Biosimilars , un update

Prof. Dr. H. Schellekens
Utrecht University
The Netherlands

The generic paradigm

- Only applicable to small molecules taken orally
- Based on the assumption that pharmaceutical equivalence and bioequivalence = therapeutic equivalence
- Has led to the introduction of many safe, effective and affordable drugs
- Is an important part of the innovation cycle

The first article describing the issues when patents of biologics will expire

Opinion TRENDS in Pharmacological Sciences Vol.23 No.3 March 2002 119

‘Biogenerics’: the off-patent biotech products

Huub Schellekens and Jean-Charles Ryff

The first patents of biopharmaceuticals derived from recombinant DNA will expire shortly, which raises the possibility of marketing generic products (‘biogenerics’) with limited documentation, similar to that which occurs with conventional pharmaceuticals. We propose the term off-patent biotechnological products (OPBPs) as an alternative to biogenerics when describing such products. It is questionable whether the majority of OPBPs can be classified as similar to the innovator products, considering the size and complexity of the molecules and the many factors that influence biological activity. There are three classes of OPBPs, each of which needs to meet different regulatory demands when seeking marketing authorization.

study in volunteers that compares pharmacokinetics and/or pharmacodynamics. The question is whether such limited information is sufficient to ensure the efficacy and safety of the majority of biopharmaceuticals that are derived from recombinant DNA.

Biopharmaceuticals

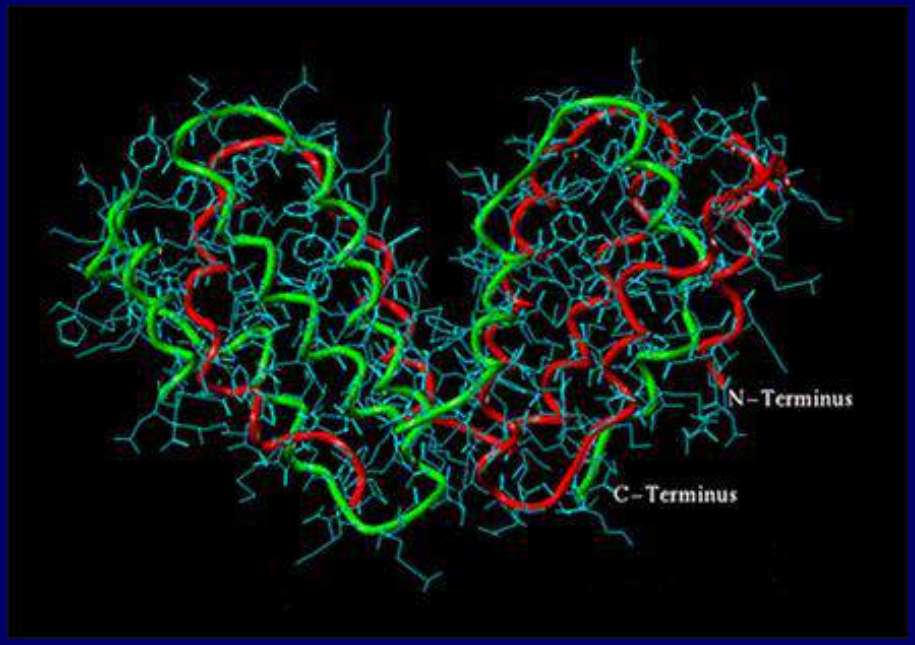
Most biopharmaceuticals are large, complex molecules that, for several reasons, are heterogeneous. Some heterogeneity is caused by the combination of vector and host cell used to produce the biopharmaceutical, and includes clipping (premature termination of translation) and differences in the sites and amount of glycosylation [1,2]. Protein modification might occur during production, depending on the fermentation and cell culture conditions [3]. The extraction and purification procedures can also add to the heterogeneity, as can process-related impurities and the introduction of contaminants that might appear in the final product [4–6]. Lastly, formulation and storage conditions might alter the biological properties and, thus, the response, as a result of physicochemical or physical

