Regulatory approval of the first biosimilar monoclonal antibody

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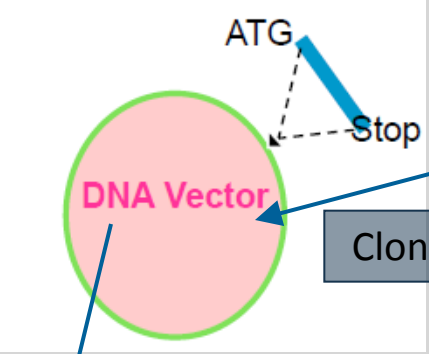
How to make a similar biological product?

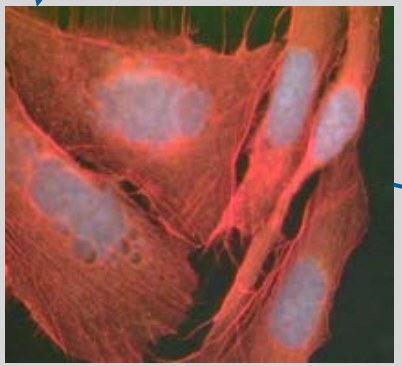
Biologics have a complex manufacturing process that makes them difficult to copy; the end product is likely not to be the same as the originator



Coding gene mutation

Cloning into DNA vector

Transfer into host cell expression



Different cell culture processes

Different purification and formulation protocols

Dörner T, et al. *Ann Rheum Dis*. 2013;72(3):322-328.
Ahmed I. Clinical Therapeutics 2012; 34(2):400–419.

The complexity of biologicals

Inherent complexity

- Size
- Structure
- Physicochemistry
- **Intrinsic heterogeneity**

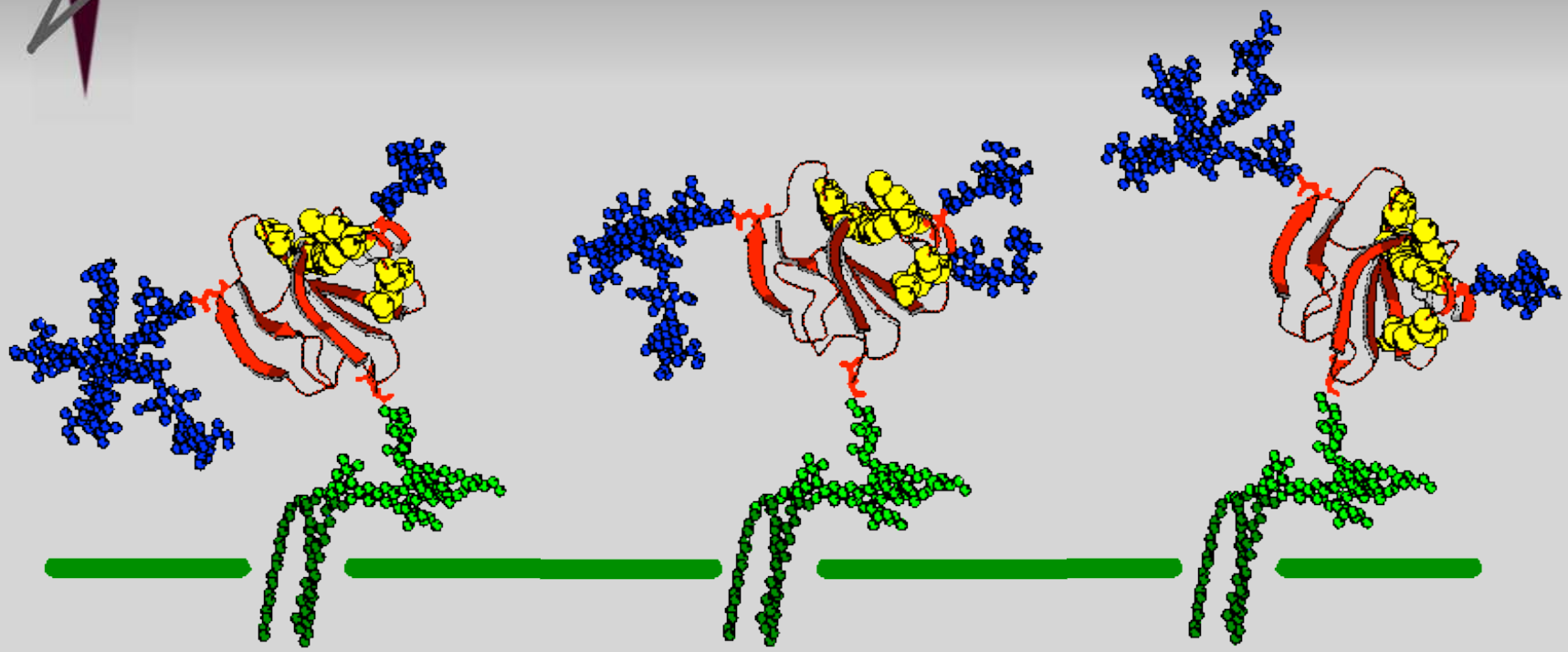
Additional complexity

- Manufacturing process **in living organisms**
- Formulation
- Routes of administration

→ An exact copy is impossible to achieve

Courtesy of Betrand Coiffier.

