
PhAMA
Innovative Medicines for Malaysia
1ST NATIONAL
BIO-THERAPEUTICS
CONGRESS – PUTTING PATIENT FIRST
22 NOVEMBER 2014

Biosimilars - Interchangeability and Substitution

Dr. Paul Cornes

PhAMA

1ST NATIONAL BIO-THERAPEUTICS

Dr Paul Cornes
Conflict of interest

- **Salary received:**
  - **United Kingdom National Health Service**
- **Honoraria received:**
  - **Roche**
  - **Janssen**
  - **Sandoz**
  - **Lilly**
  - **European Generics Association**
  - **Teva**
  - **Hospira**

Biosimilars - Interchangeability and substitution

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Consultant Oncologist,
Bristol Haematology& Oncology Centre

Comparative Outcomes Group

ESO Task Force Advisory Board on Access to Innovative Treatment in Europe

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6500 Bellinzona - Switzerland

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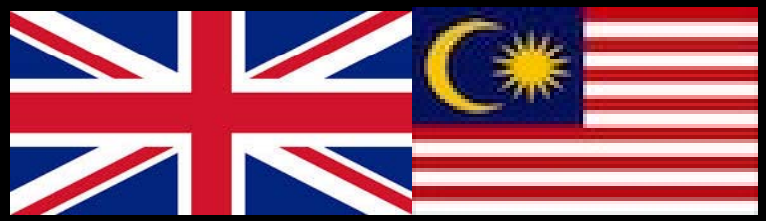
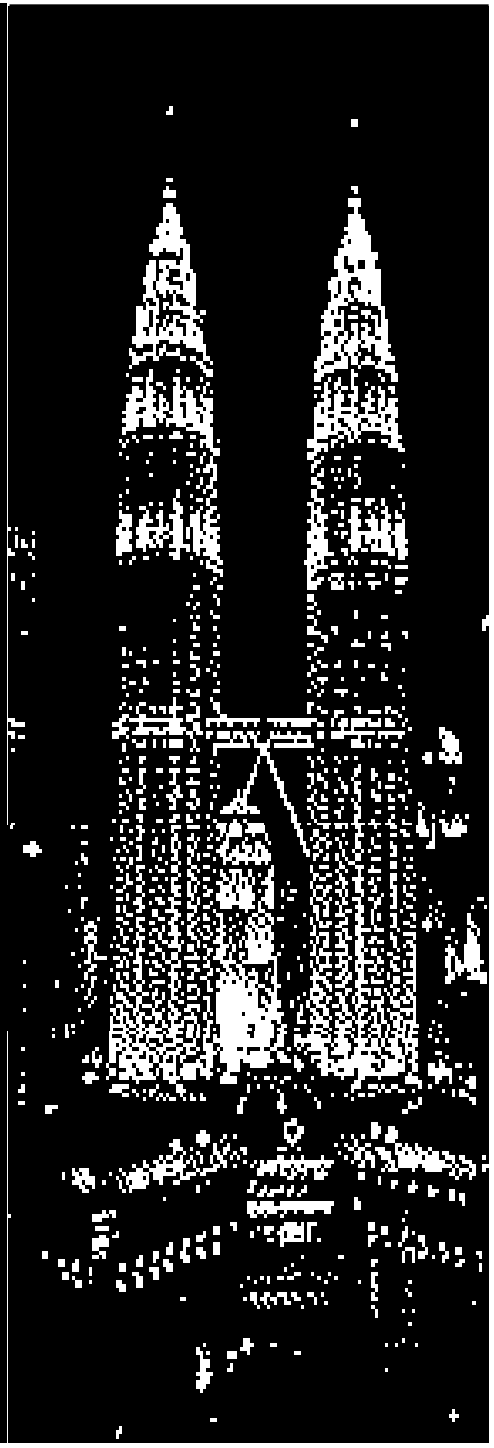
Biosimilars - Interchangeability and substitution





Question 1

- **You are part way through a course of treatment with infliximab for rheumatoid disease - The patient is responding without serious toxicity**
- **Your pharmacy colleagues tell you that the next treatment is likely to come from a new purchase of biosimilar infliximab (approved for use by the EMEA)**

- **Do you? – please chose your best response:**

1. **Refuse – as the patient is part way through treatment and switching is not advised by Malaysian Guidelines**
2. **Agree – but worry there is no data to support this change**
3. **Agree to the switch – as no excess adverse events are expected**

Question 2

- **You are part way through a course of dose dense chemotherapy for breast cancer – supported by Filgrastim GCSF to prevent neutropaenia. The patient is responding without serious toxicity**
- **The patient will transfer mid-way through treatment to stay with her family in another area. Your colleague tells you that in their hospital, they use only biosimilar Filgrastim (approved for use by the EMEA and Malaysian Regulators)**

- **Do you? – please chose your best response:**

1. **Refuse – the patient is part way through treatment and switching is not advised by Malaysian Guidelines**
2. **Agree – but worry there is no data to support this change**
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Biosimilars - Interchangeability and substitution

- Questions

- Why have we been worried?
- Terminology
- Rules
- Evidence for safety
  - Regulatory
- Observational studies of substitution & switching
  - Originator to Originator
  - Originator to Biosimilar
- RCTs of switching

- Questions Revisited

Biosimilars may share primary DNA and amino acid sequence with originators

- But with
  - Different vectors to transform host cells
  - Different Cell Banks
  - Different cell culture medium
  - Different culture vessels - “Bioreactors”
  - …..

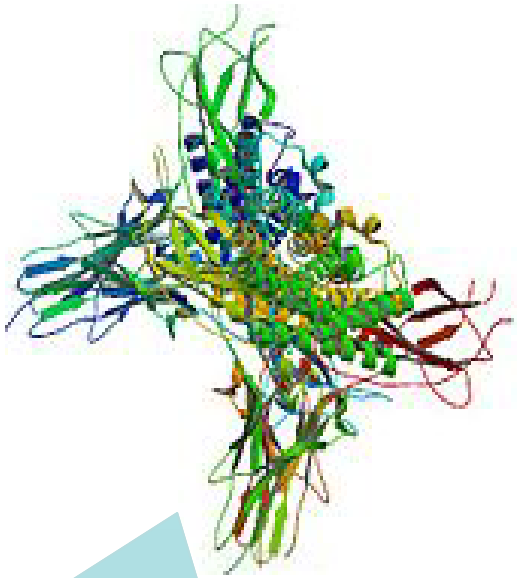
- Different tertiary structure could result
  - Which could alter the functionality or safety of the drug

Ref Schiestl M et al: Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat Biotechnol. 2011 Apr;29(4):310-2.

What might make physicians hesitate?

- **Immunogenicity**

- **A protein can be modified in many ways:**
  - **side chains can be added,**
  - **protein misfolding makes different tertiary structure**
  - **degradation by oxidation or deamidation**



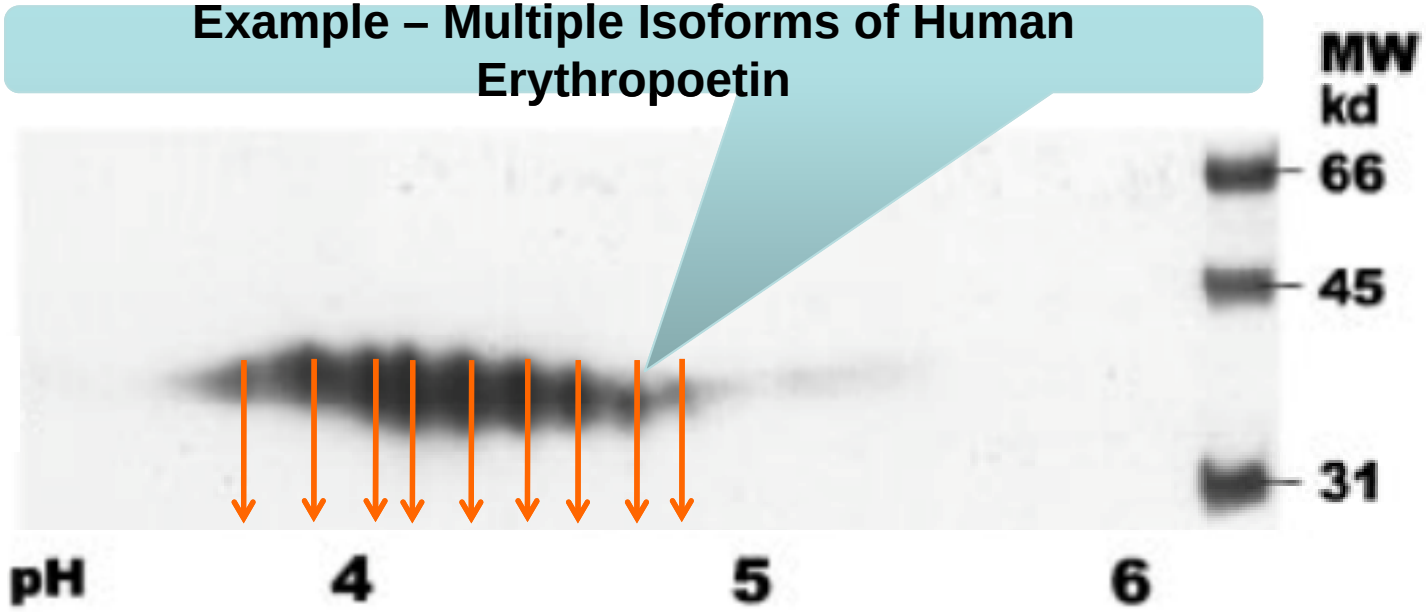
Different patented manufacturing processes may invariably lead to structural differences in the final product

Unlike classical generics, biosimilars are not *identical* to their originator products

– Committee for medicinal products for human use. Annex guideline on similar bi
medicinal products containing biotechnology-Derived proteins as active substa
clinical and clinical issues: Guidance on biosimilar medicinal products containin
recombinant erythropoietins. European Medicines Agency. EMEA/CHMP/94526/2
2005

“Highly similar but not identical”

- Is not new to biotechnology
- Natural proteins come in a spectrum of isoforms



Human serum EPO (65 ng). Two-dimensional gel electrophoresis of human serum EPO. IEF was carried out by using IPG strips with a pH gradient of 3 to 6. SDS-PAGE was performed in 12% gels followed by immunoblotting

“Highly similar but not identical”

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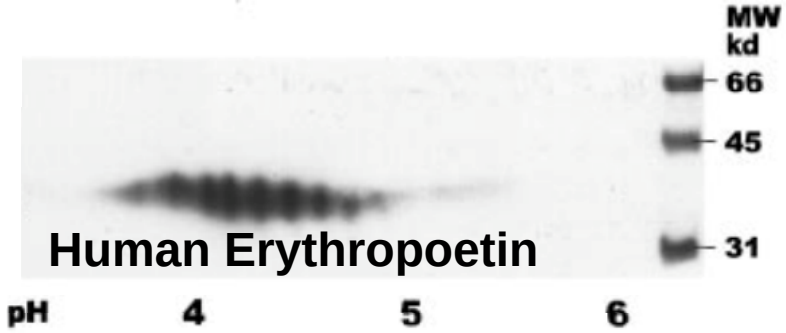

Skibeli V et al. Sugar profiling proves that human serum erythropoietin differs from recombinant human erythropoietin. Blood. 2001 Dec 15;98(13):3626-34.

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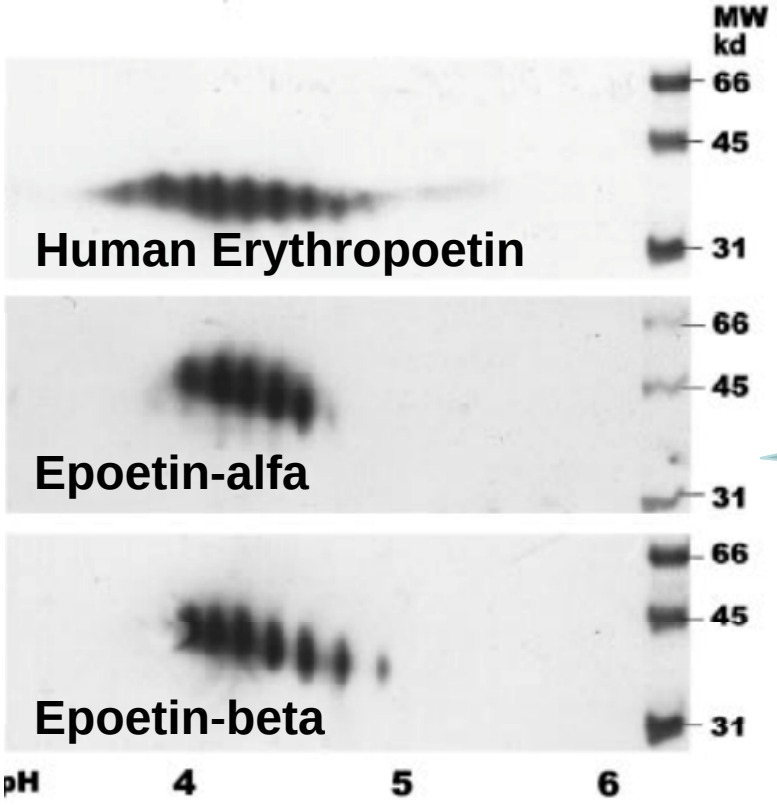


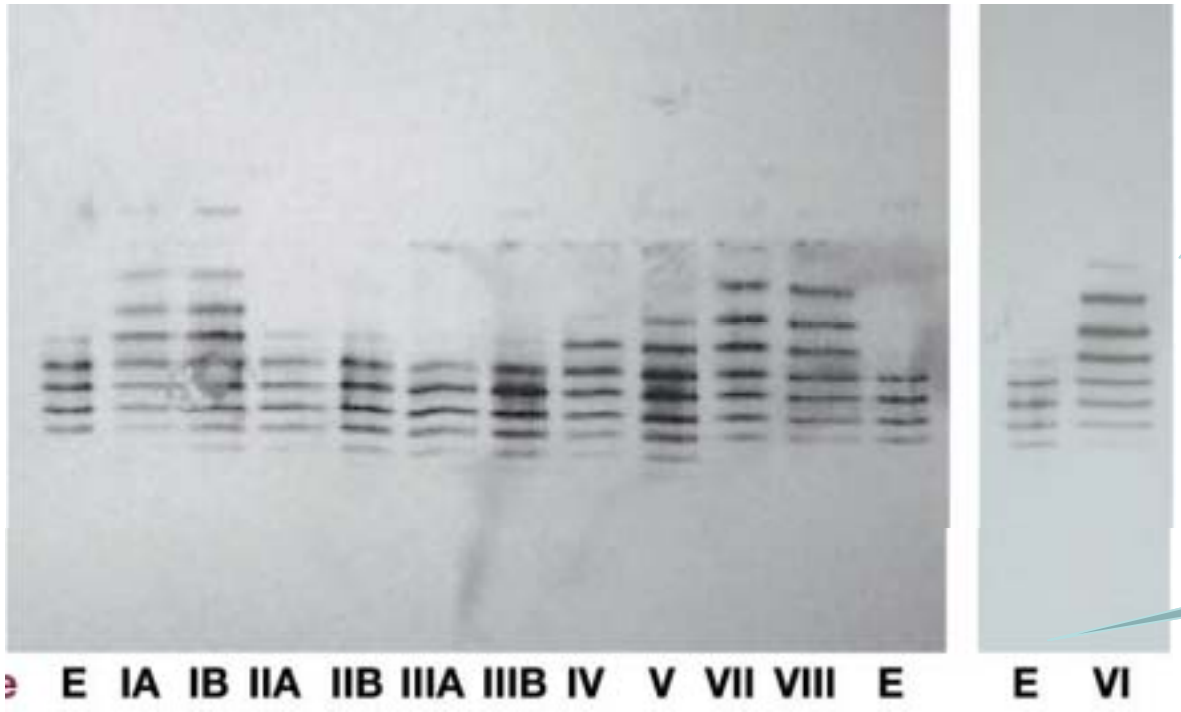
Recombinant drugs try to copy the spectrum of structure of natural proteins

There is no single “unique” structure of the drug

ıman serum EPO (65 ng). Two-dimensional gel electrophoresis of human serum EPO. ⁼ was carried out by using IPG strips with a pH gradient of 3 to 6. SDS-PAGE was rformed in 12% gels followed by immunoblotting

Skibeli V et al. Sugar profiling proves that human serum erythropoietin differs from recombinant human erythropoietin. Blood. 2001 Dec 15;98(13):3626-34.