Schellekens H and Ryff JC. *Trends Pharmacol Sci* 2002;23:119–121

The arguments for a separate pathway for biologics

Biologics are large, complex molecules

- Biologics are much larger, with more complicated structures than classical drugs

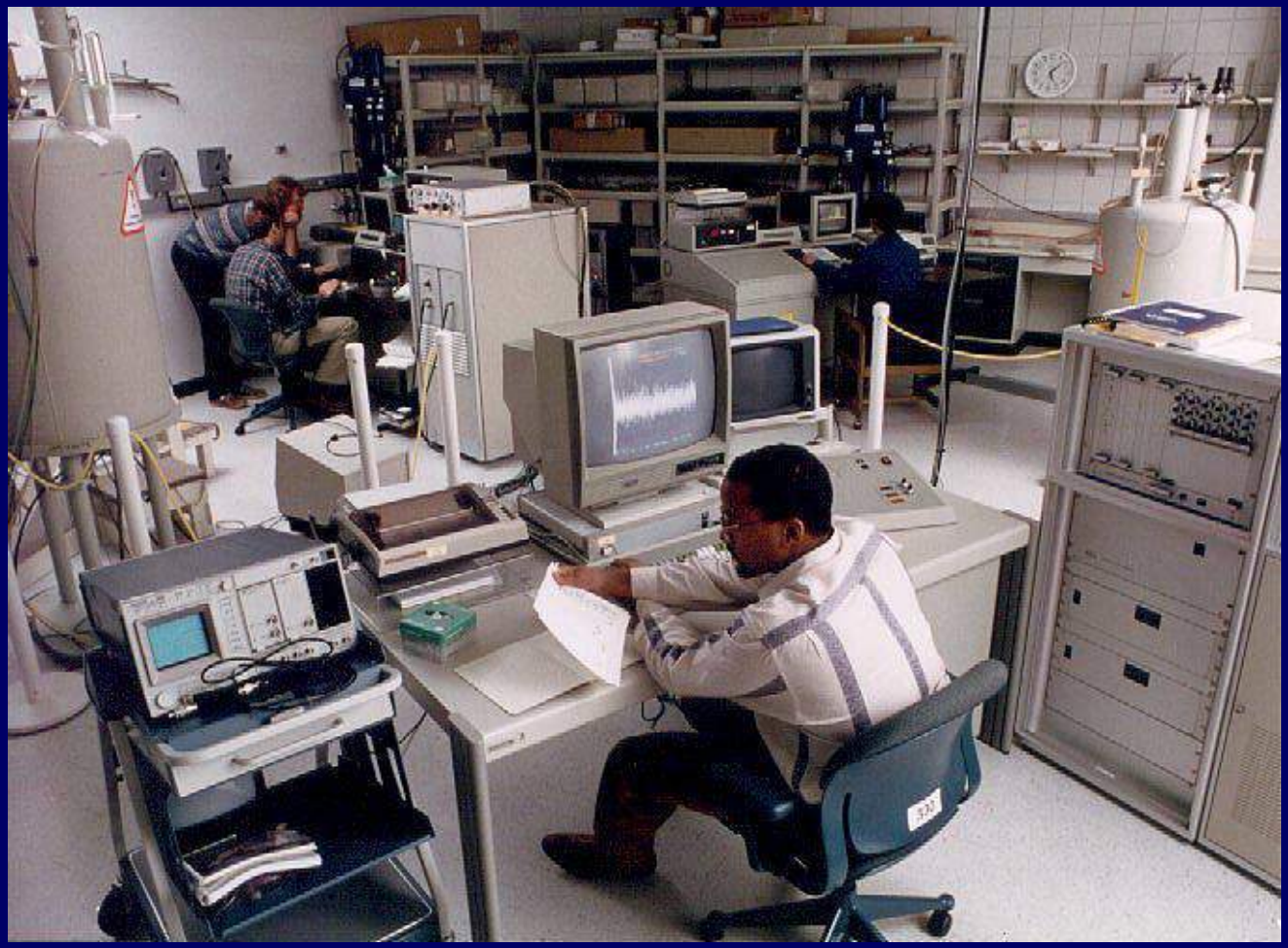


Interferon beta: Molecular weight 19,000

Aspirin: Molecular weight 180

Schellekens H. *Nephrol Dial Transplant* 2009;2(Suppl 1):iv27–36

Physical chemical analyses do not predict the biological and clinical properties of biologics