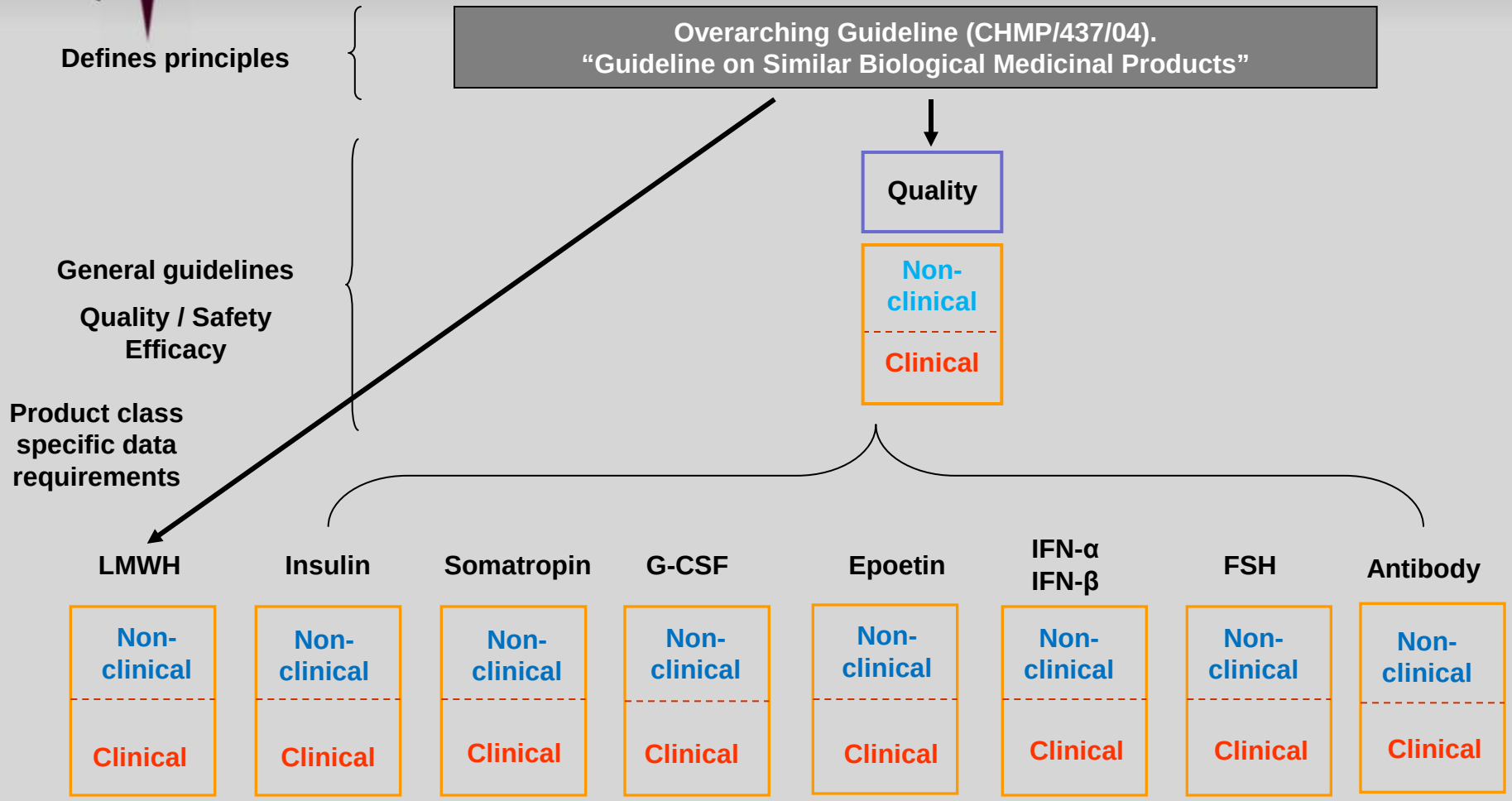
Intrinsic heterogeneity: e.g. glycoforms



Biologicals are microheterogeneous mixtures of several isoforms, each of which may differ in terms of potency, half-life, and immunogenicity

Rudd PM, *et al.* The glycosylation of the complement regulatory protein, human erythrocytes CD59. *J Biol Chem.* 1997;272(11):7229-7244.

How to get a biosimilar approved in the EU (EMA)



FSH, follicle-stimulating hormone; G-CSF, granulocyte colony-stimulating factor; IFN, interferon; LMWH, low-molecular-weight heparin

European Medicines Agency. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp. Accessed 25 September 2014.