Protein variation in products marketed internationally as epoetin alpha



Multiple different isoforms of proteins naturally occur

E is the original reference product

Unregulated copy drugs bought in Asia and South America

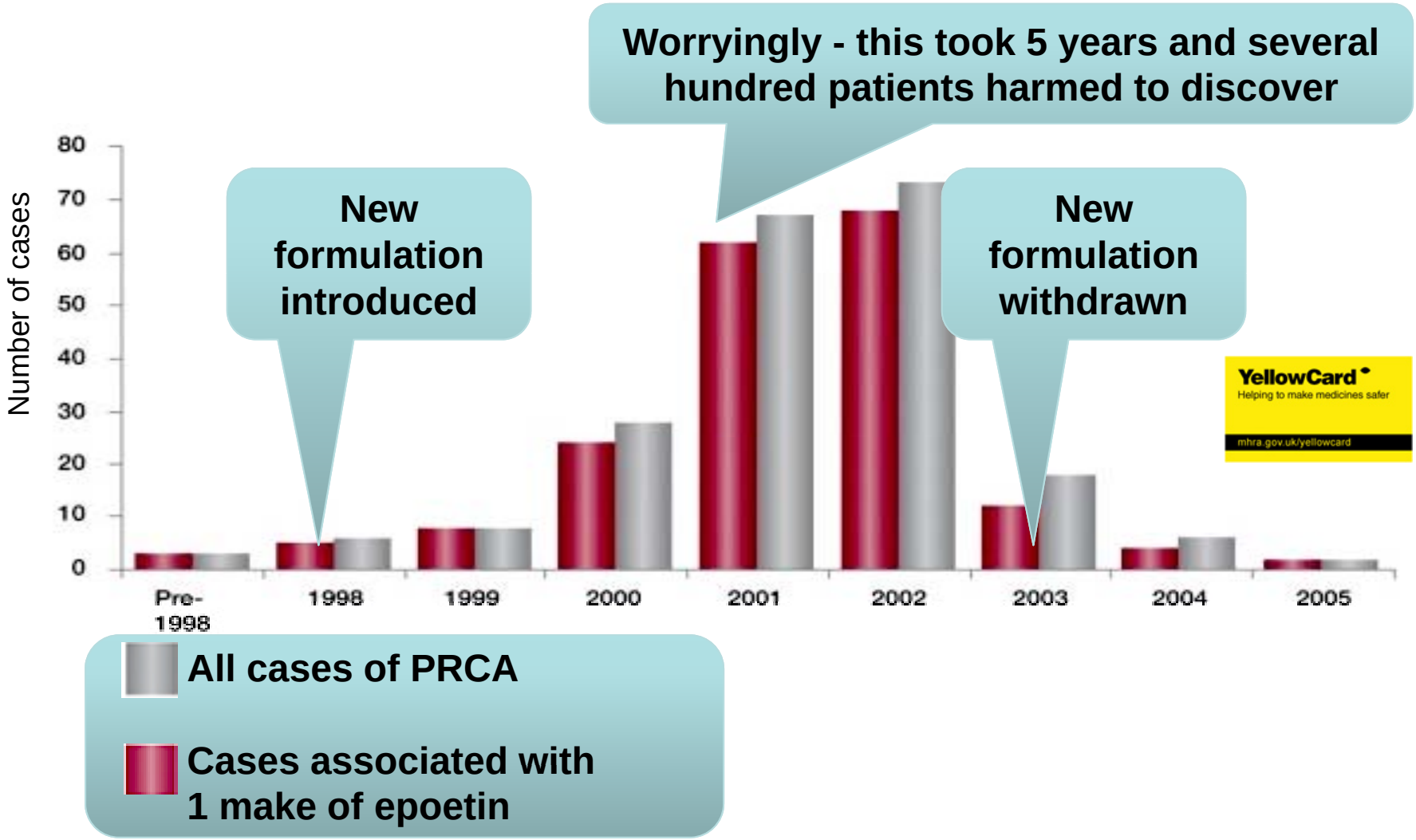
Ref: Schellekens H. Follow-on biologics: challenges of the “next generation”. Nephrol Dial Transplant 2005;20(suppl 4):iv31-6

Immunogenicity from small manufacturing changes

- **Eprex® (epoetin alfa)**

- **Two production changes made….**
  1. **uncoated rubber stoppers used in the syringe**
  2. **a new stabiliser added**
     - K. Boven. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. Kidney Int, 67:2346-2353, 2005.
- **Several hundred patients developed anti-epoetin antibodies**
  - **these neutralised both endogenous erythropoietin and injected epoetin,**
  - **and stopped the bone marrow making red cells with development of profound anaemia**
  - **leading to some fatalities**
    - A. Kromminga. Antibodies against erythropoietin and other protein-based therapeutics: an overview. Ann N Y AcadSci, 1050:257-265, 2005.

Time-course of PRCA

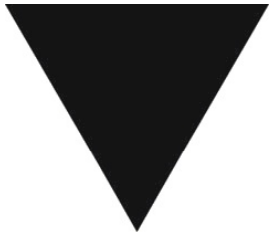


Ref: Kuhlmann M. Lessons learned from biosimilarepoetins and insulins. British Journal of Diabetes & Vascular Disease 2010 10: 90

Safety of biosimilar medicines: “EU DRA Vigilance”

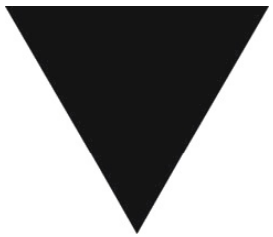
- **New EU pharmacovigilance legislation came into force in July 2012**
  - **legal obligation for the systematic tracking of medicines from manufacturer to patient**
    - Sträter B. New pharmacovigilance rules in the EU and their impact on biosimilars and automatic substitution. Scrip Regulatory Affairs. 10 Nov 2011.
  - **puts biosimilars in the same class as new substances**
  - **this means that manufacturers must include a ‘black symbol’ in the product information**

EMEA: 2 weekly reports on any new drug or indication or if safety worries



EMA. First Annual Report on EudraVigilance for the European Parliament, the Council and the Commission. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146607.pdf. Accessed March 6th, 2014

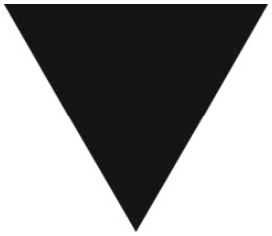

IF YOU SEE SOMETHING, SAY SOMETHING.
BE SUSPICIOUS OF ANYTHING UNATTENDED.
Tell a cop, an MTA employee or call 1-888-NYC-SAFE.




YellowCard
Helping to make medicines safer
mhra.gov.uk/yellowcard

How good is the new vigilance system?

- **EUDRA – Vigilance**
  - **2,108,742 unique ADR reports**
  - **439,971 biologic ADRs**



  - **A total of 13,790 biopharmaceuticals (9,759 suspected) for which a biosimilar has been approved in the EU were identified in EV.**
  - **For 90.4 % of these biopharmaceuticals and 96.2 % of the suspected biopharmaceuticals the product was clearly identifiable.**

Vermeer NS et al. Traceability of biopharmaceuticals in spontaneous reporting systems: a cross-sectional study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilancedatabases.DrugSaf. 2013 Aug;36(8):617-25.

Neutralizing antibodies to epoetinalfa triggered by soluble tungsten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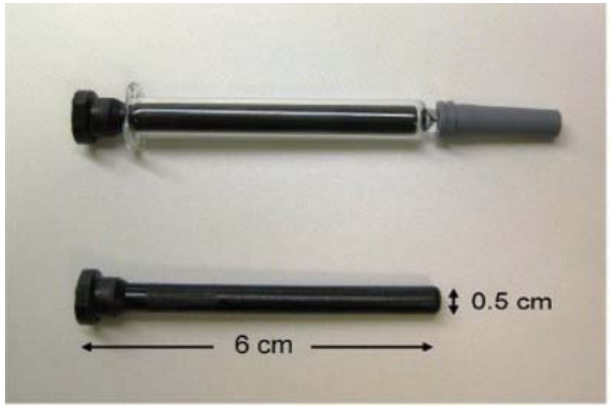
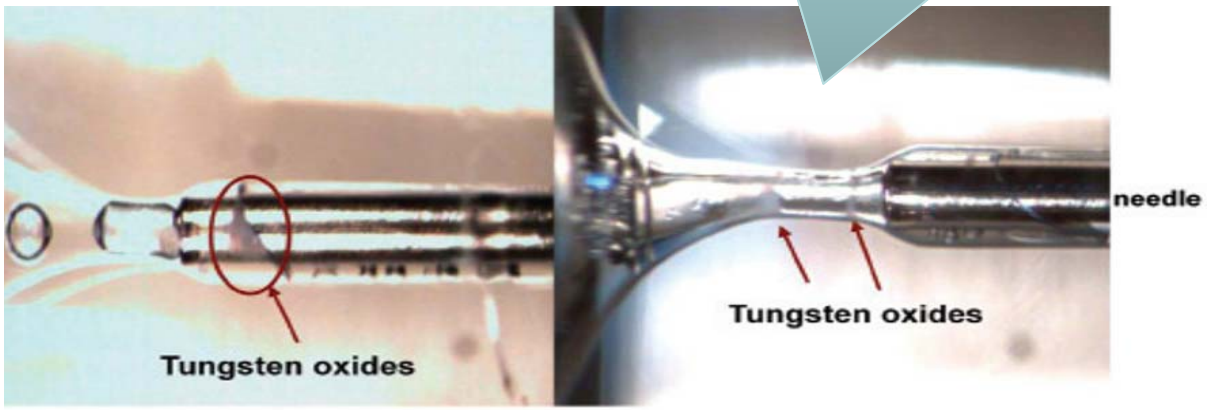
Extractable and Leachable Implications on Biological Products in Prefilled Syringes
Posted: January 01, 2011
Tweet 0 Like 0 Email Print Comments (0)
Yasser Nashed- Samuel
Dengfeng Liu
Kiyoshi Fujimori
Lourdes Perez
Hans Lee, Ph.D.
• Amgen Inc.
0.5 cm
6 cm

- **Amgen Study:**
- **Tungsten pins are used to form the needle cavity in glass pre-filled drug syringes**

1,200 °C used to melt glass is sufficient to release some tungsten from the metal moulding pin

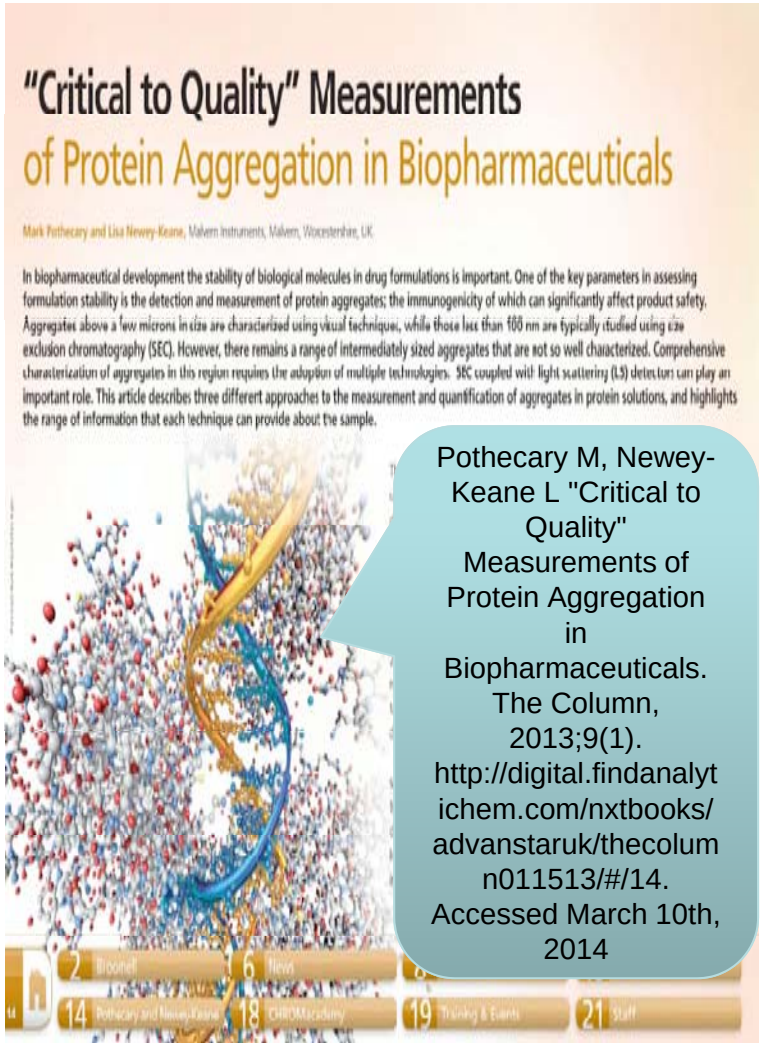




Yasser Nashed- Samuel et al. Extractable and Leachable Implications on Biological Products in Prefilled Syringes. American pharmaceutical review. January 01, 2011. http://www.americanpharmaceuticalreview.com/Featured-Articles/37011-Extractable-and-Leachable-Implications-on-Biological-Products-in-Prefilled-Syringes/. Accessed March 10th, 2014

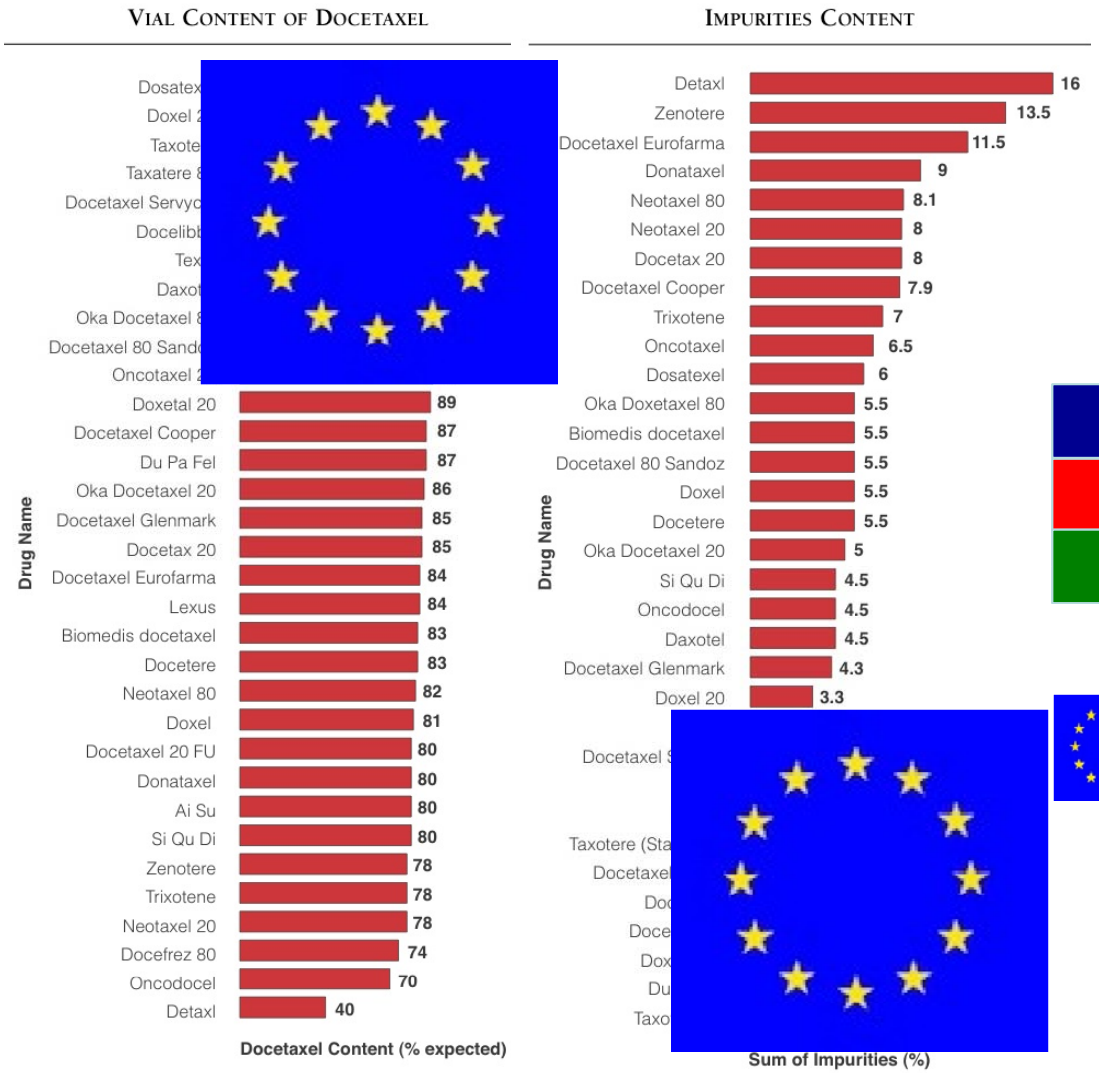
Neutralizing antibodies to epoetinalfa triggered by soluble tungsten

- **Protein aggregates in biologic drugs stimulate immune responses.**
- **2 cases from 337 in a trial of subcutaneous epoetin developed neutralizing antibodies**
- **a small number of individual syringes in 2 product batches were found to contain unusually high levels of aggregation & soluble tungsten**
  - **Tungsten induced denaturation and aggregation of the epoetin**
  - **Increasing the potential for immunogenicity**



Seidl A et al. Tungsten-induced denaturation and aggregation of epoetinalfa during primary packaging as a cause of immunogenicity. Pharm Res. 2012 Jun;29(6):1454-67. doi: 10.1007/s11095-011-0621-4. Epub 2011 Nov 18.