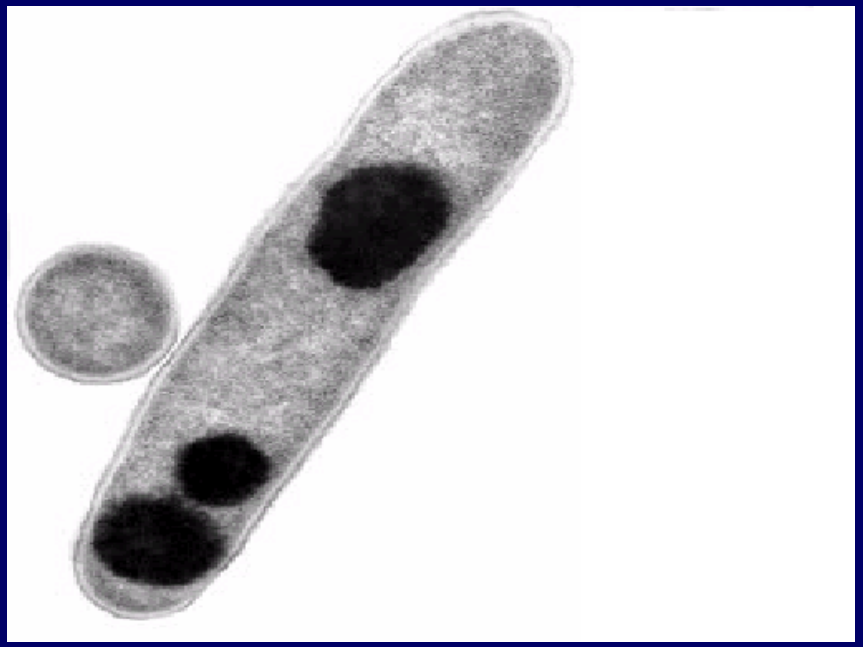


The analytical tools for biologics are 10–100 times less sensitive than for classical drugs

