeutic products' and Health Canada's (Toronto) 'subsequent-entry biologicals'

EU Biosimilar Guidelines –Overview



Other Relevant EMA Guidelines

Nov 2007

GUIDELINE ON COMPARABILITY OF BIOTECHNOLOGY-DERIVED MEDICINAL PRODUCTS AFTER A CHANGE IN THE MANUFACTURING PROCESS

NON-CLINICAL AND CLINICAL ISSUES

April 2008

GUIDELINE ON IMMUNOGENICITY ASSESSMENT OF BIOTECHNOLOGY-DERIVED THERAPEUTIC PROTEINS

May 2012

Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use.

Some complexities of the system

1- Biosimilarity is technology-dependent

- **(437/04)**

« In principle, the concept of a “biosimilar” is applicable to any biological MP. However, in practice, the success of such a development approach **will depend on the ability to characterise** the product and therefore to demonstrate the similar nature of the concerned products. »

« Whether a MP would be acceptable using the “biosimilar” approach **depends** on the state of the art of analytical procedures, the manufacturing processes employed, as well as clinical and regulatory experiences. »

www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Accessed: 14 November 2012.

2- The issue of different formulations

- **(437/04)**

« The pharmaceutical form, strength, and route of administration of the similar biological MP should be the same as that of the reference medicinal product. If not, additional data should be provided. »

Ex. Binocrit® was not able to provide those data for the sc route *vs* Eprex for chronic renal failure patients → Binocrit® is only biosimilar for the iv route in CRF patients (Retacrit® is approved for both sc and iv routes in that indication)

www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Accessed: 14 November 2012.

3- The comparator

- **(437/04)**

« The chosen reference medicinal product must be a MP authorised in the EC on the basis of a complete dossier. »

➛ This requirement will be removed when the revision of the overarching guideline comes into force (possibly end 2013)

www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Accessed: 14 November 2012.