Not all drugs are equal – your drug regulatory authority is crucial



International copies of docetaxel compared for

- **Activity**
- **Impurities**

Key

Acceptable

Unacceptable

Original reference drug

All EMEA approved generics were safe and active

Bate R. Dangerous Substandard Medicines: An Increasing Global Problem. Health Policy Outlook. No. 6 • July 2011. http://www.aei.org/files/2011/07/06/HPO-2011-07-No-6-g-new.pdf


ONLY


SPEED
LIMIT
25

Biosimilars - Interchangeability and substitution

- Questions

- Why have we been worried?
- Terminology
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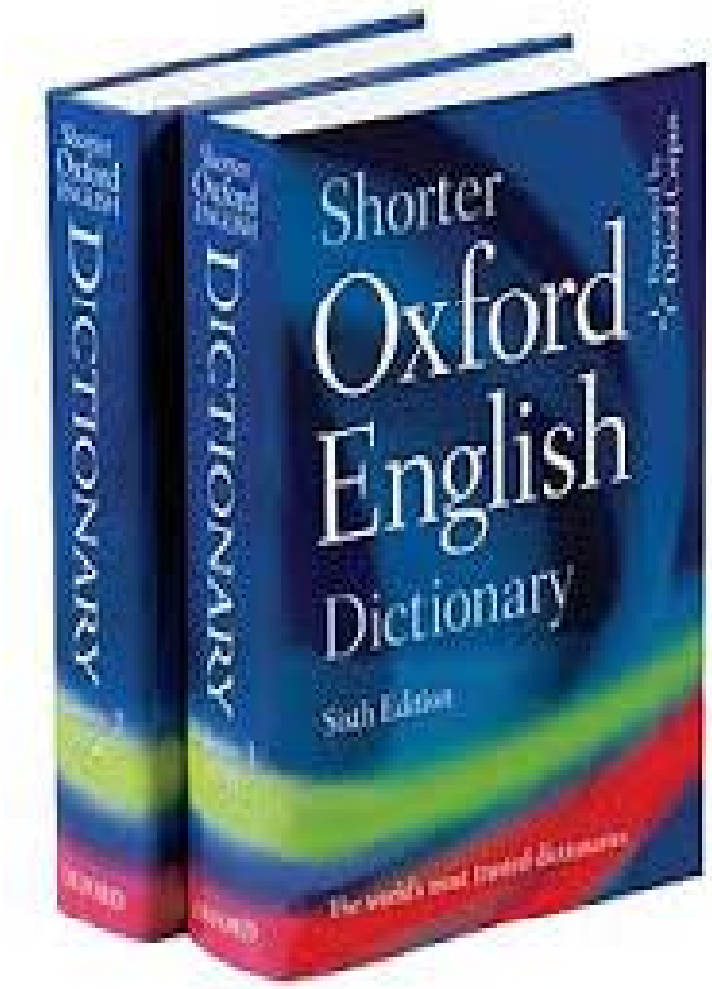
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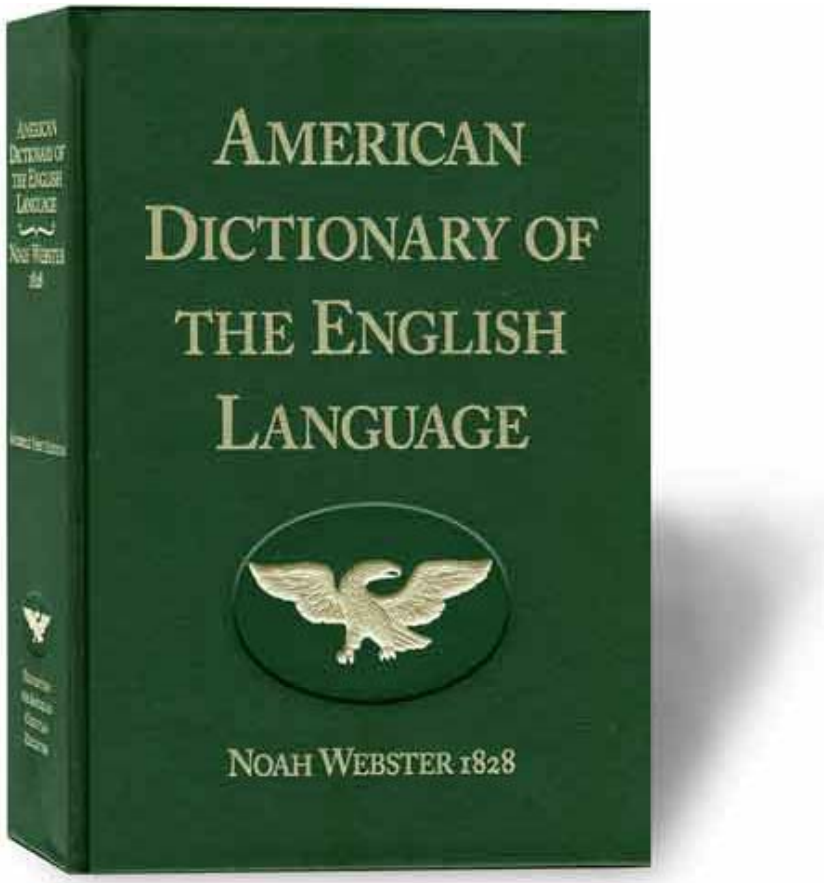
DICTIONARY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THE ENGLISH
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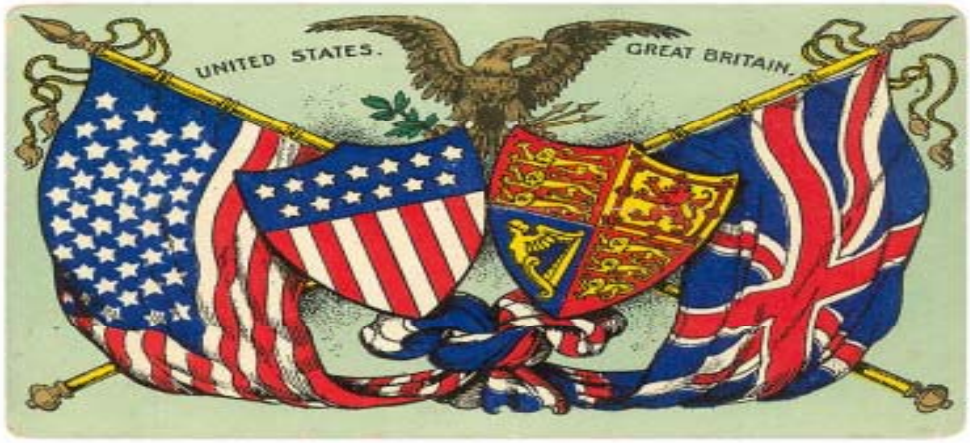
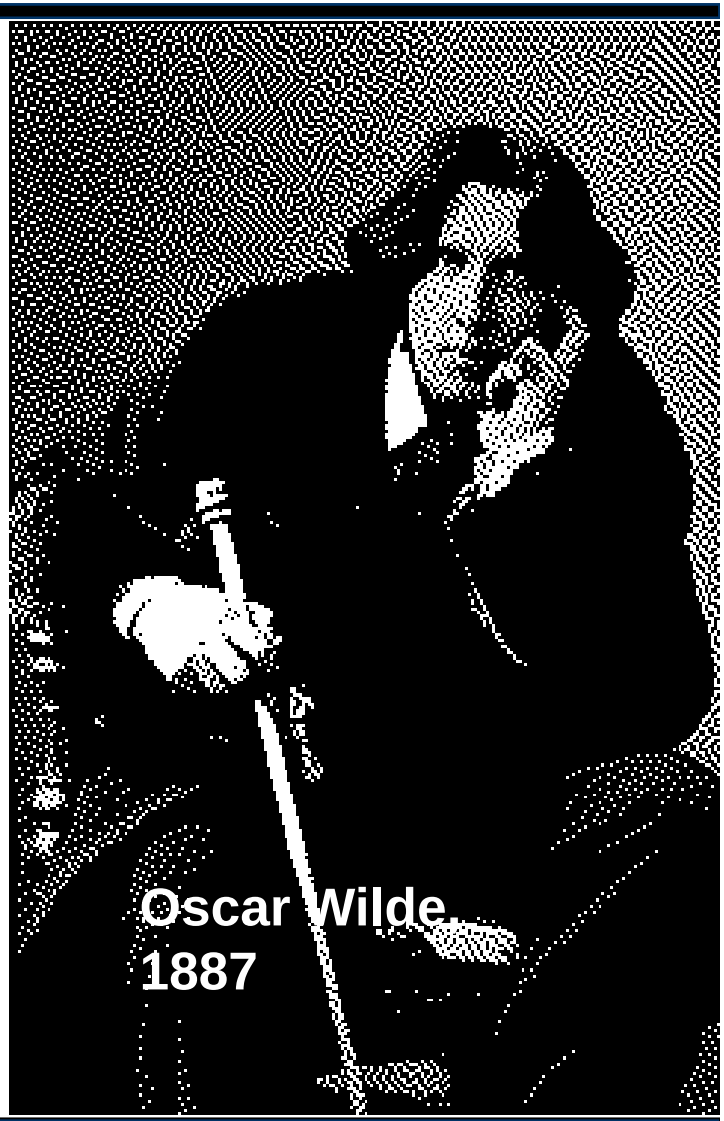
Definitions



‘We have really everything in common with America nowadays except, of course, language’.



Ref: Oscar Wilde. The Canterville Ghost (1887)

Definitions: interchangeable & substitutable

- **interchangeable**
  - **A product is interchangeable with another if both products are used and approved for the same indication.**
- **substitutable**
  - **Two products can be substitutable with each other if they can both be used in lieu of each other during the same treatment period.**

And so – in theory, be substituted by a pharmacist.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Ref: Regulation guidelines - Biosimilars clinical research and regulation. Quintiles.com. URL: http://www.quintiles.com/microsites/biosimilars-knowledge-connect/regulation-guidelines. Accessed Oct 15, 2014

Definitions: interchangeable & substitutable

USA: US Food and Drug Administration (FDA) does have the authority to designate two sorts of follow-on biologic drugs after patent expiry

1. **“ biosimilar ”**
2. **“ Interchangeable biosimilar ”**

Guidance on similar biological medicinal products (draft). European Medicines Agency, March 2013.

FDA. Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. URL: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm41

Definitions: interchangeable & substitutable

FDA Definition of Interchangeability

- **Interchangeability means that the biologic product is biosimilar to the U.S.-licensed reference biological product and can be expected to produce the same clinical result as the reference product in any given patient.**
- **For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product will not be greater than the risk of using the reference product without such alternation or switch.**
- **Interchangeable biological products may be substituted at the pharmacy level without the intervention of a healthcare provider.**

Guidance on similar biological medicinal products (draft). European Medicines Agency, March 2013. Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. URL: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm41

FDA. Purple Book: Lists of Licensed Biological Products with

Definitions: interchangeable & substitutable

FDA Definition of Interchangeability

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- **Interchangeable biological products may be substituted at the pharmacy level without the intervention of a healthcare provider.**

This power is not an EMEA or European Union issue. The decision is delegated to member countries of the E.U.

Guidance on similar biological medicinal products (draft). European Medicines Agency, March 2013. Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. URL: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm41

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This also explains why there can be so much confusion between the terms "interchangeable" "substitution" and "switchable"

Guidance on similar biological medicinal products (draft). European Medicines Agency, March 2013.

FDA. Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. URL: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm41

Definitions: interchangeable & substitutable

- **interchangeable**
  - **A product is interchangeable with another if both products are used and approved for the same indication.**

You could substitute the biosimilar drug in your protocols and expect no clinically meaningful difference in outcomes

- **Substitutable / USA "Interchangeable"**
  - **Two products can be substitutable with each other if they can both be used in lieu of each other during the same treatment period.**

Implies – that the batch to batch variation of the original product is similar to its differences with the biosimilar drug.