Schellekens H. *Nephrol Dial Transplant* 2009;2(Suppl 1):iv27–36

Biologics are produced by living cells

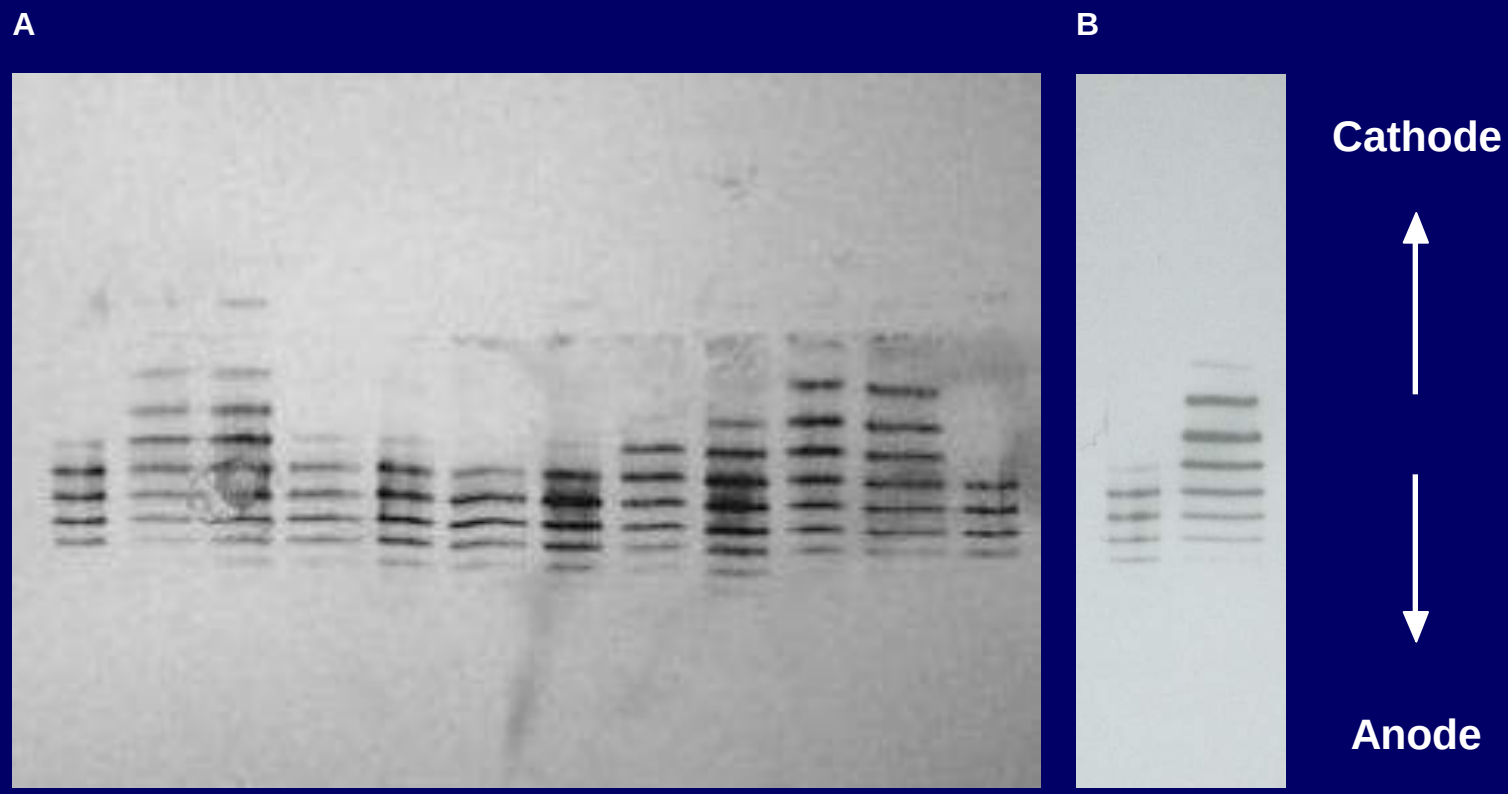
- Biologics are produced under controlled conditions
- Newly generated proteins undergo complex post-translational modifications:
  - Highly sensitive to production conditions
  - Minor changes can have major impacts on biological activity



Escherichia coli bacterium producing interferon gamma

Roger SD. *Nephrology* 2006;11:341–346
Schellekens H. *Nephrol Dial Transplant* 2009;2(Suppl 1):iv27–36

Biologics are heterogeneous: isoelectric focusing of epoetins



Schellekens H and Combe C. ERA-EDTA Congress 2004, Poster MP282
Schellekens H. *Nephrol Dial Transplant* 2009;2(Suppl 1):iv27–36

Conventional drugs vs biologics

	Conventional Drugs	Biologics
Size	Small	Large
Structure	Simple	Complex
Stability	Stable	Unstable
Modifications	Well-defined	Many options
Manufacturing	• Defined, reproducible chemical process • Identical copies can be made	• Unique biological processes within living cell lines • Impossible to ensure identical copies
Characterisation	Easy to fully characterise	Difficult to characterise fully due to a mixture of related molecules
Immunogenicity	Non-immunogenic	Immunogenic

Schellekens H. *Nephrol Dial Transplant* 2009;2(Suppl 1):iv27–36

Immunogenicity of therapeutic proteins is a key issue

Factors influencing immunogenicity

- Structural properties
  - Sequence variation
  - Glycosylation
- Other factors
  - Assays
  - Contaminants and impurities
  - Formulation
  - Downstream processing
  - Route of administration
  - Dose and length of treatment
  - Patient characteristics
  - Unknown factors