The EMA abbreviated pathway to approval

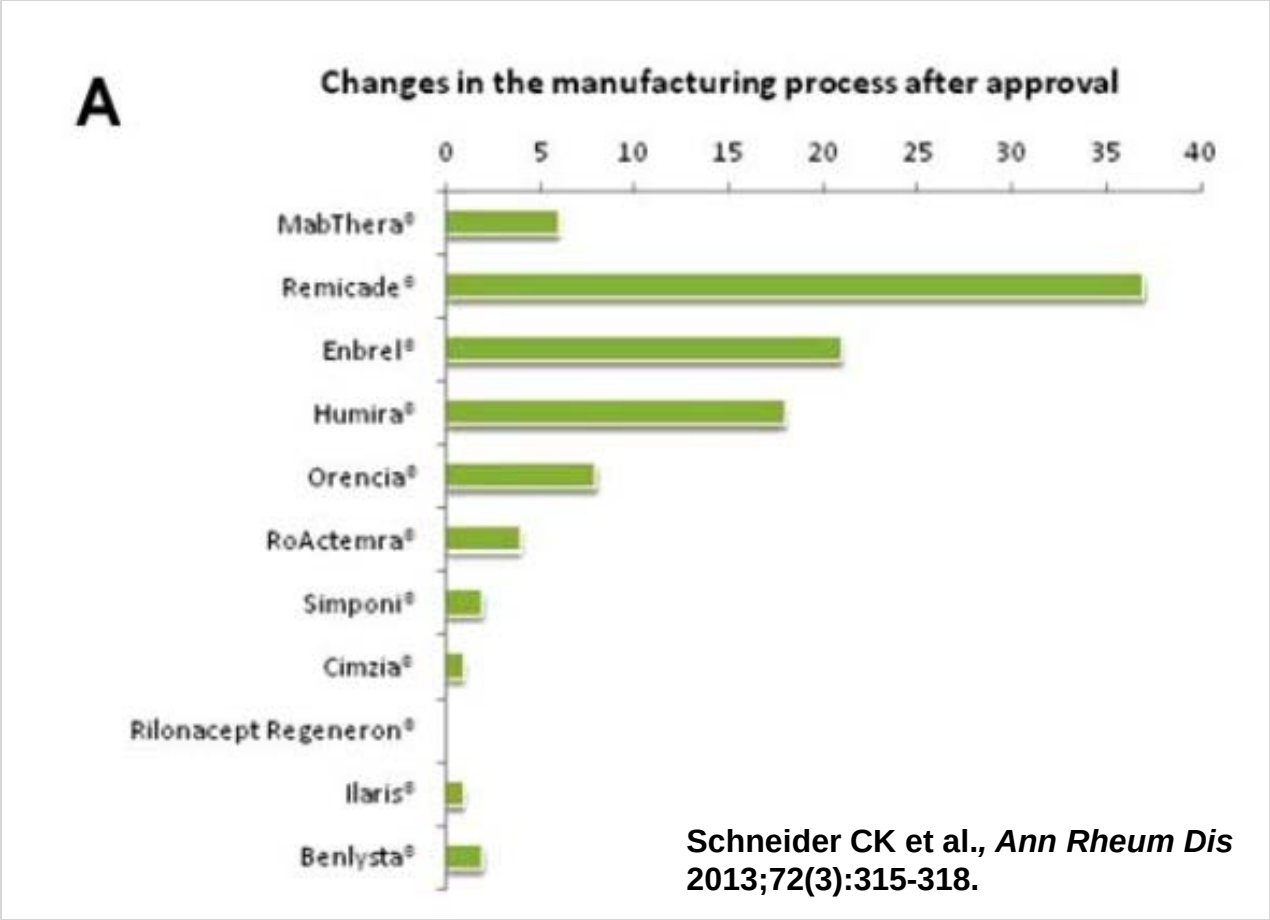
EMA: Abbreviated Pathway to Approval

Assessment	Originator Biologic	Biosimilar
Quality	• Individual quality assessment[a]	• Individual quality assessment[a] • Comprehensive comparison with reference product
Preclinical	• Full preclinical programme	• Abbreviated program; tolerance, PK/PD
Clinical	• Phase 1 • Phase 2 • Phase 3 in all indications • Risk management plan	• Phase 1 (PK/PD) • No phase 2 • Phase 3 in one representative indication • Risk management plan

[a] Consisting of: analytical techniques, characterisation (physicochemical, biological activity, immunochemical, purity), and specifications.

Comparability Exercise for existing products

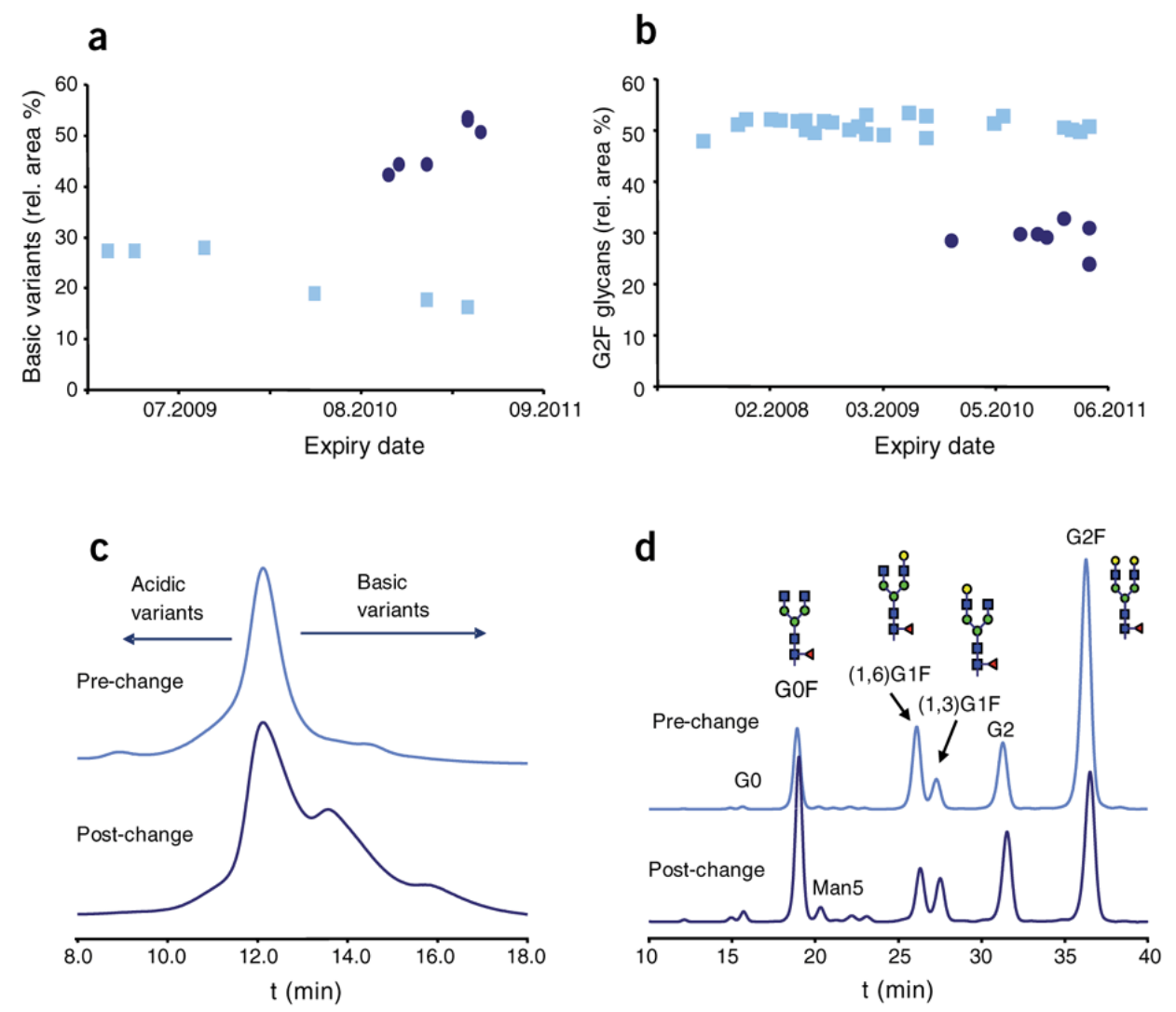
Number of manufacturing changes approved for – mabs/-cepts in rheumatology