Switching does not then increase risks. Either could be used during the same course of treatment for an individual patient

Reff: FDA. Information for Healthcare Professionals (Biosimilars). URL: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241719.htm. Accessed Oct 16, 2014

Interchangability

- **US FDA is very keen to develop “interchangeable biosimilars”**
  - **interchangeable approval requires extensive additional clinical testing beyond that required for biosimilars.**
  - **In return for this additional expense, the first approved interchangeable version of any reference biologic is rewarded with one year of exclusivity, during which the FDA cannot approve any additional interchangeables for that biologic.**

Ref:

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Interchangeability

- **By definition, when a Biosimilar has been approved for an indication by your regulatory authority**
  - **It is interchangeable with the reference product**
  - **Which means you could use either drug and expect no clinically meaningful differences to occur**

World Health Organization

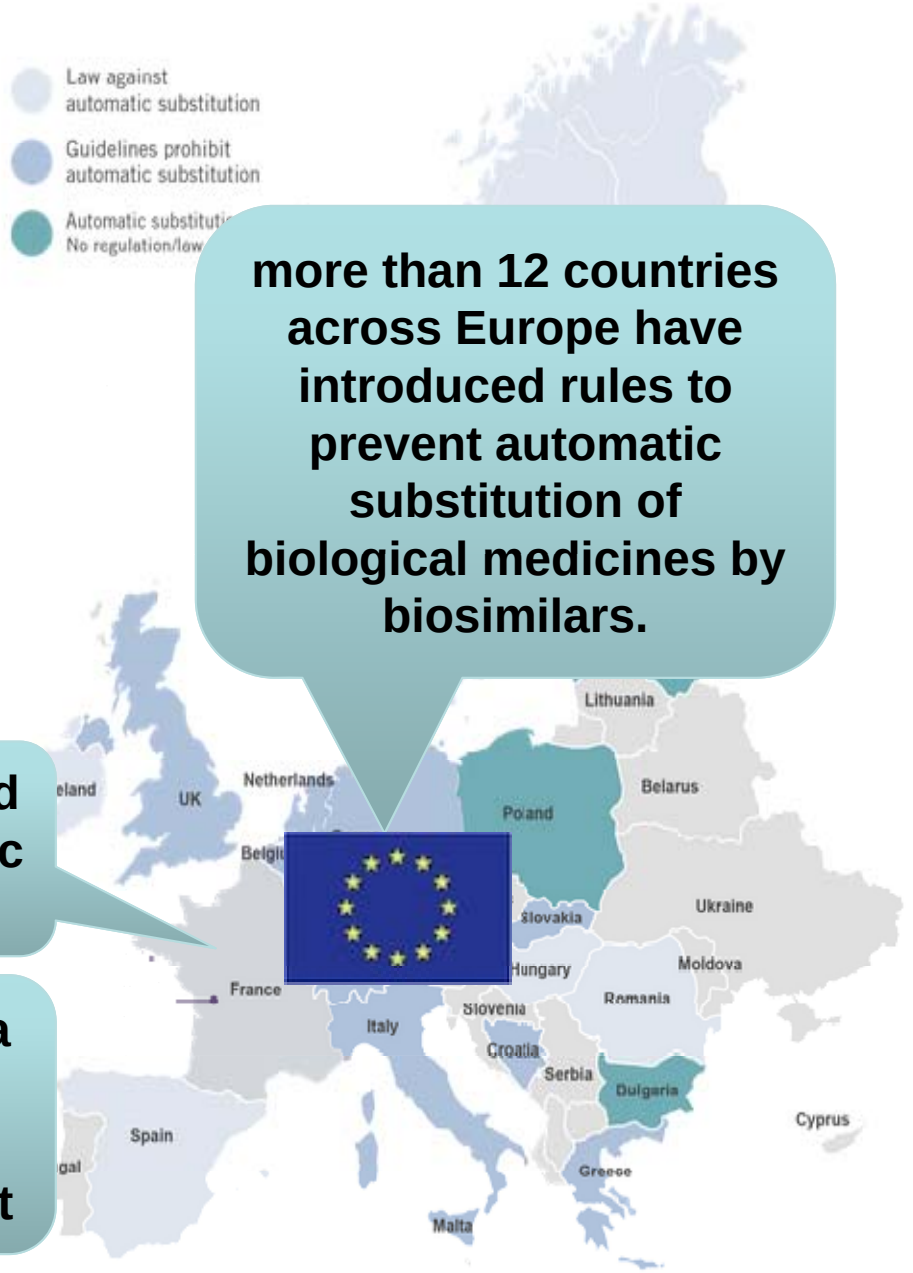
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

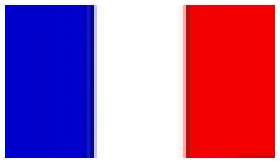
FDA

National Pharmaceutical Control Bureau

Substitution

- **The EMEA can approve biosimilars for the EU**
- **But the issue of substitution is in the hands of member states of the EU**





2014: France has passed a law to permit automatic substitution

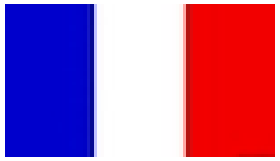
2014: USA has passed a law to permit interchangeability & switching mid-treatment

Ref Sood R et al. Five Strategic Considerations for Biosimilar Commercialization. obroncology.com October 2014 Edition | Vol. 8, Issue 9. URL: http://obroncology.com/obrgreen/print/Five-Strategic-Considerations-for-Biosimilar-Commercialization. Accessed oct 29, 2014. GABI Online. Efficacy, extrapolation and interchangeability of biosimilars. Posted 19/04/2013. http://gabionline.net/Biosimilars/Research/Efficacy-extrapolation-and-interchangeability-of-biosimilars. Accessed March 11th, 2014

Substitution

- The WHO issue guidelines for biosimilar regulation
- But the issue of substitution is in the hands of member states of the WHO

Malaysian guidelines of 2011 prevent automatic substitution of biological medicines by biosimilars at pharmacy a level.



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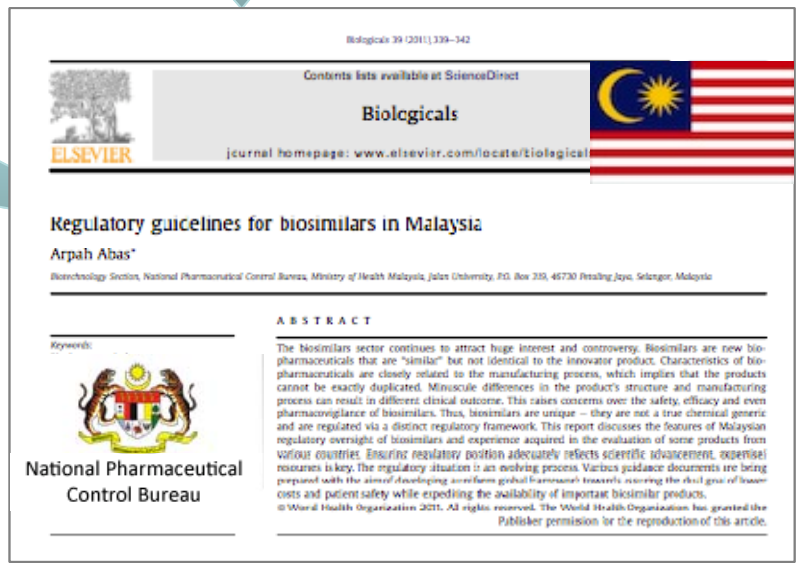

Biologicals 39 (2011) 339–342

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journal homepage: www.elsevier.com/locate/biologicals

Regulatory guidelines for biosimilars in Malaysia

Arpah Abas*

Biotechnology Section, National Pharmaceutical Control Bureau, Ministry of Health Malaysia, Jalan University, P.O. Box 319, 46730 Petaling Jaya, Selangor, Malaysia

Keywords:

National Pharmaceutical Control Bureau

ABSTRACT

The biosimilars sector continues to attract huge interest and controversy. Biosimilars are new biopharmaceuticals that are "similar" but not identical to the innovator product. Characteristics of biopharmaceuticals are closely related to the manufacturing process, which implies that the products cannot be exactly duplicated. Minuscule differences in the product's structure and manufacturing process can result in different clinical outcome. This raises concerns over the safety, efficacy and even pharmacovigilance of biosimilars. Thus, biosimilars are unique – they are not a true chemical generic and are regulated via a distinct regulatory framework. This report discusses the features of Malaysian regulatory oversight of biosimilars and experience acquired in the evaluation of some products from various countries. Ensuring regulatory position adequately reflects scientific advancement, expertise/resources is key. The regulatory situation is an evolving process. Various guidance documents are being prepared with the aim of developing a uniform global framework towards securing the dual goal of lower costs and patient safety while expediting the availability of important biosimilar products.

Ref Sood R et al. Five Strategic Considerations for Biosimilar Commercialization. obroncology.com October 2014 Edition | Vol. 8, Issue 9. URL: http://obroncology.com/obrgreen/print/Five-Strategic-Considerations-for-Biosimilar-Commercialization. Accessed oct 29, 2014. ArpahAbas. Regulatory guidelines for biosimilars in Malaysia. Biologicals 2011:39;339e342

Automatic substitution

- **EMA and WHO**
  - **automatic substitution by pharmacist is not an EMA or WHO power**
  - **France has proposed it**
- **US - FDA**
  - **Will permit for “interchangeable biosimilars”**
  - **But not for “biosimilars”**
- **Malaysia**
  - **Advises against automatic substitution**

Ref: GABI Online. Efficacy, extrapolation and interchangeability of biosimilars. Posted 19/04/2013. http://gabionline.net/Biosimilars/Research/Efficacy-extrapolation-and-interchangeability-of-biosimilars. Accessed March 11th, 2014

Biosimilars - Interchangeability and substitution

- Questions

- Why have we been worried?
- Terminology
- Rules
- Evidence for safety
  - Regulatory
- Observational studies of substitution & switching
  - Originator to Originator
  - Originator to Biosimilar
- RCTs of switching

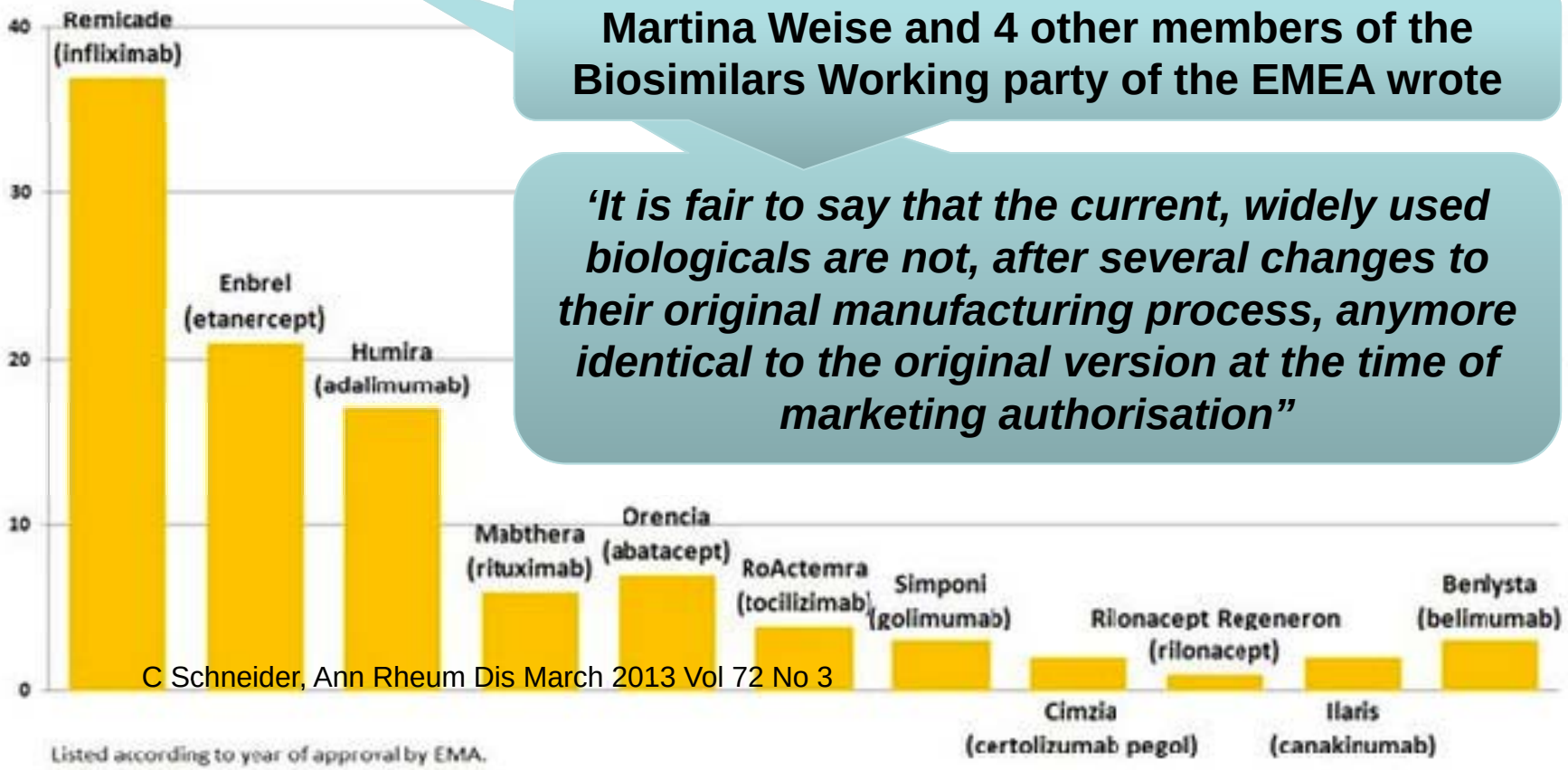
- Questions Revisited

Manufacturing changes are frequent in biologic drugs over time

- **Example: every single biologic agent used in rheumatology has had a manufacturing change – some had >35 changes**

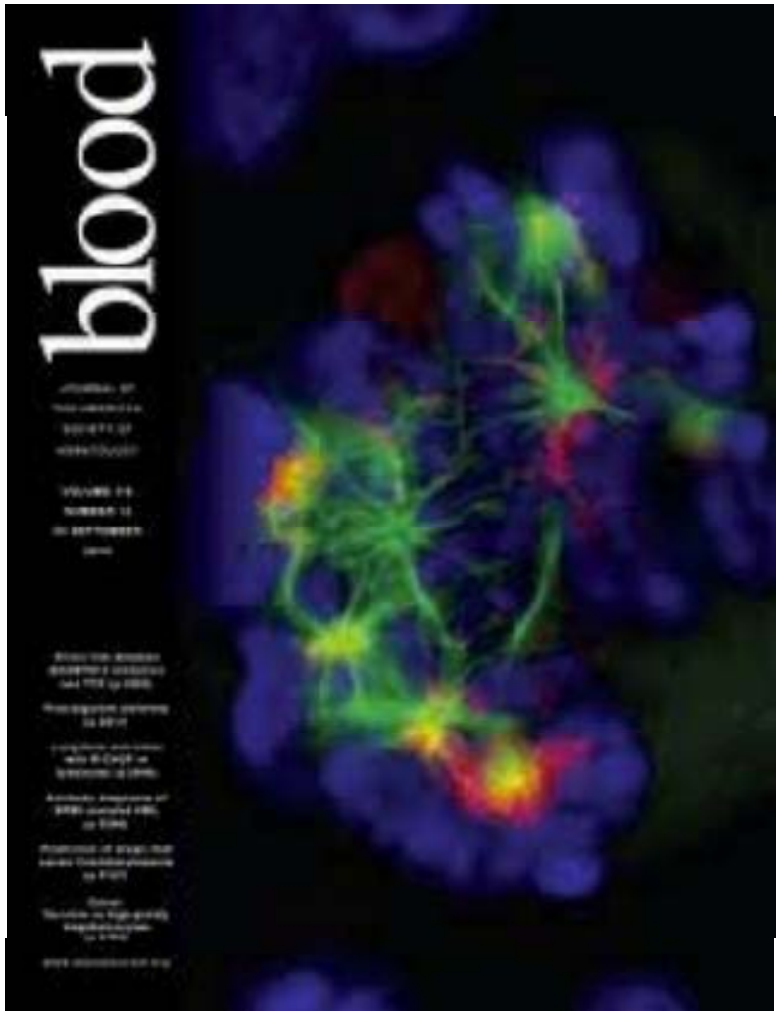
Martina Weise and 4 other members of the Biosimilars Working party of the EMEA wrote

'It is fair to say that the current, widely used biologicals are not, after several changes to their original manufacturing process, anymore identical to the original version at the time of marketing authorisation"



C Schneider, Ann Rheum Dis March 2013 Vol 72 No 3

Ref Biosimilars in rheumatology. GABI-Online. Posted 29/03/2013. URL: http://gabionline.net/Biosimilars/Research/Biosimilars-in-rheumatology. Accessed Oct 29, 2014
Weise M et al. Biosimilars: the science of extrapolation. Blood. Prepublished online October 8, 2014; doi:10.1182/blood-2014-06-583617



- **“..the “similar but not identical” paradigm of biosimilars appears to fuel uncertainties about [biosimilars]. However, this principle is not new to biotechnology; even consecutive batches of originator products are never identical to each other...this is normal and is why adequate controls on batch consistency have to be imposed.”**

  - **Weise et al. Blood 2012; 120: 5111-5117**

Manufacturing changes are frequent in biologic drugs over time

Relative content of the individual isoforms of originator Darbepoetin before and after a manufacturing change
pre-change (n = 18) batches, post-change (n = 4) batches