Schellekens H. *Nat Rev Drug Discov* 2002;1:457–462

Consequences of immunogenicity

Loss of efficacy

- Insulin
- Streptokinase
- Staphylokinase
- ADA
- Salmon calcitonin
- Factor VIII
- Interferon alpha-2
- Interferon beta
- IL-2
- GnRH
- TNFR55/IgG1
- Denileukin diftitox
- HCG
- GM-CSF/IL3

Enhancement of efficacy

- Growth hormone

Neutralisation of native protein

- MDGF
- EPO

General immune effects

- Allergy
- Anaphylaxis
- Serum sickness, etc.

EU regulatory requirements

Biological products: Overview of relevant EU guidelines

Overarching Guideline (CHMP 437/04)
Guideline on Similar Biological Medicinal Products
Defines concept, principles and provides user guide

Quality	**Clinical & Non-clinical**	**Immunogenicity Assessment**
CHMP/BWP/49348/2005	CHMP/BMWP/42832/2005	CHMP/BMWP/14327/2006

Product-specific

EPO	Insulin
G-CSF	HGH
LMWH	IFNα
FSH	IFNβ

Monoclonal antibodies

Guideline on Similar Biological Medicinal Products. European Medicines Agency. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Last accessed: January 2014; Guideline On Immunogenicity Assessment Of Biotechnology-derived Therapeutic Proteins. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003947.pdf. Last accessed: January 2014

Principles of the EMA approach for biosimilars

- Full quality dossier, including comparisons with original
- Limited preclinical dossier, including pharmacokinetic comparison with original
- Clinical similarity – hard clinical endpoint not needed
- Extrapolation possible
- Risk management plan needed with post-marketing safety studies, including immunogenicity

Guideline on Similar Biological Medicinal Products. European Medicines Agency. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Last accessed: January 2014

Experience with biosimilars in the EU

Current EU approved biosimilars

- First-wave of biosimilars approved in the EU:

Class	Product	Medicine Name	Active Substance (INN)	EU Authorisation Date
Epoetins	HX575	Abseamed	epoetin alfa	28/08/2007
		Binocrit	epoetin alfa	28/08/2007
		Epoetin alfa Hexal	epoetin alfa	28/08/2007
	SB-309	Retacrit	epoetin zeta	18/12/2007
		Silapo	epoetin zeta	18/12/2007
Granulocyte colony-stimulating factor (G-CSF)	XM02	Biograstim	filgrastim	15/09/2008
		Ratiograstim	filgrastim	15/09/2008
		Tevagrastim	filgrastim	15/09/2008
	EP2006	Filgrastim Hexal	filgrastim	06/02/2009
		Zarzio	filgrastim	06/02/2009
	PLD108	Nivestim	filgrastim	08/06/2010
Human growth hormone	NA	Omnitrope	somatropin	12/04/2006
	~~NA~~	~~Valtropin~~	~~somatropin~~	Withdrawn

- Biosimilar infliximab approved in the EU for inflammatory disorders:
  - Remsima/Inflectra (Celltrion/Hospira): September 2013

Biosimilars Approved in Europe. Available from: http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe. Last accessed January 2014

The biosimilar landscape in the EU

- Biosimilar regulations have resulted in the introduction of safe, effective biosimilars of high quality
- However, the cost savings have been modest (20–30%)

Cornes P. *Target Oncol* 2012;7(Suppl 1):57–67
Jelkmann W. *Am J Hematol* 2010;85:771–780