Schneider CK et al., *Ann Rheum Dis* 2013;72(3):315-318.

Physicochemical characteristics of subsequent products do not have to be identical but « highly similar »” (they may be slightly improved)

Comparison of Enbrel® batches before (■) and after (■) main manufactoring changes



Schiestl M, et al. *Nature Biotech.* 2011;29(4):310–312.

Comparability Exercise *vs* Biosimilarity

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

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

Biosimilars at the European Medicines Agency (1)

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 Filgrastim Ratiopharm (filgrastim)	Ratiopharm	Authorized	5
	13 Biograstim (filgrastim)	CT Arzneimittel	Authorized	
	14 Tevagrastim (filgrastim)	Teva	Authorized	
2009	15 Zarzio (filgrastim)	Sandoz (Novartis)	Authorized	6
	16 Filgrastim Hexal	Hexal (Novartis)	Authorized	
	17 Biferonex (interferon beta-1a)	BioPartners	Negative	
2010	18 Nivestim (filgrastim)	Hospira	Authorized	7

Biosimilars at the European Medicines Agency (2)

MAb

In all indications !!

2013	19 Remsima (infliximab)	Celltrion	Authorized	8 **
	20 Inflectra (infliximab)	Hospira	Authorized	
	21 Ovaleap (follitropin alpha)	Teva	Authorized	9
	22 Gastrofil (filgrastim)	Apotex	Authorized	10
2014	23 Bemfola (follitropin alpha)	Finox Biotech AG	Authorized	11
	24 Abasria (insulin glargine)	Lilly-Boehringer	Cleared CHMP	12
	NB. At FDA: Basaglar (not a biosimilar – 505(b) procedure		Cleared FDA	

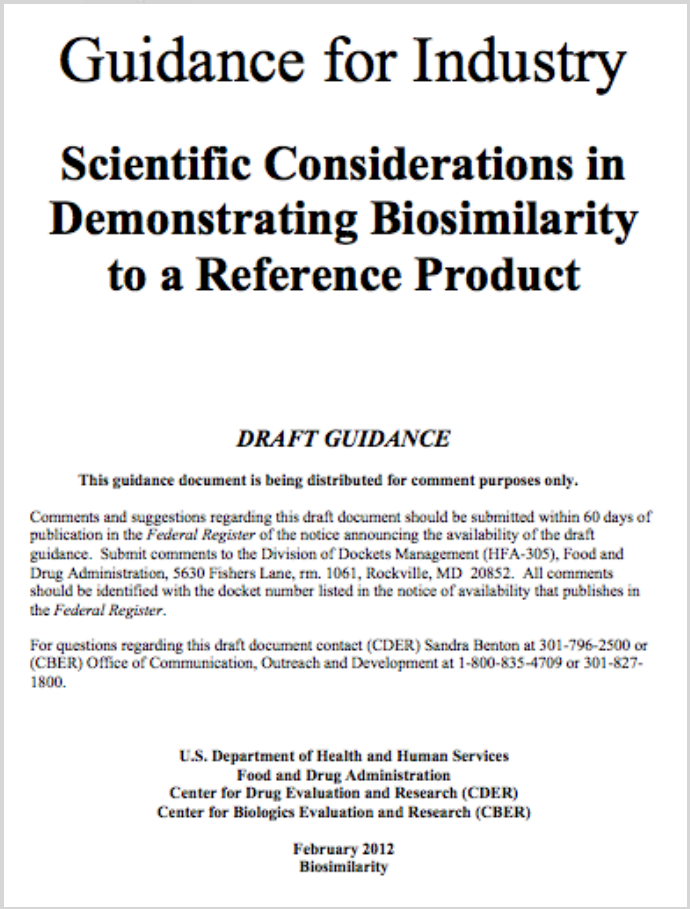
Biosimilars under evaluation

None at EMA – NB. Celltrion's trastuzumab approved in N. Korea (January 2014)