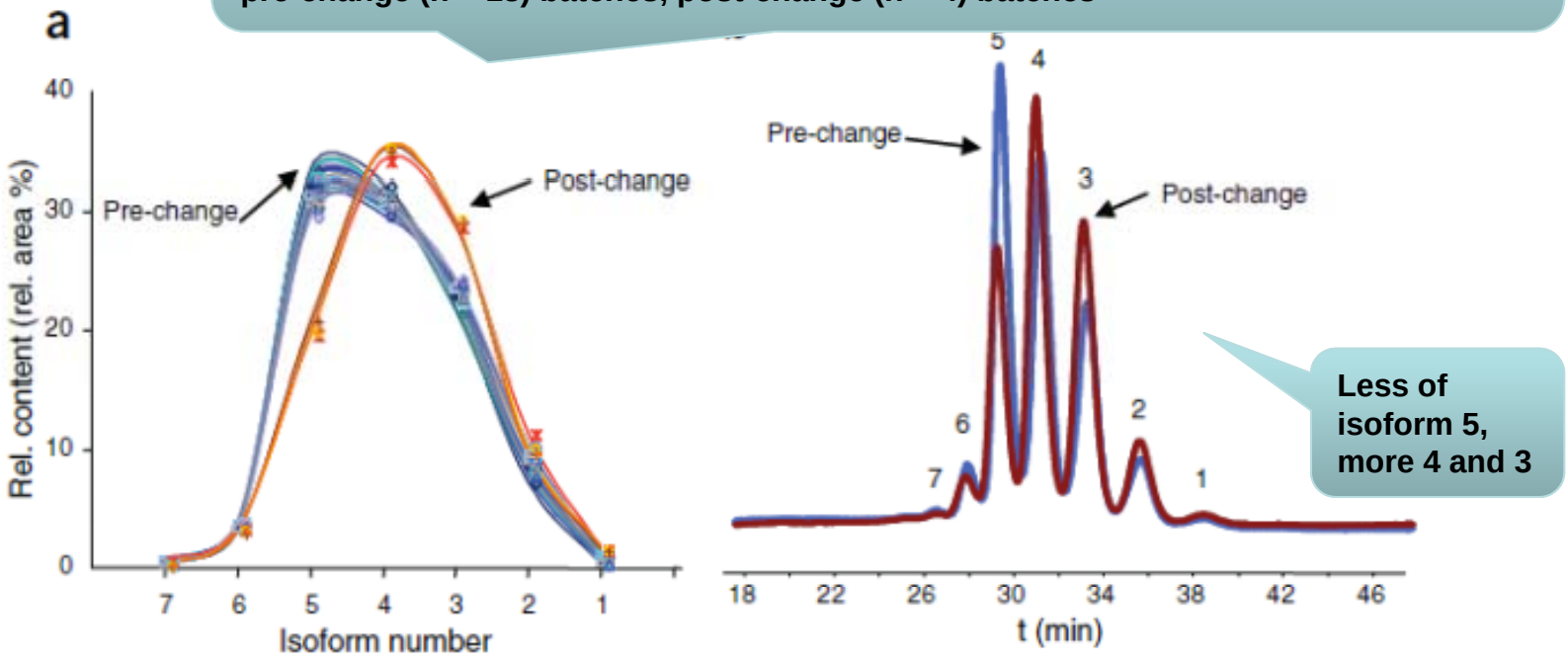


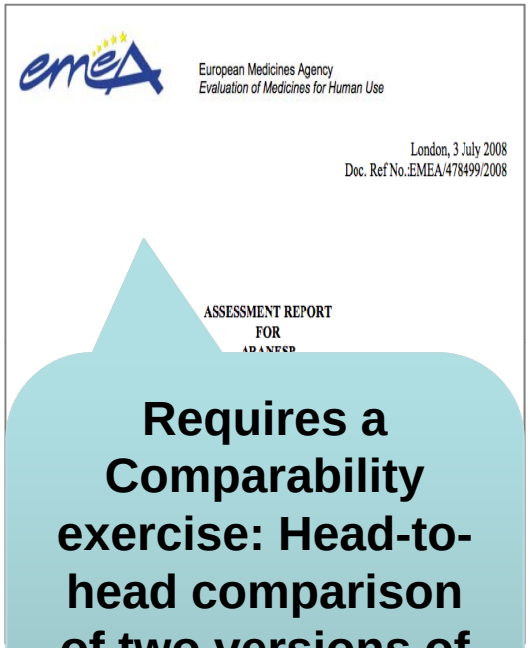
Figure 1 Comparison of the pre- and post-change Aranesp batches measured by capillary zone electrophoresis. (**a**) Relative content of the individual isoforms of the pre-change ($n = 18$) and the post-change ($n = 4$) batches. (**b**) Representative electropherograms; peaks are labeled with the isoform number.

Ref Schiestl M et al: Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat Biotechnol. 2011 Apr;29(4):310-2.

Manufacturing changes are frequent in biologic drugs over time

- **Example of darbepoetin changes**
  1. **Re-establishment of master cell bank**
  2. **Modification of the vector used to produce the antigen/source material, incl. new master cell bank**
  3. **Change from roller bottle (RB) manufacturing process to a more scaleable high throughput (HT) process using cells in suspension**
  4. **Change of cell culture medium**

Change was rated as "Replacement of a biological substance or product of biotechnology with one of a slightly different molecular structure.


European Medicines Agency
Evaluation of Medicines for Human Use

London, 3 July 2008
Doc. Ref No.:EMEA/478499/2008

ASSESSMENT REPORT
FOR

Requires a Comparability exercise: Head-to-head comparison of two versions of a biological medicine with the goal to establish similar quality, safety, and efficacy.

Ref: Assessment report for aranesp. EMEA Doc. Ref No.:EMEA/478499/2008. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000332/WC500026148.pdf. Accessed Oct 29, 2014

Biosimilars

- **From a scientific and regulatory point of view, the active substance of the biosimilar is just another version of the active substance of the originator product.**
  - Weise M et al. Biosimilars: the science of extrapolation. Blood. Pre-published online October 8, 2014; doi:10.1182/blood-2014-06-583617
- **This is important to state since the same scientific principles that underlie the comparability exercise for the purpose of demonstrating similarity of a product before and after a change in manufacturing process also apply to the comparability exercise for the purpose of demonstrating biosimilarity.**
  - European Medicines Agency, Committee for Medicinal Products for Human Use: Guideline on similar biological medicinal products (CHMP/437/04/Rev1). http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c

Example of darbepoetin changes

- **In addition to in-vitro binding studies – the manufacturer provided**

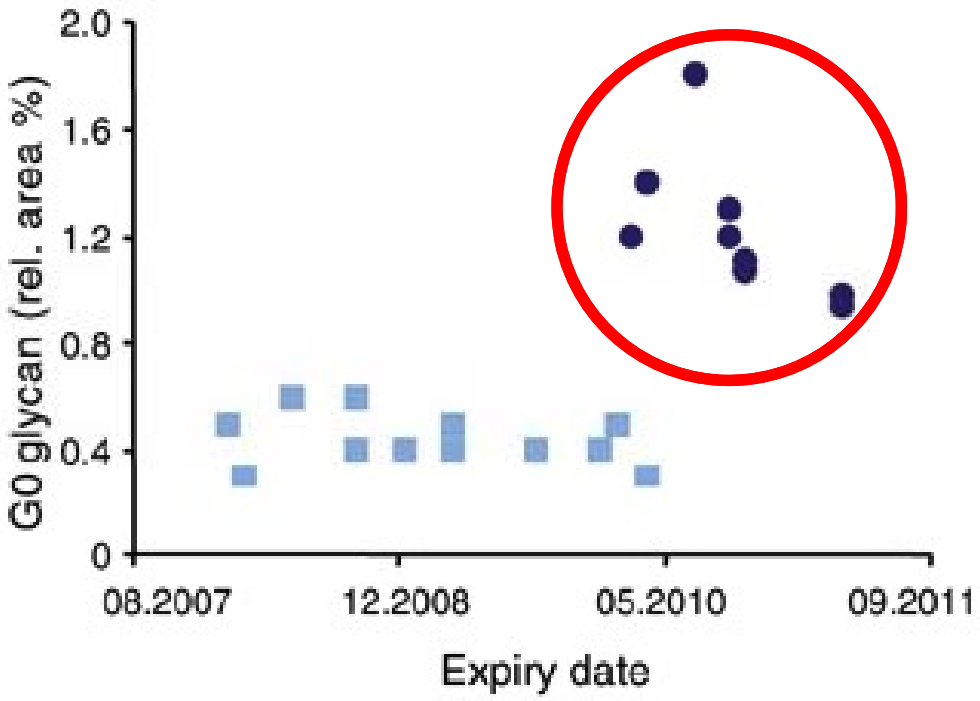
1. **Single dose PK study in male beagle dogs**
2. **4 week repeated (3x/week) tox study in beagles- For toxicity, PK, PD, Immunological measurements**
3. **Phase I comparative PK study (randomized, 2-way, open-label, crossover, SC) with 2 single doses in 48 healthy volunteers**
4. **Phase III comparative efficacy study (controlled, randomized, in 446 CKD haemodialysis patients, SC or IV, maintenance)**
5. **Single arm safety study with HT (open label, in 1172 CKD patients)**

The new version was approved based on demonstrated comparability of quality, non-clinical, and (limited) clinical data

Ref: Assessment report for aranesp. EMEA Doc. Ref No.:EMEA/478499/2008. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000332/WC500026148.pdf. Accessed Oct 29, 2014

Example of rituximab changes

- **Schiestl, M. et al., Nature Biotechnology 29, 310-312, 2011**
- **Found a structural change in rituximab in batches sampled over time**



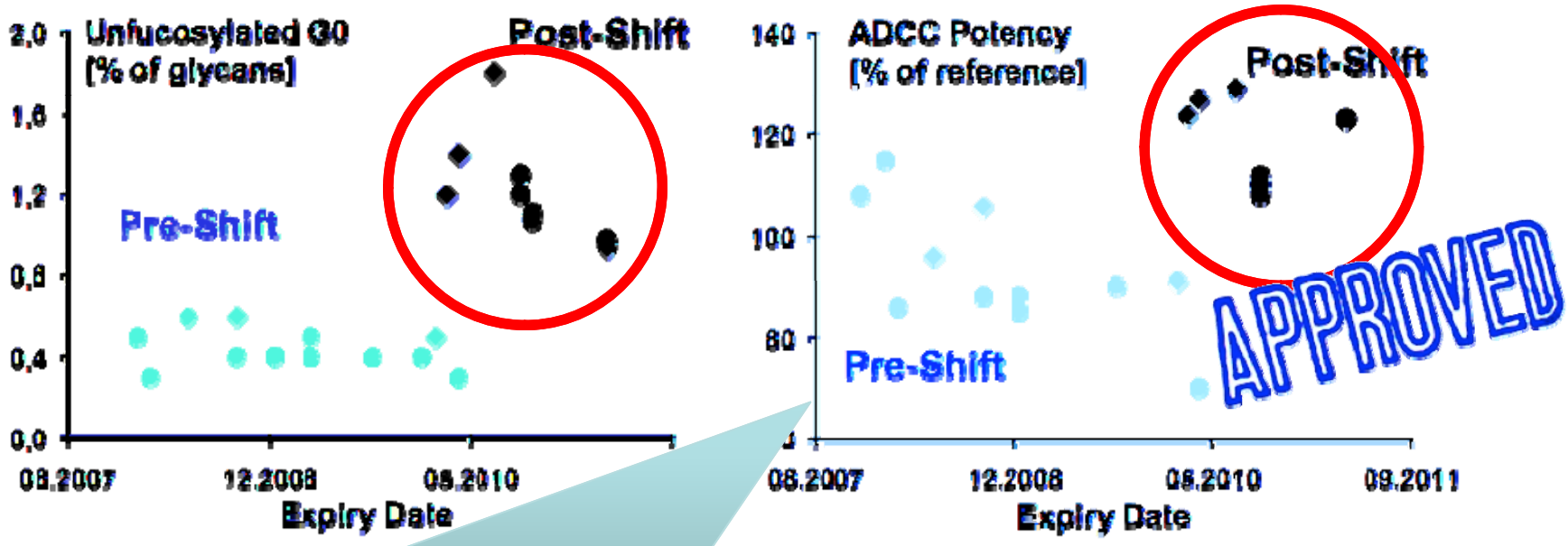
Comparison of the different pre- and post-change batches of Rituxan/Mabthera

Relative amount of the G0 glycan of the pre-change (n = 13) and post-change (n = 11) batches

Ref Schiestl M et al: Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat Biotechnol. 2011 Apr;29(4):310-2.

Example of rituximab changes

- Schiestl, M. et al., Nature Biotechnology 29, 310-312, 2011
- Which was associated with a functional change in rituximab



The change led to a difference in potency of the drug measured by ADCC assay

Example of etanercept-Enbrel changes

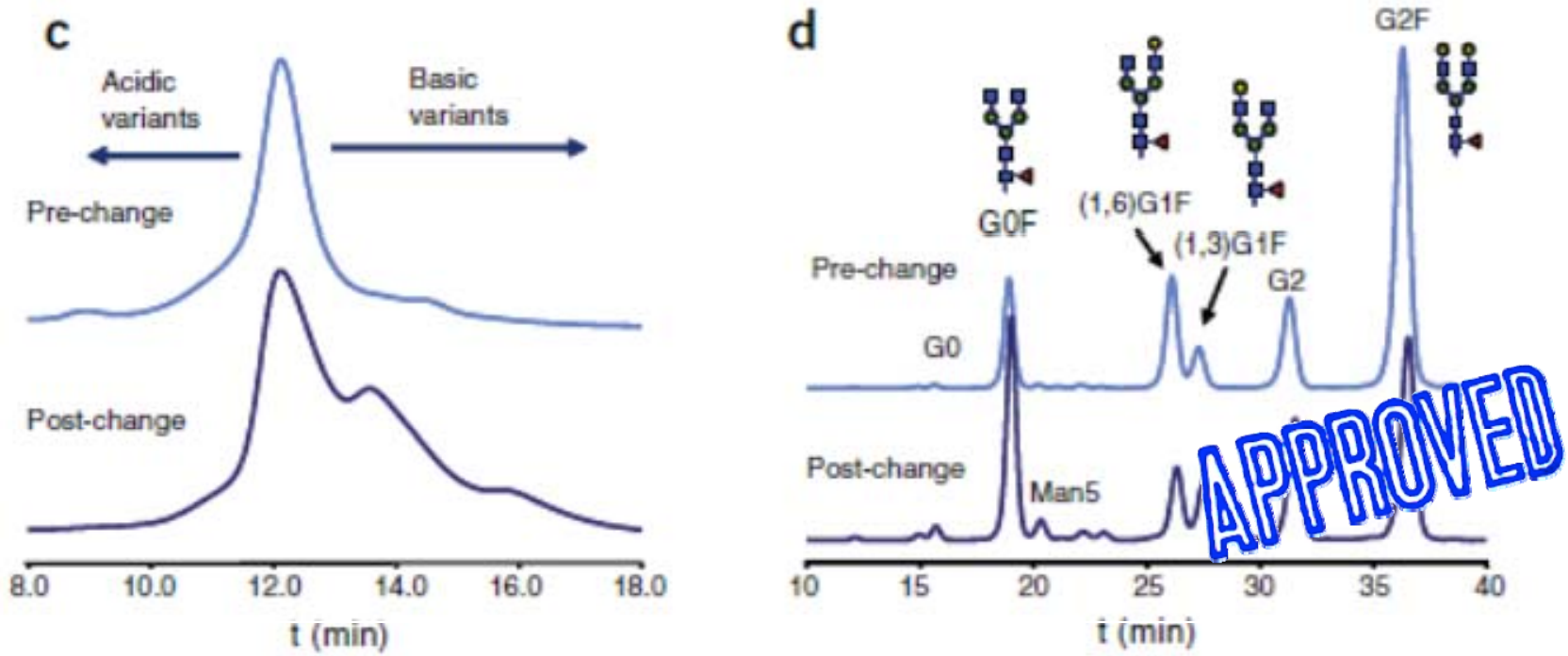


Figure 3 Comparison of the different pre- and post-change batches of Enbrel. (**a**) Relative amounts of basic variants of the pre-change ($n = 6$) and the post-change ($n = 6$) batches as measured by CEX. (**b**) Relative amount of the G2F glycan of the pre-change ($n = 25$) and the post-change ($n = 9$) batches. (**c**) Exemplary CEX chromatograms. (**d**) Exemplary glycan mapping chromatograms.