WHO guideline for biosimilars

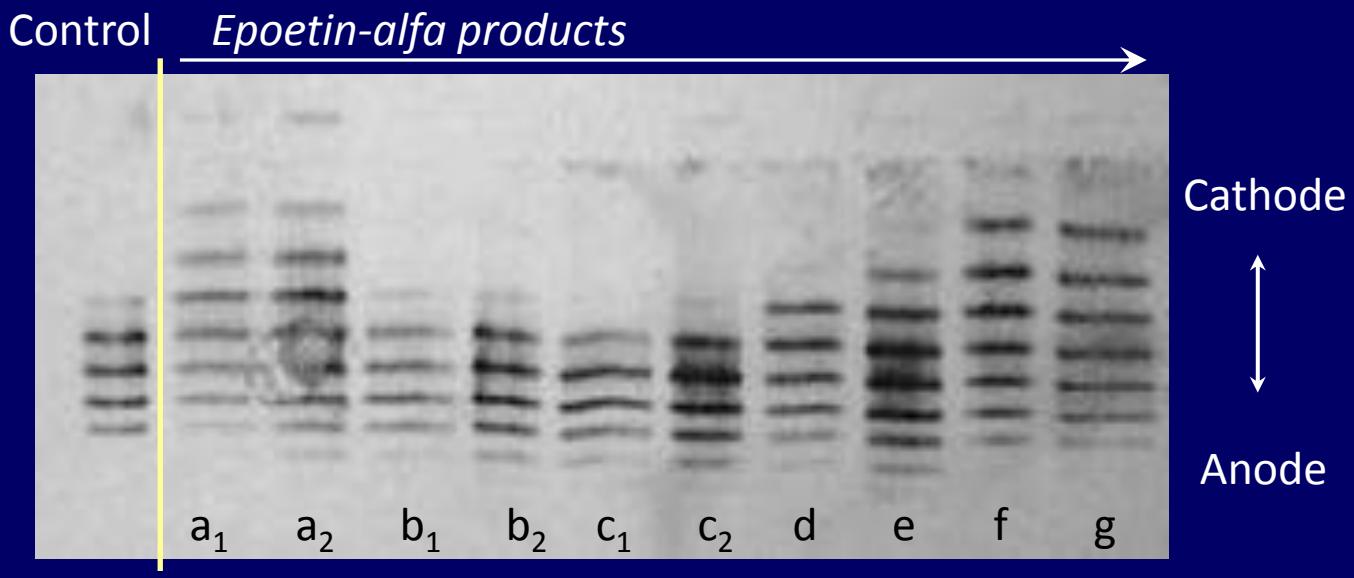
- Clinical data are necessary
- Immunogenicity should always be tested
- Pharmacovigilance is essential

Guidelines on evaluation of Similar Biotherapeutic Products (SBPs). World Health Organization. Available from: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf. Last accessed: January 2014

Non-regulated copies are not biosimilars, but “bioquestionables”

Products made by different independent, follow-on manufacturers' processes are different

- Even batches from the same manufacturer may vary in composition



Letter labels a–g refer to independent manufacturers; numbers refer to batches from same manufacturer.

Adapted from: Schellekens H. *Eur J Hosp Pharm* 2004;10:43–47

The “biosimilar” landscape in the developing world

Challenges with “biosimilars” in the developing world

Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies

Kearkiat Praditpornsilpa, Khajohn Tiranathanagul, Pawinee Kupatawintu, Saengsuree Jootar, Tanin Intragumtornchai, Kriang Tungsanga, Tanyarat Teerapornlertratt, Dusit Lumlertkul, Natavudh Townamchai, Paweena Susantitaphong, Pisut Katavetin, Talerngsak Kanjanabuch, Yingyos Avihingsanon and Somchai Eiam-Ong

Recombinant human erythropoietin (r-HuEpo) has been used for the treatment of renal anemia. With the loss of its patent protection, there has been an upsurge of more affordable biosimilar agents, increasing patient access to treatment for these conditions. The complexity of the manufacturing process for these recombinant proteins, however, can result in altered properties that may significantly affect patient safety. As it is not known whether various r-HuEpo products can be safely interchanged, we studied 30 patients with chronic kidney disease treated by subcutaneous injection with biosimilar r-HuEpo and who developed a sudden loss of efficacy. Sera from 23 of these patients were positive for r-HuEpo-neutralizing antibodies, and their bone marrow biopsies indicated pure red-cell aplasia, indicating the loss of erythroblasts. Sera and bone marrow biopsies from the remaining seven patients were negative for anti-r-HuEpo antibodies and red-cell aplasia, respectively. The cause for r-HuEpo hyporesponsiveness was occult gastrointestinal bleeding. Thus, subcutaneous injection of biosimilar r-HuEpo can cause adverse immunological effects. A large, long-term, pharmacovigilance study is necessary to monitor and ensure patient safety for these agents.