August 2014: FDA accepted Sandoz's Zarzio (filgrastim) application as a biosimilar

** Marketed in Norway, Portugal, Ireland, Finland, Eastern Europe; pending patent issues in other EU States

Biosimilars: other guidelines



Guidance for Industry

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

DRAFT GUIDANCE

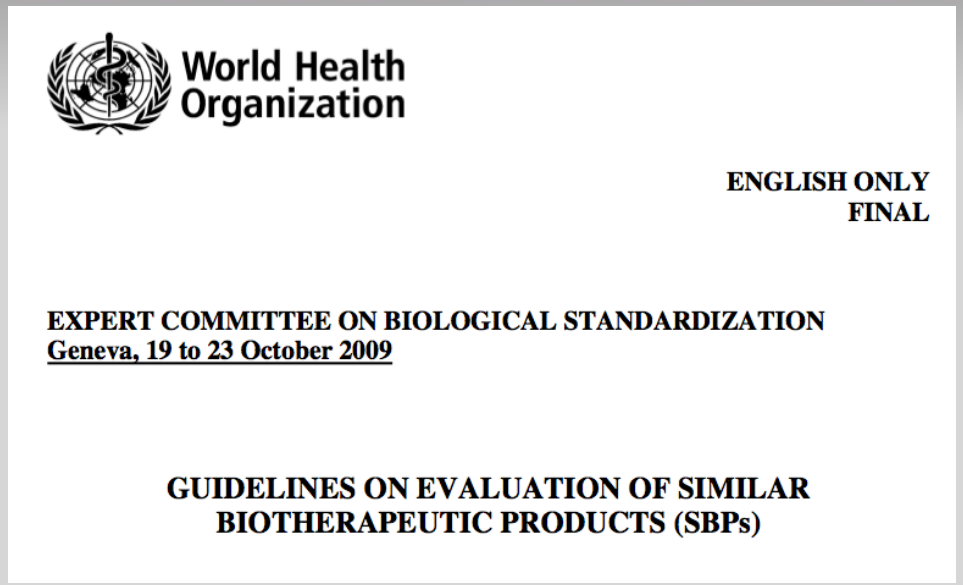
This guidance document is being distributed for comment purposes only.

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

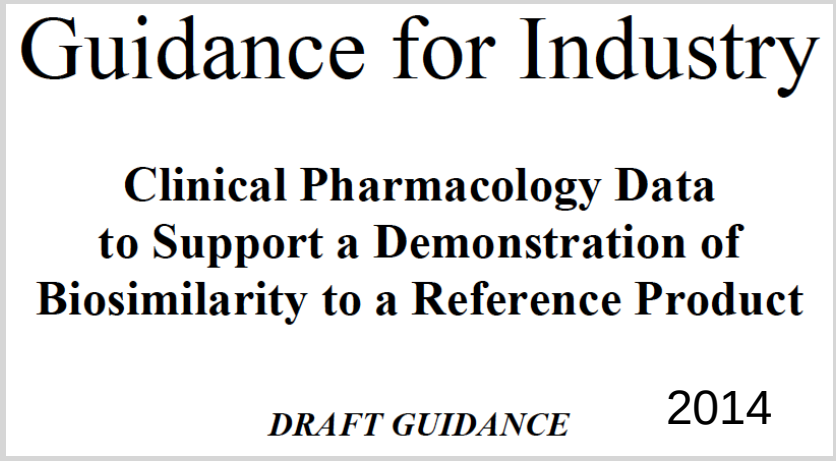


World Health Organization

ENGLISH ONLY
FINAL

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

GUIDELINES ON EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs)



Guidance for Industry

Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

DRAFT GUIDANCE

2014

http://www.who.int/biologicals/areas/biological_therapeutics/en/. Accessed: 25 September 2014.
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm. Accessed: 15 September 2014.

The contentious points
The debate on biosimilars

- Without a reduction in regulatory requirements, the biosimilar concept is not (economically) tenable

- How can regulatory requirements be reduced without undue risks (unacceptable loss of efficacy, or unexpected immunogenicity)?

Methods agreed by regulators to reduce regulatory requirements for biosimilars

1. Accurate PK studies (if possible, PK/PD data)

2. Fewer patients but enough statistical power to detect differences:
   - *more homogenous population*
   - *“in principle, the most sensitive endpoints”*
   - *sufficiently large equivalence margins (➞ leads to some additional uncertainty)*

3. Extrapolation of (many) indications

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 clinicians expect the most relevant population…