Ref Schiestl M et al: Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat Biotechnol. 2011 Apr;29(4):310-2.

Variation in the production process is a normal occurrence in biologic drugs

- **Christian K. Schneider, MD, is Senior Medical Officer at the Danish Medicines Authority.**
- **He is Chairman of the EMA's Committee for Advanced Therapies**

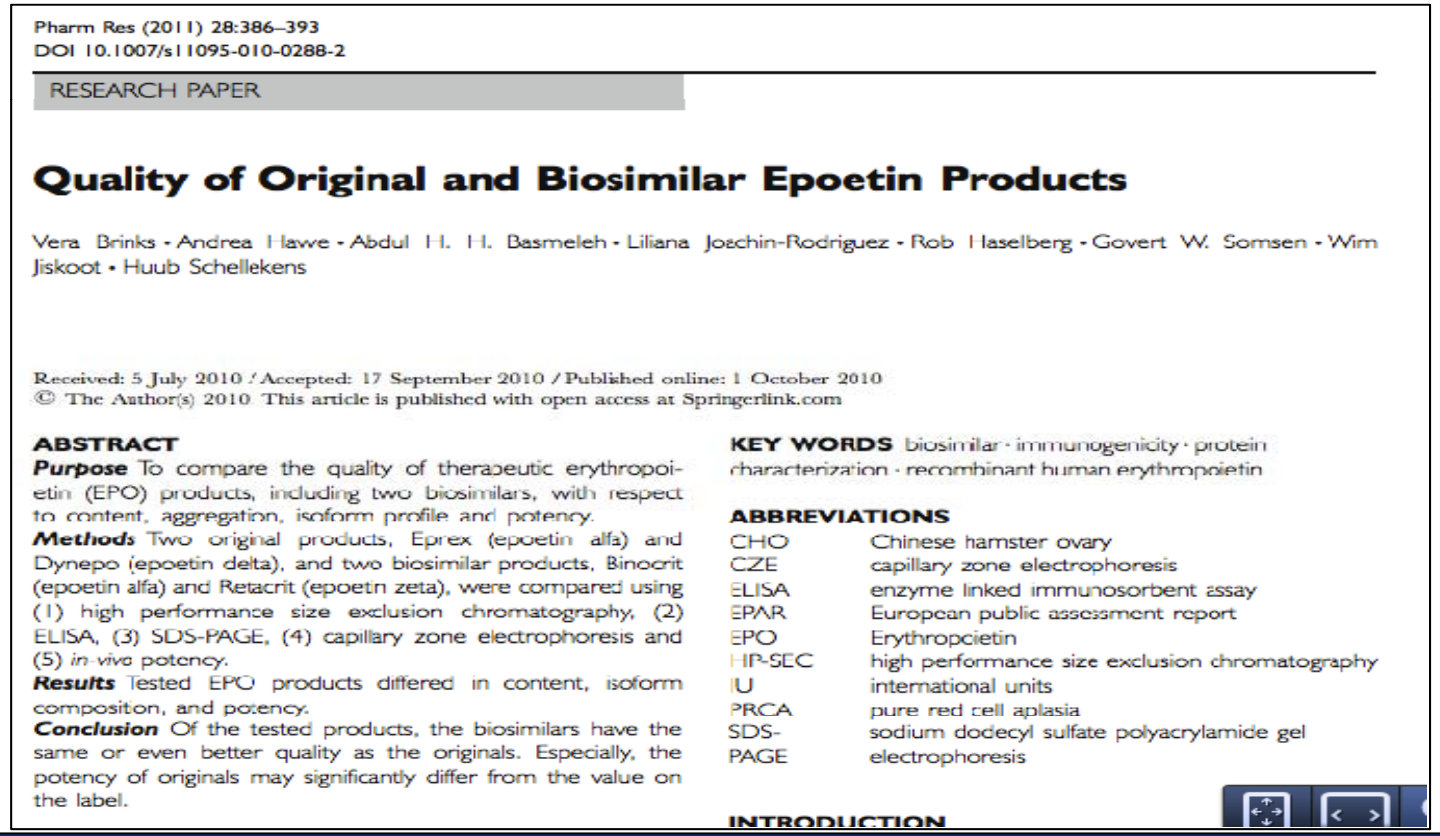
"…The scientific principles of a change in manufacturing process of an originator mAb/cept molecule and the generation of a biosimilar are the same"

- Further references:
- Schneider CK, Kalinke U. Toward biosimilar monoclonal antibodies. Nat Biotechnol 2008;26:985–90.
- Weise M, Bielsky MC, De Smet K, et al. Biosimilars—why terminology matters. Nat Biotechnol 2011;29:690–3.

Christian K Schneider. Biosimilars in rheumatology: the wind of change. Ann Rheum Dis 2013;72:315-318 doi:10.1136/annrheumdis-2012-202941. Schneider CK. http://www.eucraf.com/msc-committee, Accessed 2 Nov 2013

Quality of biosimilar medicines

- **Brinks V, et al. Quality of original and biosimilar epoetin products. Pharm Res. Published online: 01 October 2010. Doi: 10.1007/s11095-010-0288-2**



Pharm Res (2011) 28:386–393
DOI 10.1007/s11095-010-0288-2

RESEARCH PAPER

Quality of Original and Biosimilar Epoetin Products

Vera Brinks · Andrea Hawe · Abdul H. H. Basmeleh · Liliana Joachin-Rodriguez · Rob Haselberg · Govert W. Somsen · Wim Jiskoot · Huub Schellekens

Received: 5 July 2010 / Accepted: 17 September 2010 / Published online: 1 October 2010

ABSTRACT

Purpose To compare the quality of therapeutic erythropoietin (EPO) products, including two biosimilars, with respect to content, aggregation, isoform profile and potency.

Methods Two original products, Eprex (epoetin alfa) and Dynepo (epoetin delta), and two biosimilar products, Binocrit (epoetin alfa) and Retacrit (epoetin zeta), were compared using (1) high performance size exclusion chromatography, (2) ELISA, (3) SDS-PAGE, (4) capillary zone electrophoresis and (5) *in-vivo* potency.

Results Tested EPO products differed in content, isoform composition, and potency.

Conclusion Of the tested products, the biosimilars have the same or even better quality as the originals. Especially, the potency of originals may significantly differ from the value on the label.

KEY WORDS biosimilar · immunogenicity · protein characterization · recombinant human erythropoietin

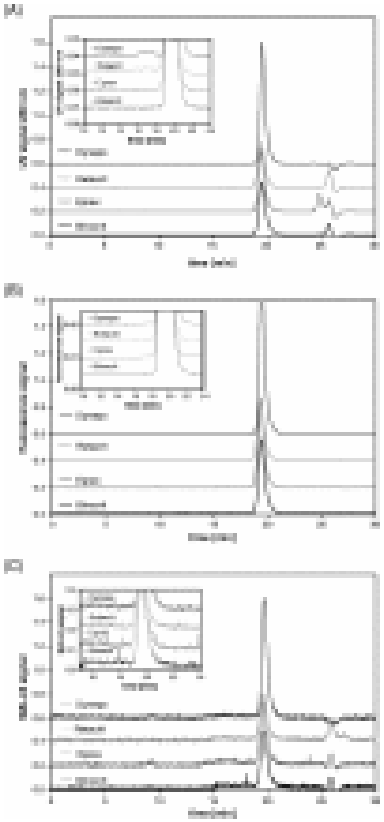
ABBREVIATIONS

CHO	Chinese hamster ovary
CZE	capillary zone electrophoresis
ELISA	enzyme linked immunosorbent assay
EPAR	European public assessment report
EPO	Erythropoietin
HP-SEC	high performance size exclusion chromatography
IU	international units
PRCA	pure red cell aplasia
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis

INTRODUCTION

Quality of biosimilar medicines

- **Brinks V, et al. Quality of original and biosimilar epoetin products. Pharm Res. Published online: 01 October 2010. Doi: 10.1007/s11095-010-0288-2**



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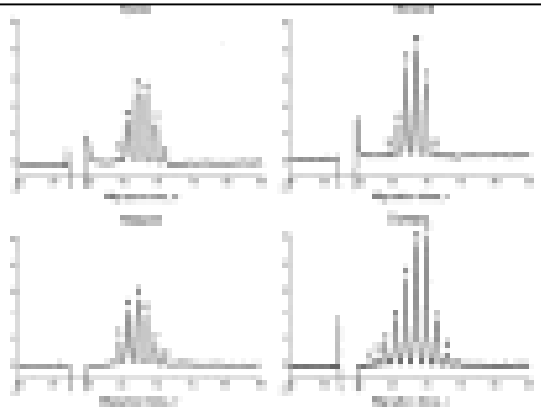
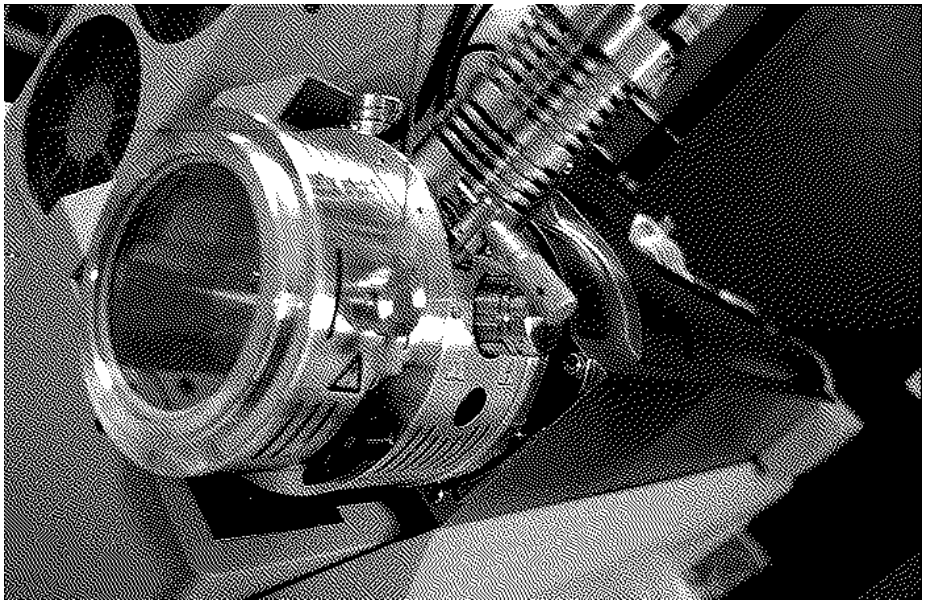


Biosimilar drugs rely on analytics to ensure similarity

- That technology has increased sensitivity enormously
- Example: Mass Spectrometry

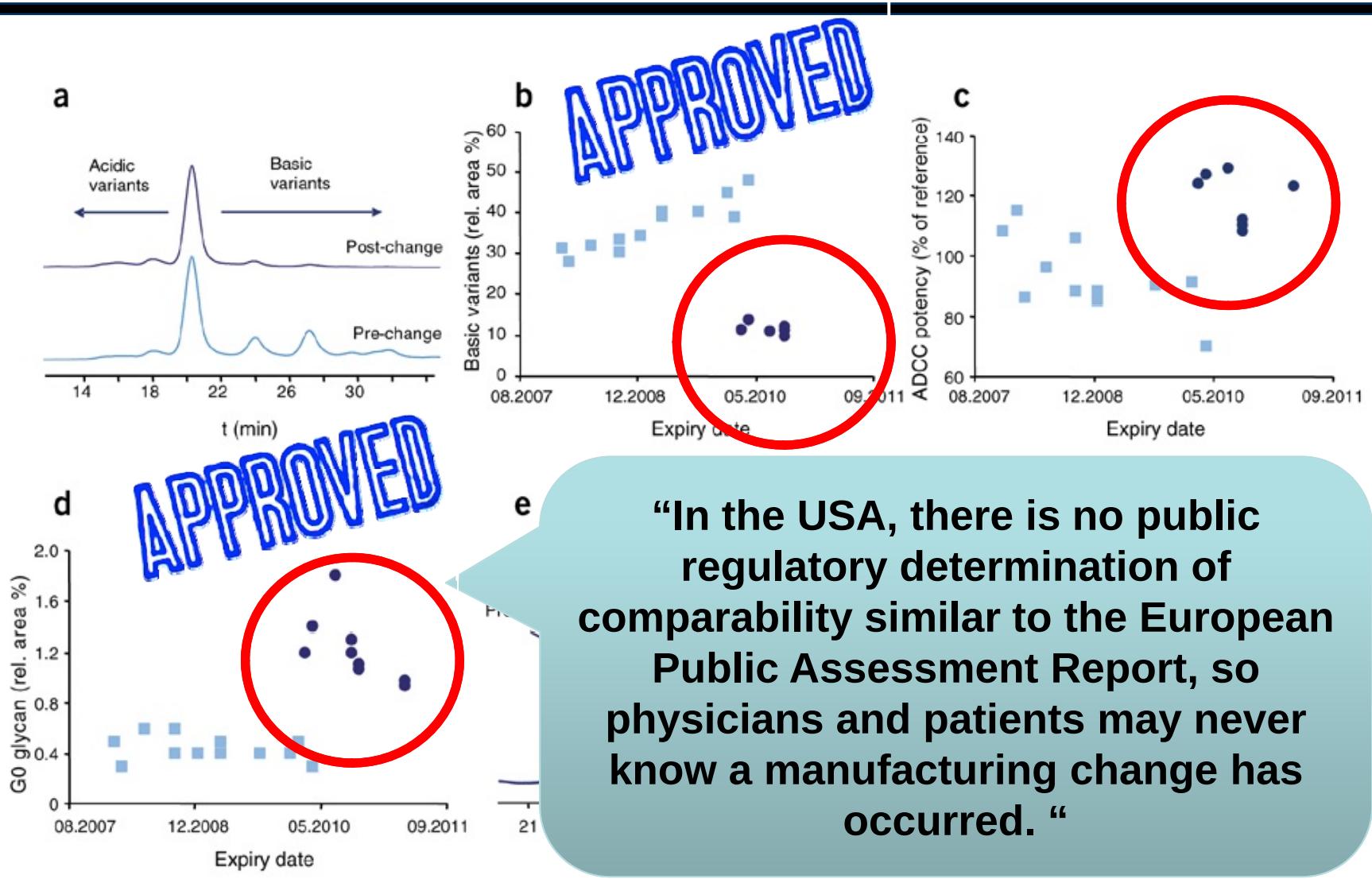
Year	Detection limit for peptides (pmol)
1990	100
1993	10
1997	1
2000	0.1
2003	0.01
2005	0.001
2008	0.0001
2011	0.00001



10 Million-fold increase

Ref: Image modified from - https://www.flickr.com/photos/heypaul/116593721/in/photolist-bizfz-3pEidF-bizdA-dQot5D-4ze5n6-4zijm3-bizh2-3eRgg-bizfn-bizfa-3eR1J-3pJQAm-bizex-bizga-bizd5-3pEh7x-3pJS7s-2dAyW-9UgC-89g5jn-bT4rZH-oxRRqY-6TfKKJ-dUq43U-2Qbqz-3pEii6-3pEio4-3pJRzC-3pEhqx-bizcD-bizdP-bizeS-3eRgh-3eR1H-bizcu-bizcW-bize4-4JPTk5-4JKEEz-4JKEUM-4JPSEQ-4JPSP1-4JPNe5-6SL9cZ-6SQbDY-6SQbHs-5NuTGB-7HA85c-aJfVhH-e88hWF. Accessed Nov 7, 2014

Schiestl M. Nat Biotechnol. 2011;29(4):310–2.