Praditpornsilpa K, et al. *Kidney Int* 2011;80:88–92

Distinguishing biosimilars from "bioquestionables"

Biosimilars need comparative clinical data

To the Editor: We have read with great interest the study by Praditpornsilpa *et al.*[1] in *Kidney International* about the association between antibody-associated pure red cell aplasia (PRCA) and the use of copies of epoetins alpha and beta, for which the marketing authorization was based on the generic regulatory approach used for small molecules, which does not demand comparative clinical data.

Nicole Casadevall[1], Robin Thorpe[2] and Huub Schellekens[3]

[1]Hôpital Saint Antoine, Paris, France; [2]Biotherapeutics Group, NIBSC-HPA, Herts, UK and [3]Faculty of Sciences, Utrecht University, Utrecht, The Netherlands

Correspondence: *Nicole Casadevall, Hôpital Saint Antoine, Paris 75571, France. E-mail: nicole.casadevall@sat.aphp.fr*

Casadevall N, et al. *Kidney Int* 2011;80:553

Ongoing study in Bangkok

- 19 epoetins available in Thailand registered by the classical generic pathway
- All CKD patients treated with epoetin in registry
- All batches used are being analysed in Utrecht University
- Study blinded until March 2014

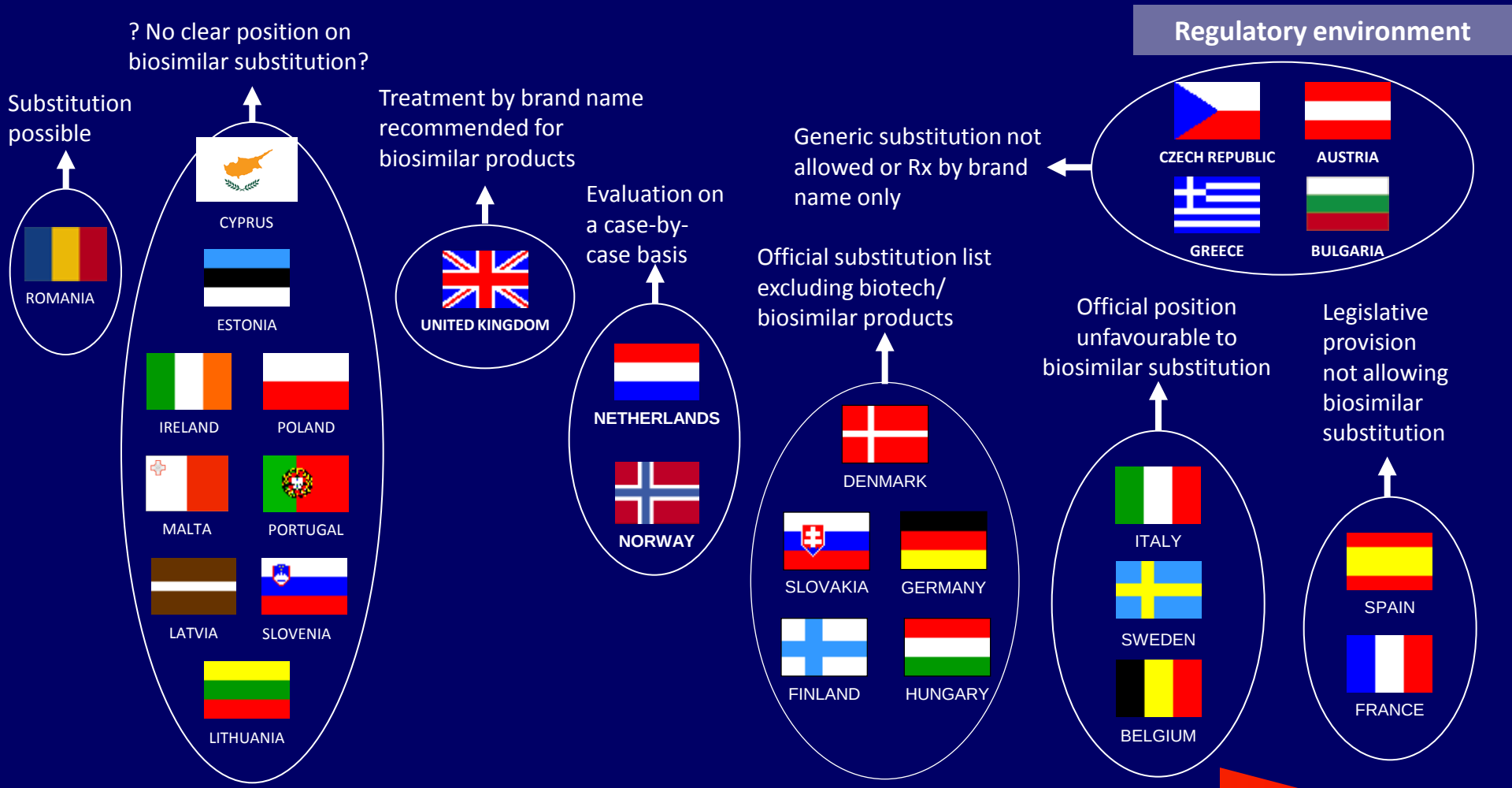
Data on file.