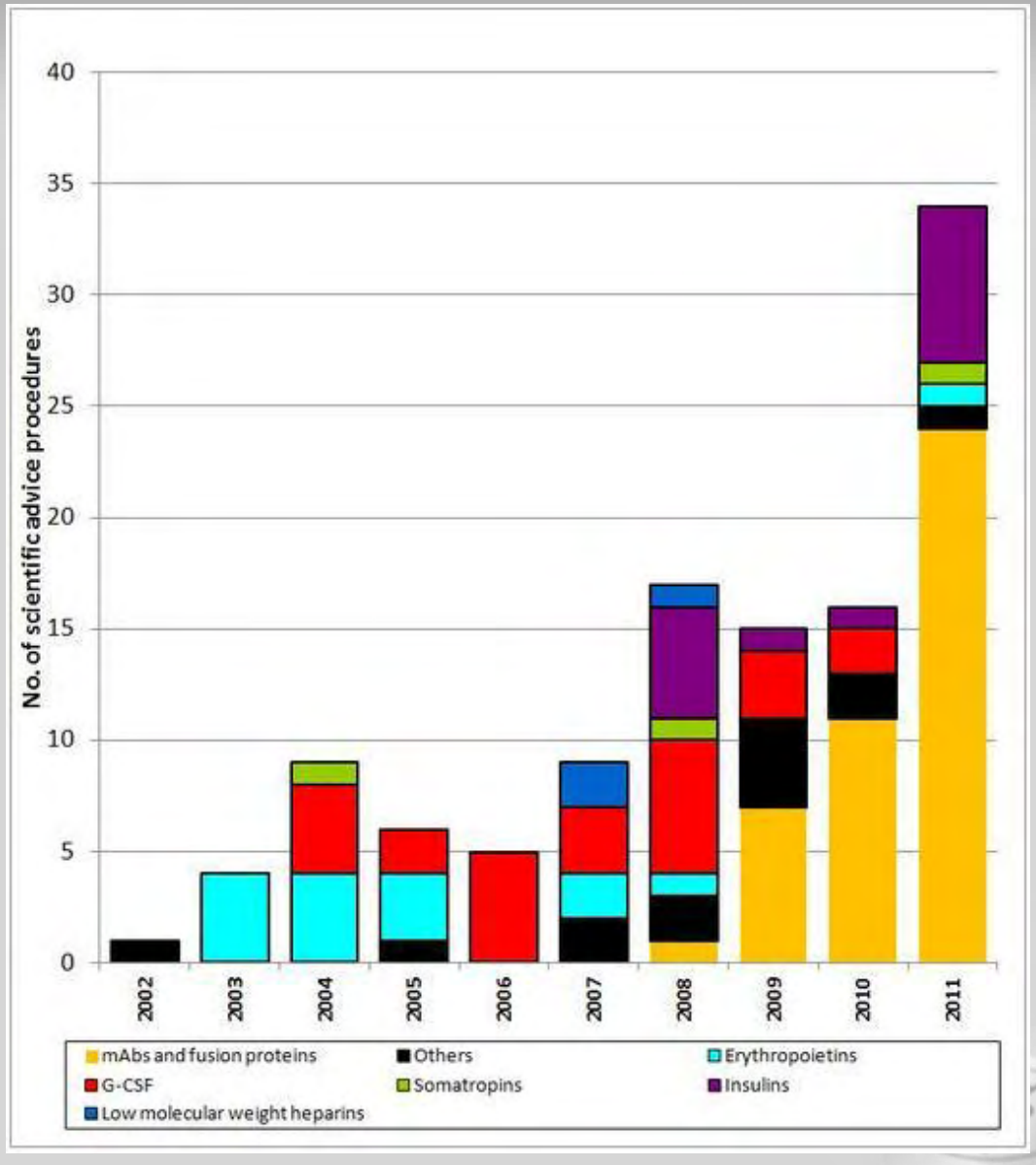
4- Legislation *vs* science

1. Scientific guidelines have no legal force → applicants are invited to justify any lack of compliance

2. Development of guidelines follows science (eg, experience from scientific advice procedures and previous marketing authorization applications)