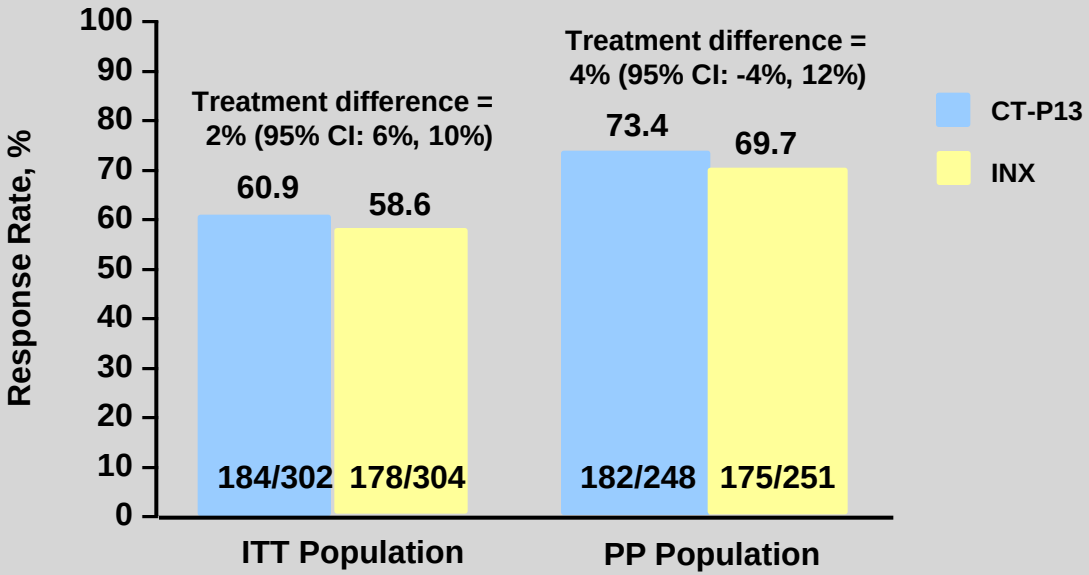
Justification for extrapolation of indications

According to EMA

1. Case by case (according to guideline if there is one)
2. Sufficient clinical experience
3. Consistent scientific literature
4. **Similar mechanism of action in the extrapolated indications**: target/receptor localisation and expression; binding affinity; concentration-response relationship…)
5. PK/PD & biodistribution data
6. Expected adverse events in various indications
7. Expected immunogenicity in various indications

Results From CT-P13 Phase III Equivalence Trial

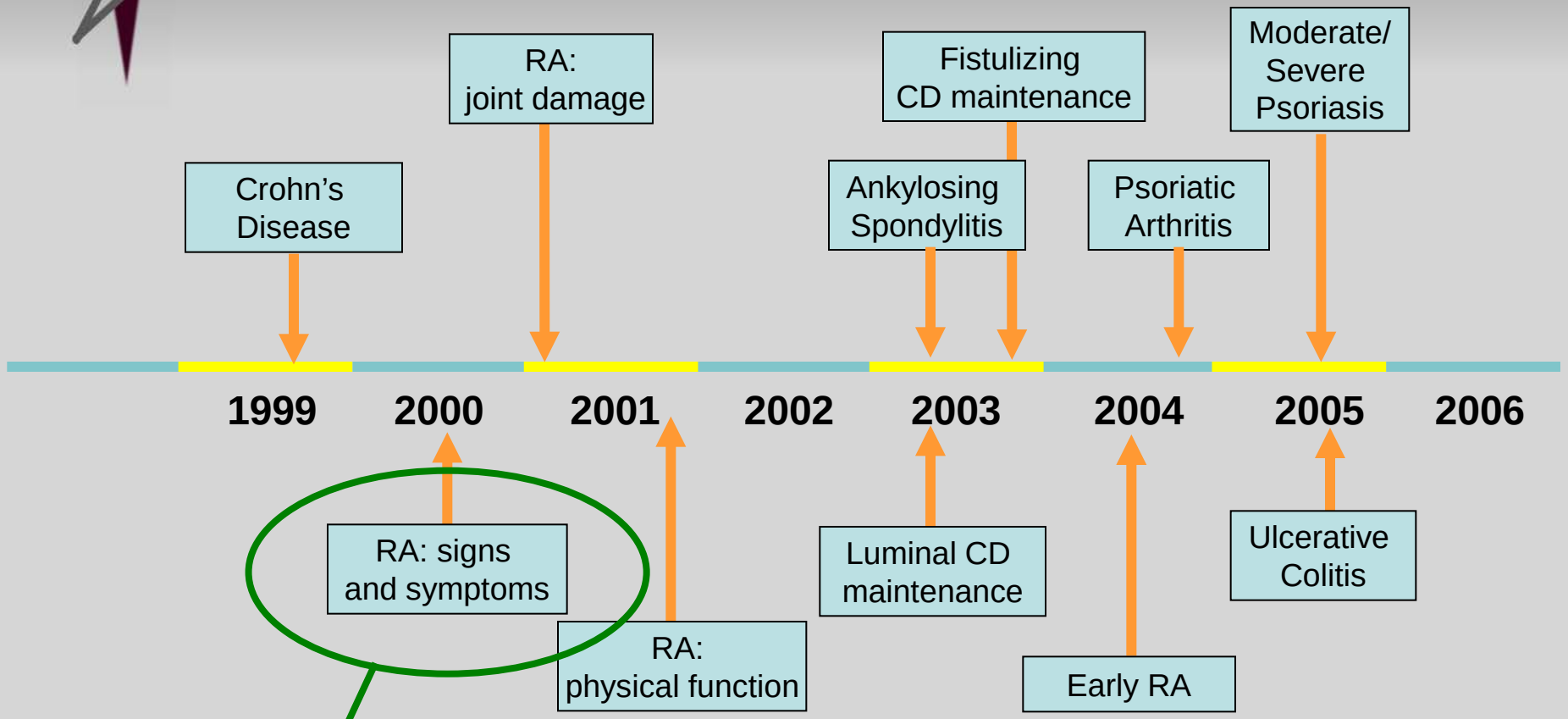
- N = 606. Primary efficacy endpoint:ACR20 response at week 30



- Safety: Treatment-emergent adverse events were seen in 35.2% of patients treated with CT-P13 and 35.9% of patients treated with INX
- Immunogenicity: Equivalent levels of anti-infliximab antibodies were detected in both treatment arms at week 14 and week 30

Yoo DH, et al. *Ann Rheum Dis.* 2013;72(10):1613-1620.