Outstanding issues with biosimilars

Outstanding issues with biosimilars

- Substitution
- Interchangeability
  - Population level
  - Individual level
- Immunogenicity
- Nomenclature
- Pharmacovigilance

Biosimilar substitution policies



The next generation of biosimilars: Monoclonal antibodies/fusion proteins

Main problems with biosimilar monoclonal antibodies

- To show clinical similarity between reference product and biosimilar
- Extrapolation of data from the reference indication

Calvo B and Zuniga L. *Curr Med Chem* 2012;19:4445–4450

The first biosimilar monoclonal antibody in the EU

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2013
EMA/CHMP/589317/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Remsima

International non-proprietary name: Infliximab

Remsima EMA Assessment Report. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002576/WC500151486.pdf. Last accessed: January 2014

Sample size calculations assuming various effect size differences Avastin trial NO16966 (Saltz, 2008)

Time to event Endpoint	Placebo efficacy	Innovator efficacy (HR 97.5% CI)†	Sample size required (δ= HR 1.05)	Sample size required (δ= HR 1.1)	Sample size required (δ= HR 1.2)
Median OS*	19.9 months	21.3 months (0.84[076-1.03])	15760	4130	1130
PFS*	8.0 months	9.4 months (0.83 [0.72-0.95])	11242	2946	806
Binary Endpoint†	**Placebo efficacy**	**Innovator efficacy †**	**(δ = 10% of Δ Bev & PBO)**	**(δ = 25% of Δ Bev & PBO)**	**(δ = 50% of Δ Bev & PBO)**
One year survival	72.1%	77.9%	126566 (δ=1.09%)	20254 (δ= 1.45%)	5066 (δ= 2.9%)
One year PFS	25.4%	31.03%	166976 (δ=0.56%)	26716 (δ= 1.41%)	6678 (δ= 2.82%)
Hypertension	6.4%	18.9%	24268 (δ=1.25%)	3887 (δ=3.125%)	978 (δ=6.25%)

Saltz L. and al. Bevacizumab in Combination With Oxaliplatin-Based Chemotherapy As First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study. J Clin Oncol (2008) 26:2013-2019

Conclusions

- Price drop by biosimilars modest
- Introduction and market penetration slow
- Mainly big companies involved
- Quality of biosimilars in the EU high
- Still a number of issues, including extrapolation
- Still a lot of low quality biologics (“bioquestionables”) around