EMA Scienitifc Advice requests on biosimilars

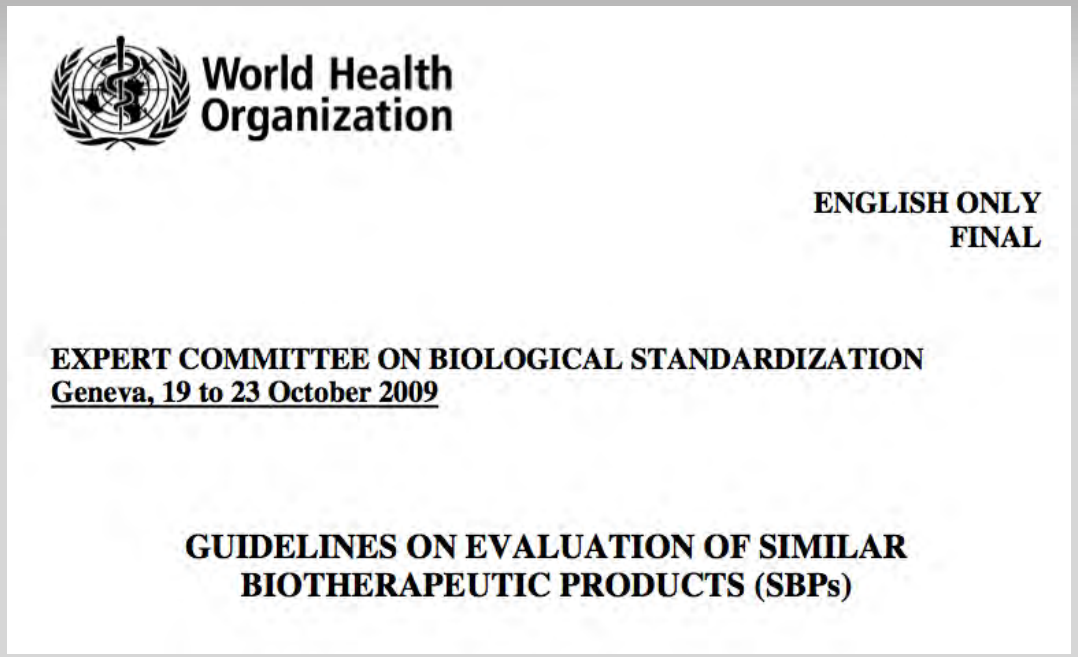
mAbs and fusion proteins



Schneider CK, Vleminckx C, Gravanis I, et al. Setting the stage for biosimilar monoclonal antibodies. *Nat Biotechnol*. 2012;30(12):1179-85