"In the USA, there is no public regulatory determination of comparability similar to the European Public Assessment Report, so physicians and patients may never know a manufacturing change has occurred. "

Thomas Dörner et al. The role of biosimilars in the treatment of rheumatic diseases. Ann Rheum Dis 2013;72:322-328 doi:10.1136/annrheumdis-2012-202715

Biosimilars - Interchangeability and substitution

- Questions

- Why have we been worried?
- Terminology
- Rules
- Evidence for safety
  - Regulatory
- Observational studies of substitution & switching
  - Originator to Originator
  - Originator to Biosimilar
- RCTs of switching

- Questions Revisited

Switching is frequent: Often between originator drugs!

- **22% of Italian patients switched epoetins in 18 months**
  - **Only 2% were to biosimilars**
    - Loiacono C et al. BioDrugs 2010;26(2):113-120
- **14.4% of US patients switched epoetins in 5 years**
  - Nurko S et al. ClinTher 2007;29(9):2010-21
- **90% of paediatricians surveyed have switched a patient's biologic drug to another brand**
  - Grimburg A et al. EndocrPract 2012;18(3):307-16A.
- **1 in 5 patients in the Prospective Immunogenicity Surveillance Registry (PRIMS) switches epoetin brands in without reported complications**
  - Iain C. Macdougall, et al. Incidence of erythropoietin antibody-mediated pure red cell aplasia: the Prospective Immunogenicity Surveillance Registry (PRIMS. Nephrol. Dial. Transplant. first published online September 19, 2014 doi:10.1093/ndt/gfu297

Loiacono C et al. How much are biosimilars used in southern Italy?: a retrospective analysis of epoetin utilization in the local health unit of Messina in the years 2010-2011.BioDrugs. 2012 Apr 1;26(2):113-20. doi: 10.2165/11630770-000000000-00000.
Nurko S et al. Dosing intervals and hemoglobin control in patients with chronic kidney disease and anemia treated with epoetinalfa or darbepoetinalfa: a retrospective cohort study. ClinTher. 2007 Sep;29(9):2010-21.
Grimberg A et al. Consequences of brand switches during the course of pediatric growth hormone treatment. EndocrPract. 2012 May-Jun;18(3):307-16. doi: 10.4158/EP11217.OR.

Switching is frequent:
Often between originator drugs!

- **Cancer and haematology patients may have different brands of filgrastim (white cell growth factor) to prevent neutropeanic fever during different courses of chemotherapy**

- **EORTC guidelines endorse biosimilar use**
  - Aapro MS, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011 Jan;47(1):8-32. doi: 10.1016/j.ejca.2010.10.013.

EORTC
European Organisation for Research and Treatment of Cancer

Review of all published data on switching between originator and biosimilar

12,039 patients in 58 clinical trials

193 Post Authorisation Adverse event reports from EU DRA Vigilance

Review

The safety of switching between therapeutic proteins

Hans C Ebbers, Michael Muenzberg & Huub Schellekens†

†*Utrecht University, Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaceutics, TB Utrecht, The Netherlands*

Ebbers HC et al. The safety of switching between therapeutic proteins. Expert OpinBiolTher 2012;12(11):1473-85

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Review

The safety of switching between therapeutic proteins

Hans C Ebbers, Michael Muenzberg & Huub Schellekens†
†Utrecht University, Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaceutics, TB Utrecht, The Netherlands

Table 1. Biosimilars marketed in the EU.

Biosimilar	Reference product
Epoetins	
HX575 (Abseamed®, Binocrit®, & Epoetin-α Hexal®)	Epoetin-alfa (Eprex®/Erypo®)
SB-309 (Retacrit® & Silapo®)	Epoetin-alfa (Eprex®/Erypo®)
G-CSFs	
XM02 (Biograstim®, Filgrastim Ratiopharm®, & Tevagrastim®)	Filgrastim (Neupogen®)
EP2006 (Zarzio® & Filgrastim Hexal®)	Filgrastim (Neupogen®)
PLD108 (Nivestim®)	Filgrastim (Neupogen®)
Human Growth Hormones	
EP 2000 (Omnitrope®)	Somatropin (Genotropin®)
Valtropin®	Somatropin (Humatrope®)

Ebbers HC et al. The safety of switching between therapeutic proteins. Expert OpinBiolTher 2012;12(11):1473-85

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The safety of switching between therapeutic proteins

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Human Growth Hormone – no safety signals

Epoetin – no safety signals

G-CSF – no safety signals

Table 2. Switching studies inclu

Study	Year	Type
Laursen *et al.*	1993	Ranc
Vahl *et al.*	1996	Ranc over
Jacobsen *et al.*	2000	Ranc
Bidlingmaier *et al.*	2006	Oper
EMA	2007	Cros
FDA	2007	Cros (exte cont
*Romer	2009	Ranc
Stanhope *et al.*	2010	Ranc over
Fuhr *et al.*	2010	Ranc over
Fuhr *et al.* (II)	2010	Ranc over
Farias *et al.*	2010	Ranc
Liedert *et al.*	2010	Cros
Ullah *et al.*	2012	Oper
Total		

Table 3. Crossover studies including erythropoiesis stimulating agents.

Study	Year	Study design	Number	patients/volunteers	Products	Outcome
Cheung *et al.*	2000	Double blind cross over	24	Volunteers	Two formulations epoetin-α	Comparable safety, n
Bren *et al.*	2002	Controlled cross over	38	HD patients	Epoetin ¢ and α sc.	Comparab
Nissenson *et al.*	2002	Randomized controlled trial with 4-week run-in period	507	HD patients	Epoetin and darbepoetin	C
Vanrenthergem *et al.*	2002	Randomized open label with 4 week run in and switch	522	HD/PD patients	Epoetin-α or β to darbepoetin	groups no s to switching reported
Locatelli	2003	Open label, single-arm study with 3-week run-in period	343	HD and PD patients	Epoetin or β to	No safety events related t switching reported
Togawa *et al.*	2004					
Brunkhorst	2004					
Milutinovic *et al.*	2006					
Akizawa	2007					
Besarab	2007					
Klinger	2007					
Levin *et al.*	2007					
Smith *et al.*	2007					
Sulowicz *et al.*	2007					
Hymes *et al.*	2007					
Roger *et al.*	2008					
Bock *et al.*	2008					
Li *et al.*	2008	Prospective randomized open label	37	PD patients	darbepoetin Epoetin and darbepoetin	switching reported Comparable safety, no AEs related to switching reported [60]
Wizeman *et al.*	2008	Double blind cross over	313	HD patients	Epoetin α and Biosimilar Epoetin-ζ	Comparable safety, no AEs related to switching reported [61]

Table 4. Crossover studies including Granulocyte Colony stimulating fa

Study	Year	Type of study	nr	patients/volunteers	Products	Study	Ref.
Hoglund *et al.*	1997	Prospective cross over	32	Volunteers	filgrastim and lenograstim	Lenograstim more CD34+ cells	[78]
Bong *et al.*	2001	Prospective randomized	11	Children treated with chemo	filgrastim and lenograstim	No safety events related to switching reported	[79]
Carlson *et al.*	2004	Open randomized	7	SCN patients	filgrastim and lenograstim	No safety events related to switching reported	[80]
Lubenau *et al.*	2009	Cross over randomized	72	Volunteers	reference filgrastim and biosimilar	No safety events related to switching reported	[81]
Lubenau *et al.*	2009	Randomized cross over	56	Volunteers	reference filgrastim and biosimilar	No safety events related to switching reported	[82]
Waller *et al.*	2010	Randomized double blind	50	Volunteers	reference filgrastim and biosimilar	No safety events related to switching reported	[83]
Gascon *et al.*	2010	Randomised cross over	40	Volunteers	filgrastim and biosimilar	No safety events related to switching reported	[84]
Gascon *et al.*	2010	Randomised cross over	26	Volunteers	filgrastim and biosimilar	No safety events related to switching reported	[84]
Gascon *et al.*	2010	Randomised cross over	56	Volunteers	filgrastim and biosimilar	No safety events related to switching reported	[84]
Gascon *et al.*	2010	Randomised cross over	24	Volunteers	filgrastim and biosimilar	No safety events related to switching reported	[84]
Total			374				

Ebbers HC et al. The safety of switching between therapeutic proteins. Expert OpinBiolTher 2012;12(11):1473-85

Review of all published data on switching between originator and biosimilar

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Review

Article highlights.

- The arrival of biosimilars has led to considerable discussion about the safety of switching between biopharmaceuticals
- We have performed a review of data from clinical trials to identify potential risks associated when switching between biopharmaceuticals within the product classes for which biosimilars are currently authorized in the EU. In addition we analysed post authorization case reports

- No safety signals were identified that were related to the switching process.

• No safety signals were identified that were related to the switching process.

This box summarizes key points contained in the article.

Human Growth Hormone – no safety signals

Epoetin – no safety signals

G-CSF – no safety signals

Ebbers HC et al. The safety of switching between therapeutic proteins. Expert OpinBiolTher 2012;12(11):1473-85

EMEA. Guideline on similar biological medicinal products containing monoclonal antibodies

Size of word is in proportion to its emphasis in the text

EMEA. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues - Executive summary. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. Accessed March 11th, 2014. Processed at http://www.wordle.net/create, March 11th, 2014

PRCA

- **Natural incidence with epoetin-alfa was 1/100,000**
  - **3 cases in first decade of Eprex Use**
- **After Eprex formulation change rose to 50/100,000**
  - Mikhail A, Farouk M. EpoetinBiosimilars in Europe: Five Years On. Adv Ther (2013) 30(1):28–40

- **Exposure to epoetin-alfa Binocrit reached 300,000 patient-years by February 2014**
  - **Approved 2007**
    - Garzotto AR et al. Erythropoiesis-stimulating agents for the treatment of chemotherapy-induced anemia: comparisons from real-world clinical experience. J Blood Med. 2014; 5: 43–48.

Strongly suggests that a similar association between PRCA and biosimilar epoetin-alfa is now very unlikely

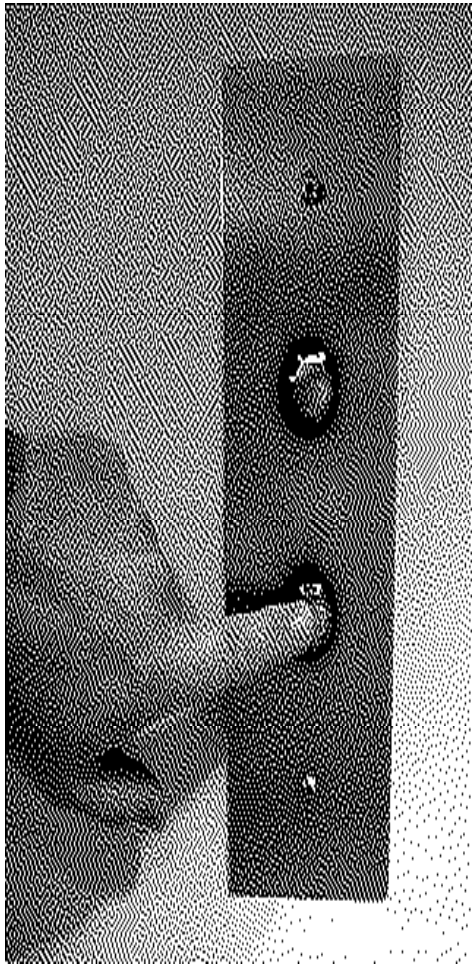
Biosimilars - Interchangeability and substitution

- Questions

- Why have we been worried?
- Terminology
- Rules
- Evidence for safety
  - Regulatory
- Observational studies of substitution & switching
  - Originator to Originator
  - Originator to Biosimilar
- RCTs of switching

- Questions Revisited

Substitution & Switching

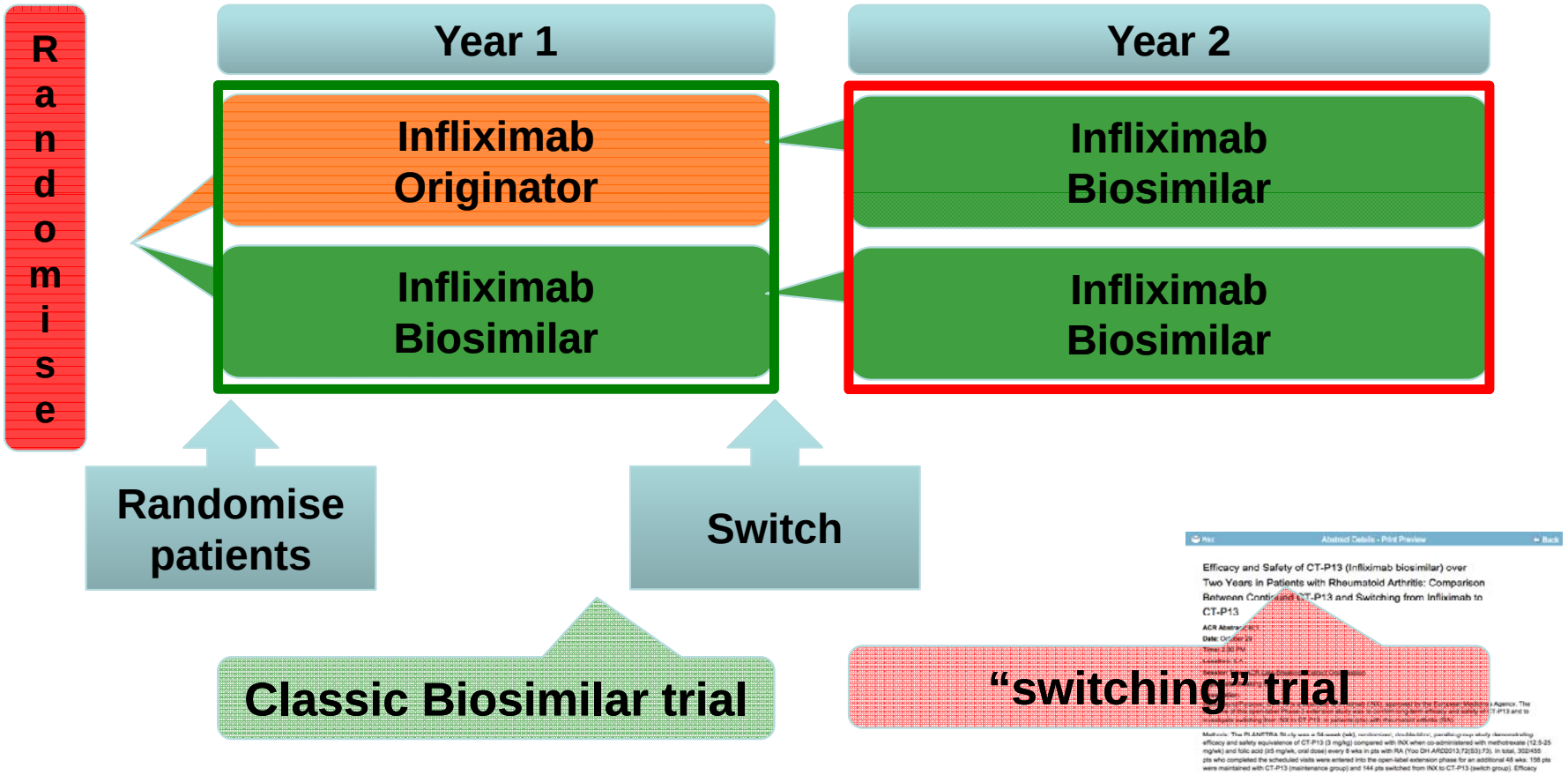


- There is a worry that switching between Innovator and Biosimilar drugs during a single cause of treatment could significantly increase the risks of adverse events
- Trials to support switching may be crucial for the concerns of some physicians and patient groups
- In the USA it may earn the registration as an “Inter-changable” biosimilar.