Evolution of Remicade (EU): Efficacy



Basis for extrapolation of indications for Remsima®, together with PK data in AS

+ Post-approval commitment for a Ph III trial in Crohn's disease

CD, Chron's disease

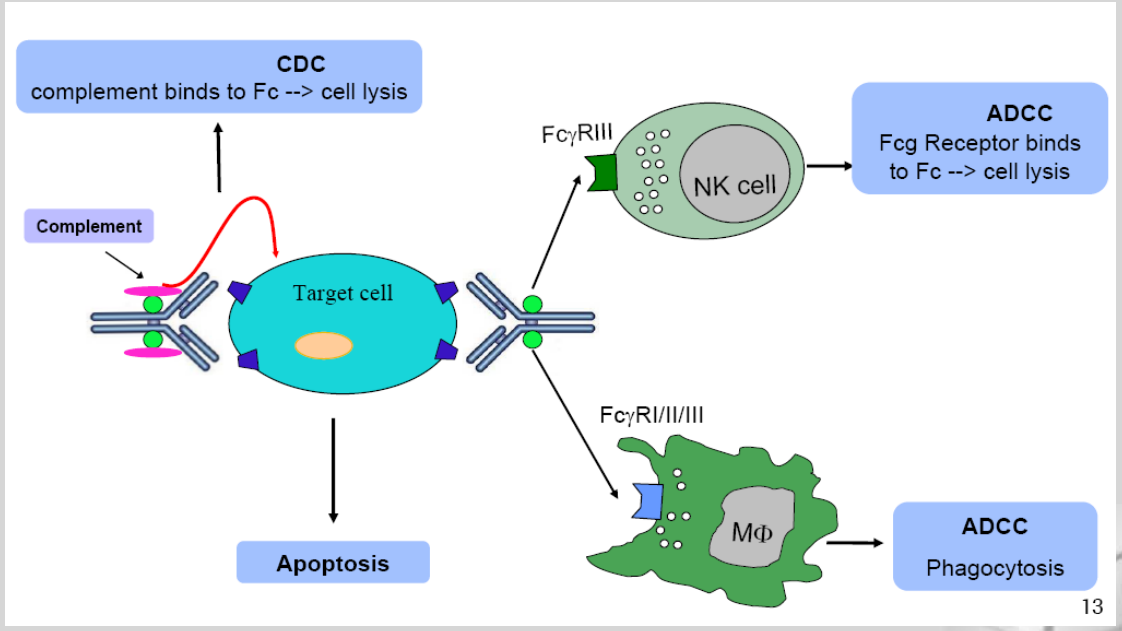
Biosimilar mAbs

Biosimilar monoclonal antibodies (mAbs): the clinical issues are not different from other biosimilars but "technically" are we pushing the concept too far?