Outside the EU

Biosimilars: WHO Guideline (2009)



World Health Organization

ENGLISH ONLY
FINAL

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 19 to 23 October 2009

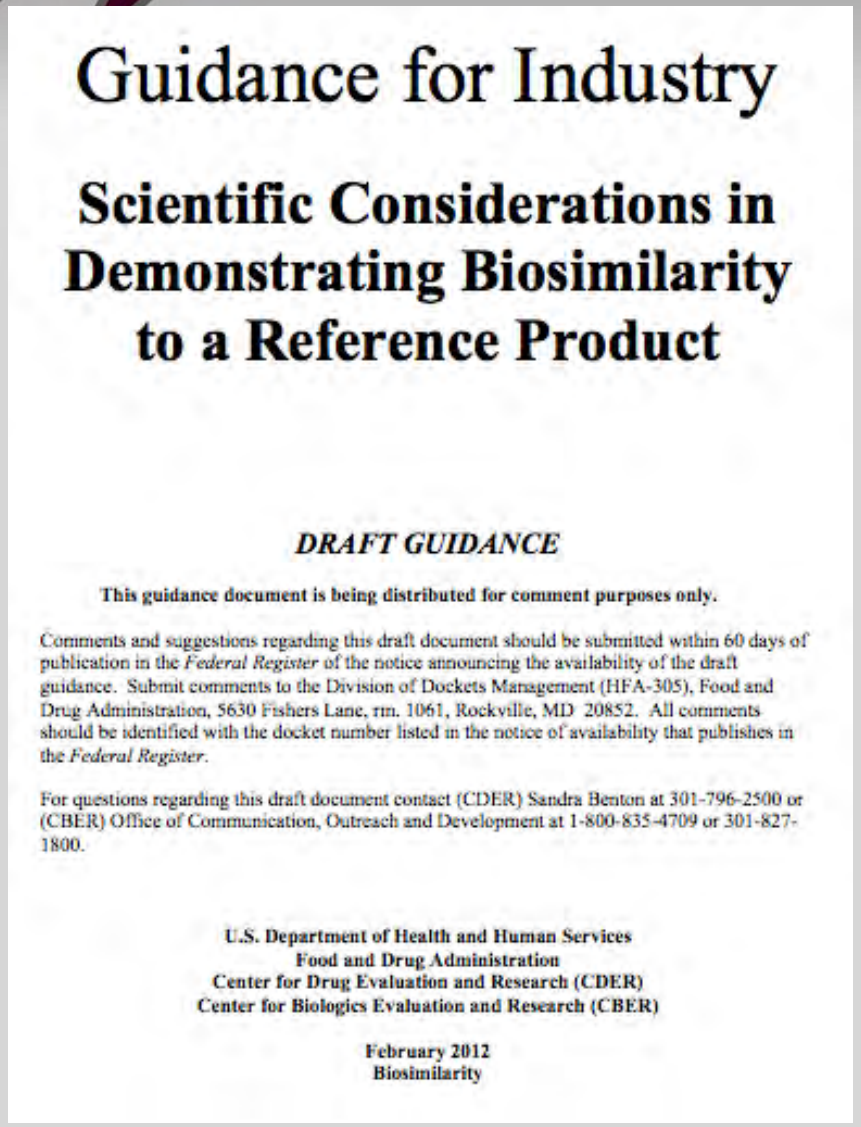
GUIDELINES ON EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs)

- To obtain a “SBP” label, a stepwise comparability exercise (quality/nonclinical/clinical) should be performed
- SBPs require regulatory oversight for the management of risks
- Extrapolation of indications is possible provided…

…

http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf. Accessed: 14 November 2012.

Biosimilars: FDA Guideline (2012)



Guidance for Industry

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Sandra Benton at 301-796-2500 or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2012
Biosimilarity

- The Affordable Care Act creates an abbreviated licensure pathway for products that are biosimilar **or interchangeable** with an FDA-licensed biologic reference product
- Stepwise approach
- FDA intends to consider the "totality of the evidence"
- Scope and magnitude of the **clinical studies will depend** on the extent of residual uncertainty about biosimilarity

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm. Accessed: 14 November 2012.

The contentious points

The debate on biosimilars

1- Phase III: which population, which endpoints ?

In principle, the most sensitive disease model to detect differences in both efficacy and safety should be used in a homogeneous patient population to reduce variability

In oncology, that would mean response rate rather than (overall) survival, possibly in early stage patients; it would also mean immunocompetent subjects

But HTA bodies (and clinicians) may require the most relevant population…

2- Extrapolation of indications

1. Without extrapolation, the biosimilar concept is dead

2. Justification of the extrapolated indication (rather than separate demonstration of equivalence) is on a case-by-case basis
   - ➙ criteria for the decision? (e.g. mechanism of action, receptor number and affinity…)
   - ➙ could guidelines help?

3- Immunogenicity & traceability

1. Immunogenicity in humans cannot be predicted from animal data → absolute need for **comparative clinical trials** including tests for neutralizing Abs and PK/PD data
2. Consider the risk to the endogenous protein
3. *How long ?*

   Usually 1 year pre-licensing if chronic use is intended; the subsequent risk management plan (RMP) is crucial

➡ **Traceability (naming) of biosimilars !**

➡ **Should be prescribed under brand names**

4- Interchangeability

1. In the EU, biosimilarity refers to a single point in time (date of Marketing Authorization)
2. Designation of interchangeability may imply need for demonstration of “continued biosimilarity” (e.g. with respect to immunogenicity)
3. Interchangeability/automatic switch should remain a national decision

A new era:

biosimilar monoclonal antibodies

A new era: biosimilar monoclonal antibodies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 May 2012
EMA/CHMP/BMWP/403543/2010
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues

Draft Agreed by Similar Biological Medicinal Products Working Party	**October 2010**
Adoption by CHMP for release for consultation	18 November 2010
End of consultation (deadline for comments)	31 May 2011
Final agreed by BMWP	March 2012
Adoption by CHMP	30 May 2012
Date for coming into effect	1 December 2012

April and September 2012: two MAAs to EMA for biosimilar infliximab (at least one from Celltrion, Korea)

Infliximab is a « simple » blockade of TNFα

What about rituximab, trastuzumab….?

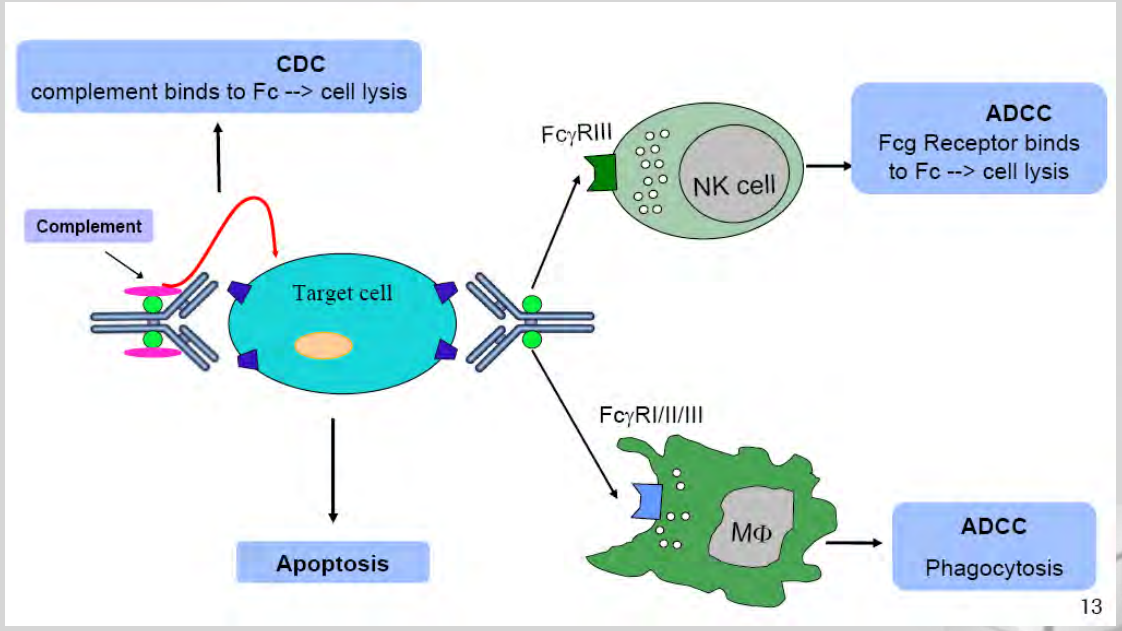
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. Accessed: 14 November 2012.