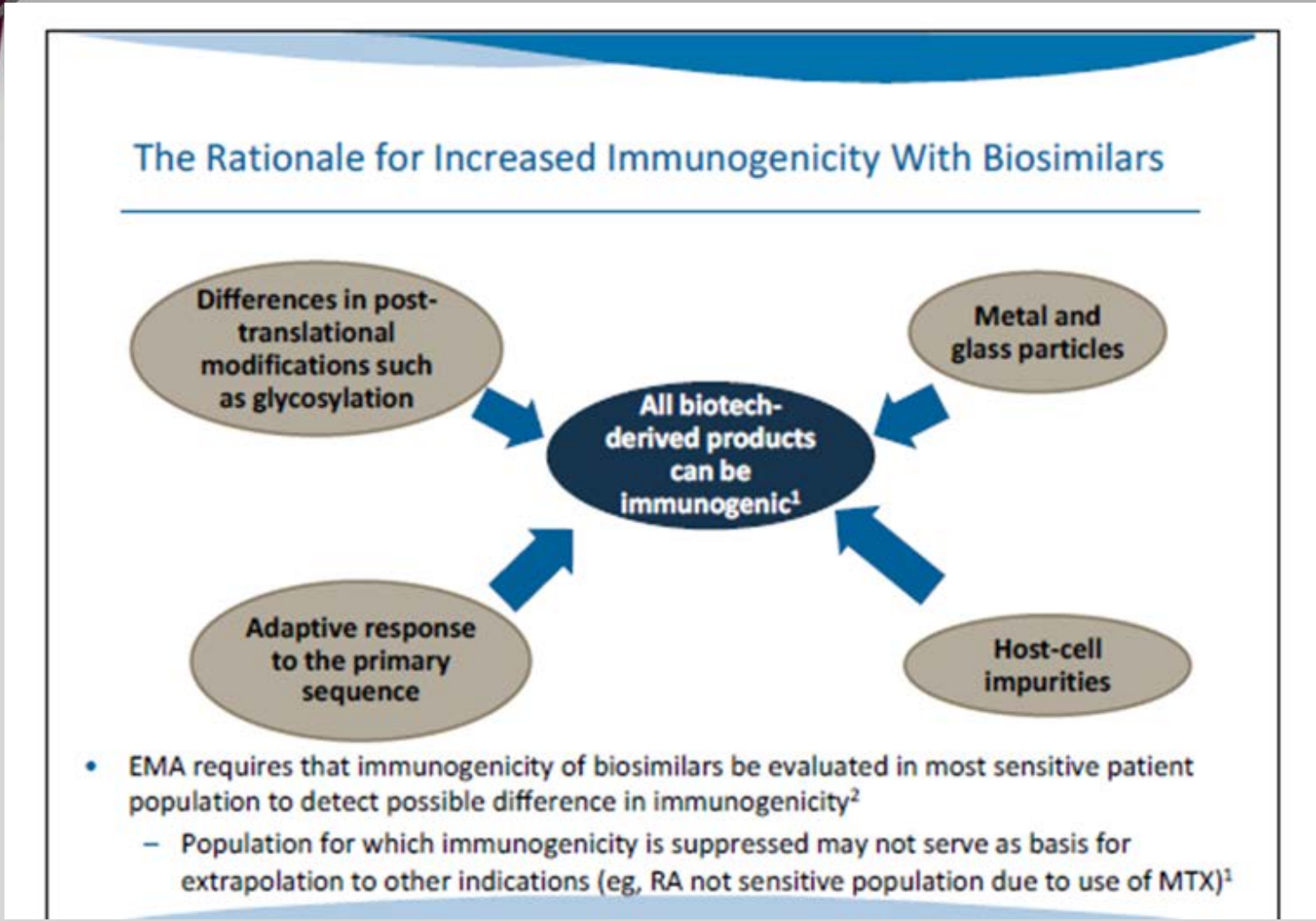
Very complex mechanism of action

Very complex production

Complex (oncology) indications



Increased immunogenicity of biosimilars?



EMA/CHMP. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf. Accessed 25 September 2014..

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 prelicensing if chronic use is intended; the subsequent risk management plan (RMP) is crucial

➞ **Interchangeability ?**

➞ **Traceability (and naming) of biosimilars**

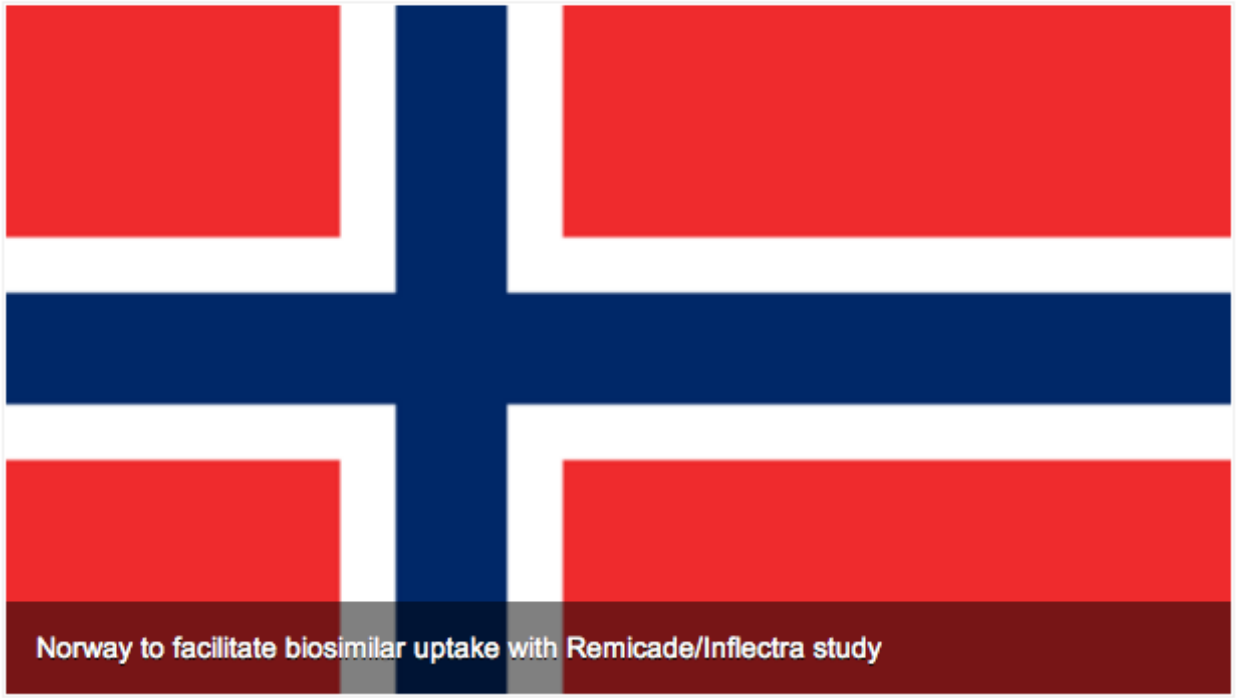
➞ **Should be prescribed under brand names**

Recent initiative towards interchangeability

Norway to facilitate switch to biosimilars with $3m Remicade study

By Dan Stanton+

06-Dec-2013



- NOR-SWITCH study
- 800 patients
- Will start recruiting in October 2014

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**" (regulatory oversight)
3. Therefore, not all **copies** of biological products worldwide can be declared "biosimilar"

Take-home messages (2)

4. The focus of the clinical part of the biosimilar exercise is on PK/PD and dose-concentration-response relationships using sensitive populations and endpoints, it is **not on patient benefit *per se***
5. **Extrapolation of indications** is key to the biosimilar concept but needs to be justified in all cases
6. Several "relatively simple" biosimilars have been approved. The application of the biosimilar concept to **mAbs in oncology** is a leap forward

Take-home messages (3)

7. Detection of **immunogenicity** and a good **risk management plan** are key elements of safety — so far there has been no safety issue with any biosimilar
8. **Traceability** should be ensured by prescribing under brand names
9. **Interchangeability** is a national (or local) issue

10. How much "reassurance" are decision makers and clinicians willing to give away in favor of lower prices?