Biosimilar monoclonal antibodies (mAbs): the clinical issues are not different but “technically” are we pushing the concept too far?

Very complex production

Very complex mechanism of action

Complex (oncology) indications



Some Take-Home Messages

Take-home messages (1)

1. The biosimilarity concept means a “low likelihood of clinically significant differences”
2. According to (EU) regulators, a product can be biosimilar only if it has successfully gone through the stepwise (Q/S/E) “comparability exercise”
3. **Therefore, not all copies of biological products are biosimilar**

Take-home messages (2)

4. Detection of immunogenicity and RMP are key elements of safety — as for all biotech products; so far there is no safety issue with any biosimilar
5. Traceability should be ensured by prescribing under brand names (and tracing batch numbers…)
6. Interchangeability is a national (or local) issue

Take-home messages (3)

7. The clinical focus of the biosimilar exercise is on PK/PD using the most sensitive populations and endpoints, it is not on patient benefit *per se*
8. Extrapolation of indications is key to the biosimilar concept but needs to be justified in all cases
9. **Clinicians should accept these concepts** (*comparability exercise and extrapolated indications*) but should discuss the equivalence margins and the increased level of uncertainty

Take-home messages (3)

10. How much “reassurance” are decision makers and clinicians willing to give away in favour of lower prices?

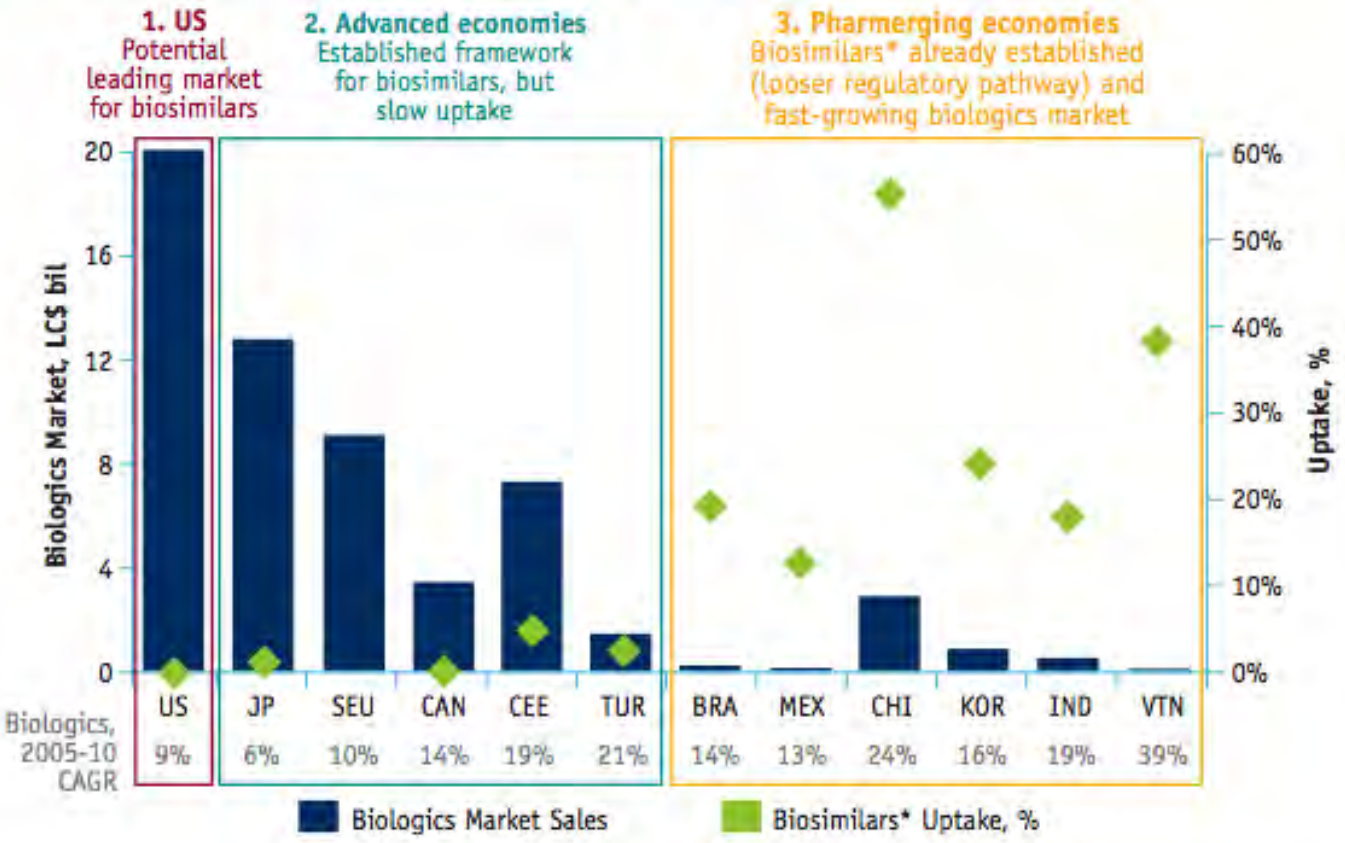
11. The application of the biosimilar concept to mAbs hangs in the balance *(in my opinion)*

Thank You !!

Back-up slides:

Market Penetration of Biosimilars

FIGURE 3: THREE GEOGRAPHICAL CLUSTERS ARISE, WITH US REPRESENTING A SIGNIFICANT PORTION OF MARKET POTENTIAL (~60%)
Pharmerging economies anticipated to be a potential growth driver



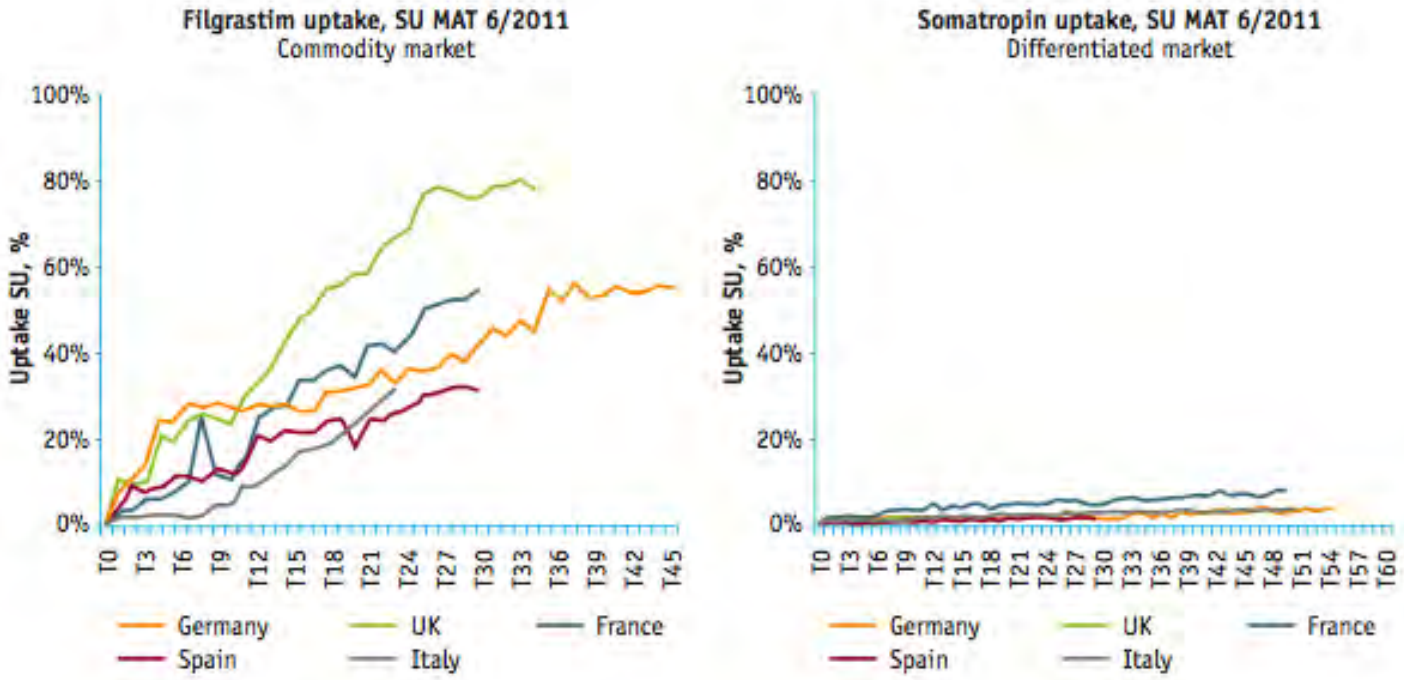
Source: IMS Health MIDAS, 2005-2010

** Biosimilars in Europe and Japan defined by regulatory pathway, in pharmerging markets looser approval processes apply for products that resemble biosimilars*

http://www.imshealth.com/ims/Global/Content/Home%20Page%20Content/IMS%20News/Biosimilars_White paper.pdf. Accessed: 14 November 2012.

FIGURE 4: OVERALL WE CAN IDENTIFY TWO UPTAKE PATTERNS FOR BIOSIMILARS, DIFFERENTIATED VS. COMMODITY

Differentiated markets will pose several challenges to biosimilars



Source: IMS Health

http://www.imshealth.com/ims/Global/Content/Home%20Page%20Content/IMS%20News/Biosimilars_White paper.pdf. Accessed: 14 November 2012.

Back-up slides:

Development of biosimilar mAbs

Clinical issues in biosimilar mAbs

- Do not really differ from non-mAb biosimilar products but the guideline insists on:…

1. The comparative PK study (in healthy volunteers or in patients) is key -- if possible, **add PK/PD** (if PD measurements are feasible)
2. A Phase III equivalence trial is expected in a sufficiently E/S **sensitive population** (demonstrating patient benefit *per se* is not the goal) – however, a relevant endpoint is key for market access
3. Extrapolation of indications is possible based on the "overall evidence of biosimilarity"
4. RMP: post-MA safety studies may be required

April and September 2012 : two requests for infliximab biosimilar MAA accepted at EMA, at least one likely from Celltrion (Korea)

Immunogenicity of biosimilar mAbs (1)

REVIEW
MINI FOCUS: BIOANALYSIS OF BIOSIMILARS

Assessing immunogenicity of biosimilar therapeutic monoclonal antibodies: regulatory and bioanalytical considerations

Paul Chamberlain, *Bioanalysis* (2013) 5(5), 1–14

Immunogenicity of biosimilar mAbs (2)

- ADA incidence and magnitude should always be assessed relative to capacity of ADAs to **neutralize** the relevant biological activity of the therapeutic mAb
- Detected differences in ADA incidence or magnitude should not, in themselves, result in a product being classified as 'not biosimilar' – the impact of the difference **on relevant clinical parameters** should be used as the arbiter.
- It follows that it would **not be feasible to predefine a margin of difference** in ADA incidence or magnitude that would result in the classification of 'not biosimilar'.
- ***A single Phase III comparative study*** in a population that is suitable to demonstrate therapeutic equivalence would be expected to identify the clinical impact of an increase in the level of immunogenicity of a biosimilar product candidate relative to the reference product.

Immunogenicity of biosimilar mAbs (3)

- Although **post-authorization data** might be useful to confirm absence of heightened immunogenicity-related risks in different patient populations, they are **unlikely to be useful** for comparative purposes because of the uncertainties of the longer term treatment outcomes for the reference product – *except, perhaps, for anti-TNF agents ?*