Ref:

Substitution & Switching

- **Plantera trial design: CTP13 Biosimilarvs originator reference**



Ref: Yoo DH et al. Efficacy and Safety of CT-P13 (Infliximabbiosimilar) over Two Years in Patients with Rheumatoid Arthritis: Comparison Between Continued CT-P13 and Switching from Infliximab to CT-P13. ACR Abstract:#L1. URL: https://ww2.rheumatology.org/apps/MyAnnualMeeting/AbstractPrint/39033. Accessed Nov 13, 2014

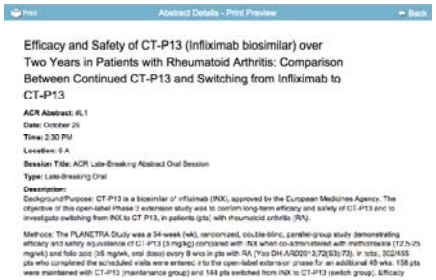
Substitution & Switching: Plantera trial

- **Response: by ACR20/50/70**

	Response		
	Week 54	Week 78	Week 102
Arm 1	Original	Biosimilar	Biosimilar
Arm 2	Biosimilar	Biosimilar	Biosimilar

Randomise

Switch



Efficacy and Safety of CT-P13 (Infliximab biosimilar) over Two Years in Patients with Rheumatoid Arthritis: Comparison Between Continued CT-P13 and Switching from Infliximab to CT-P13

ACR Abstract: #L1

Date: October 26

Time: 2:30 PM

Location: 6 A

Session Title: ACR Late-Breaking Abstract Oral Session

Type: Late-Breaking Oral

Description:

Background/Purpose: CT-P13 is a biosimilar of infliximab (INX), approved by the European Medicines Agency. The objective of this open-label Phase 3 extension study was to confirm long-term efficacy and safety of CT-P13 and to investigate switching from INX to CT-P13, in patients (pts) with rheumatoid arthritis (RA).

Methods: The PLANETRA Study was a 54-week (wk), randomized, double-blind, parallel-group study demonstrating efficacy and safety equivalence of CT-P13 (3 mg/kg) compared with INX when co-administered with methotrexate (12.5–25 mg/wk) and folic acid (≥5 mg/wk, oral dose) every 8 wks in pts with RA (Yoo DH ARD2013;72(63):73). In total, 302/455 pts who completed the scheduled visits were entered into the open-label extension phase for an additional 48 wks. 158 pts were maintained with CT-P13 (maintenance group) and 144 pts switched from INX to CT-P13 (switch group). Efficacy

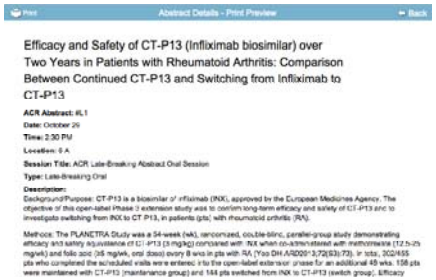
Ref: Yoo DH et al. Efficacy and Safety of CT-P13 (Infliximabbiosimilar) over Two Years in Patients with Rheumatoid Arthritis: Comparison Between Continued CT-P13 and Switching from Infliximab to CT-P13. ACR Abstract:#L1. URL: https://ww2.rheumatology.org/apps/MyAnnualMeeting/AbstractPrint/39033. Accessed Nov 13, 2014

Substitution & Switching: Plantera trial

- **Response: by ACR20/50/70**

	Response		
	Week 54	Week 78	Week 102
Arm 1	77.5%/50.0%/23.9%	78.2%/47.9%/29.6%	72.2%/48.3%/24.5%
Arm 2	76.8%/45.7%/21.9%	71.5%/48.3%/24.5%	71.8%/51.4%/26.1%

No difference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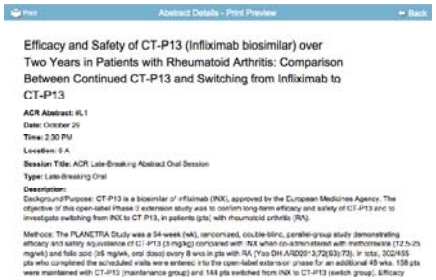
Substitution & Switching: Plantera trial

- **Anti-drug antibodies present**

	Response		
	Week 54	Week 78	Week 102
Arm 1	49.3%	49.6%	49.6%
Arm 2	49.1%	50.4%	46.4%

No difference



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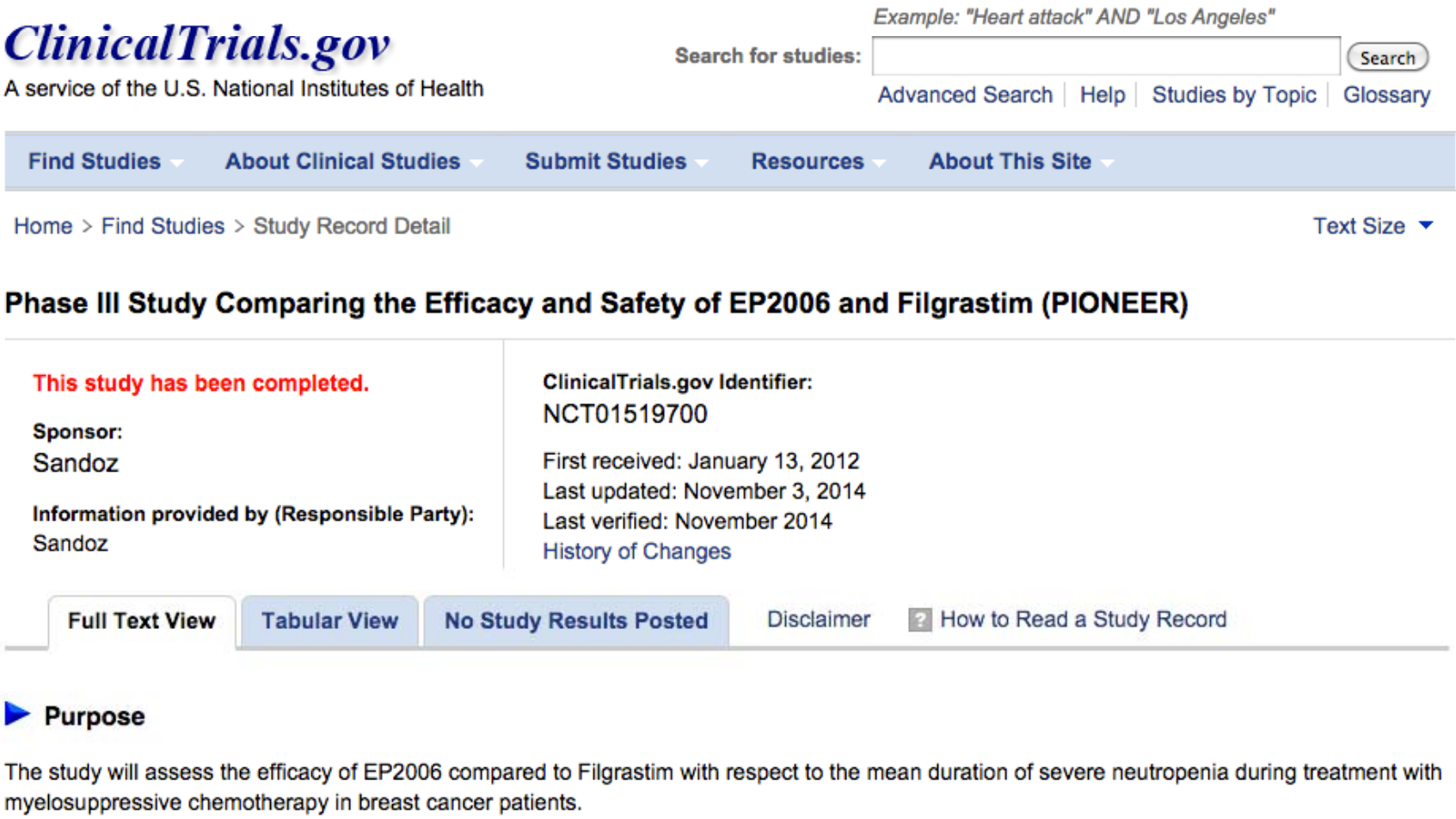

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Phase III Study Comparing the Efficacy and Safety of EP2006 and Filgrastim (PIONEER)

This study has been completed.

Sponsor:
Sandoz

Information provided by (Responsible Party):
Sandoz

ClinicalTrials.gov Identifier:
NCT01519700

First received: January 13, 2012
Last updated: November 3, 2014
Last verified: November 2014
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

The study will assess the efficacy of EP2006 compared to Filgrastim with respect to the mean duration of severe neutropenia during treatment with myelosuppressive chemotherapy in breast cancer patients.

Ref PIONEER Trial. URL: http://clinicaltrials.gov/show/NCT01519700. Accessed Nov 7, 2014

Substitution & Switching - Pioneer

- **Pioneer trial: GCSF for chemotherapy induced neutropaenia. During TAC chemotherapy for breast cancer**
- **Biosimilar filgrastim – EP2006 VS Original reference drug neupogen**

	Chemotherapy cycles					
Trial Arm	**1**	**2**	**3**	**4**	**5**	**6**

Ref PIONEER Trial. URL: http://clinicaltrials.gov/show/NCT01519700. Accessed Nov 7, 2014

Substitution & Switching - Pioneer

- Pioneer trial: GCSF for chemotherapy induced neutropaenia. During TAC chemotherapy for breast cancer
- Biosimilar filgrastim – EP2006 VS Original reference drug neupogen

	Chemotherapy cycles					
Trial Arm	1	2	3	4	5	6
A	EP2006	EP2006	EP2006	EP2006	EP2006	EP2006
2						
3						
B	Original	Original	Original	Original	Original	Original

Randomise

Classic Biosimilar trial

Ref PIONEER Trial. URL: http://clinicaltrials.gov/show/NCT01519700. Accessed Nov 7, 2014

Substitution & Switching - Pioneer

- Pioneer trial: GCSF for chemotherapy induced neutropaenia. During TAC chemotherapy for breast cancer
- Biosimilar filgrastim – EP2006 VS Original reference drug neupogen

	Chemotherapy cycles					
Trial Arm	1	2	3	4	5	6
1	EP2006	EP2006	EP2006	EP2006	EP2006	EP2006
2						
3						
4	Original	Original	Original	Original	Original	Original

Randomise

Ref PIONEER Trial. URL: http://clinicaltrials.gov/show/NCT01519700. Accessed Nov 7, 2014

Substitution & Swit

Pioneer has closed on the trials database: Results expected soon!

- **Pioneer trial: GCSF for chemotherapy induced neutropaenia. During TAC chemotherapy for breast cancer**
- **Biosimilar filgrastim – EP2006 VS Original reference drug neupogen**

	Chemotherapy cycles					
Trial Arm	**1**	**2**	**3**	**4**	**5**	**6**
1	**EP2006**	**EP2006**	**EP2006**	**EP2006**	**EP2006**	**EP2006**
2	**EP2006**	**Original**	**EP2006**	**Original**	**EP2006**	**Original**
3	**Original**	**EP2006**	**Original**	**EP2006**	**Original**	**EP2006**
4	**Original**	**Original**	**Original**	**Original**	**Original**	**Original**

Randomise

“switching” trial

Ref PIONEER Trial. URL: http://clinicaltrials.gov/show/NCT01519700. Accessed Nov 7, 2014

Promotion of Switching and Substitution

- **This is not within the power of the EMA or WHO to control**
  - **They delegate this to individual countries**

- **Some countries have legislated to promote this**
  - **Examples: USA & France**

- **Many countries have advised against "automatic substitution" by a pharmacist**
  - **So pharmacists will have to notify the prescribing physician if this is possible**

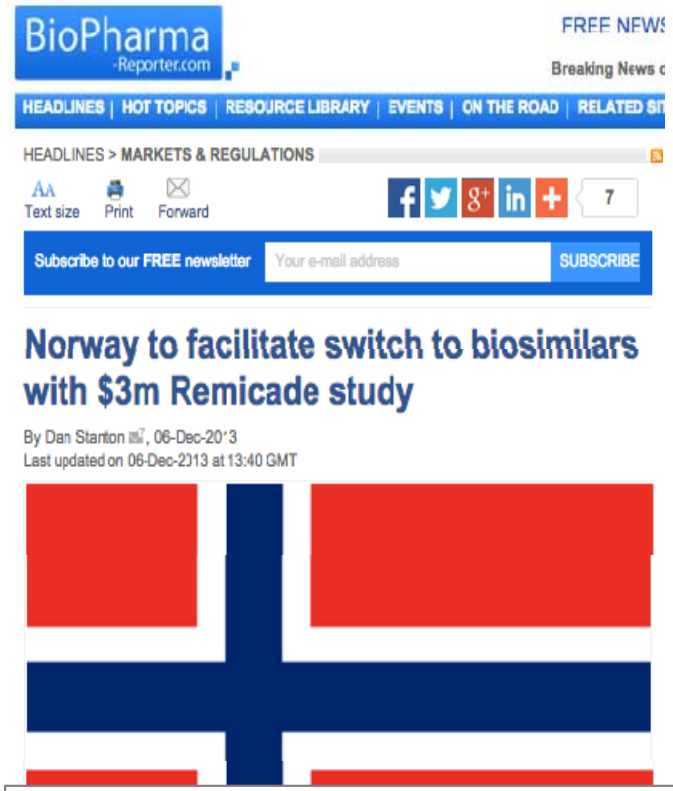
Some medical societies have requested evaluation of this process

NOR-SWITCH
ClinicalTrials.gov Identifier: NCT02148640

- **Norwegian Health department currently funds Infliximab (Remicade) for**
  - **rheumatoid arthritis, spondyloarthritis,**
  - **psoriatic arthritis, chronic plaque psoriasis**
  - **ulcerative colitis, Crohn's disease**
- **Annual cost for a compliant patient was estimated at GBP 7580 (€12,226 , 40,000 RM) in the UK**
  - Kobelt G et al. The cost-effectiveness of infliximab (Remicade®) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. Rheumatology (2003) 42 (2): 326-335. doi: 10.1093/rheumatology/keg107
- **Infliximab Biosimilar costs 39% less than Remicade in Norway**
  - **It is the first choice Inflammatory Disease Modifying Biologic for the Norwegian NHS**
    - Spotlight On: Norway unveils near 40 percent discounting for biosimilarinfliximab – can it pave the way for a broader European trend?. FirstWordPharma. URL: http://www.firstwordpharma.com/footer/benefits?tsid=17#axzz3G7Hs6Q99. Accessed oct 14, 2014

Ref: Spotlight On: Norway unveils near 40 percent discounting for biosimilarinfliximab – can it pave the way for a broader European trend?. FirstWordPharma. URL: http://www.firstwordpharma.com/footer/benefits?tsid=17#axzz3G7Hs6Q99. Accessed oct 14, 2014

Promotion of Biosimilars: Switching and Substitution



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

By Dan Stanton, 06-Dec-2013

Last updated on 06-Dec-2013 at 13:40 GMT

Related tags: Remicade, Inflectra, Norway, Biosimilars

Related topics: Biosimilars, Markets & Regulations, Analytical (technologies & services)

The Norwegian Health Department has committed 20m NOK ($3.3m) to a study in order to facilitate the use of biosimilars.

- **The NOR-SWITCH Study:**
- **Infliximab original vsInfliximab biosimilar (Remsima)**
  - ClinicalTrials.gov Identifier: NCT02148640
- **Aim: RCT to assess the safety and efficacy of switching from Remicade to the biosimilar treatment Remsima in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis**

The Norwegian Health Department has committed 20m NOK ($3.3m) to a study in order to facilitate the use of biosimilars.

- **Primary Outcome Measures: Occurrence of disease worsening**

Ref: Spotlight On: Norway unveils near 40 percent discounting for biosimilarinfliximab – can it pave the way for a broader European trend?. FirstWordPharma. URL: http://www.firstwordpharma.com/footer/benefits?tsid=17#axzz3G7Hs6Q99. Accessed oct 14, 2014

NOR-SWITCH
ClinicalTrials.gov Identifier: NCT02148640

- **Budget for 500 patients for a year:**
  - **500 x 12,226 Euro a year per patient wholesale.**
  - **= 6.1 Million Euros (26 Million RM) a year**
    - 500x12226 = 6113000
- **Infliximab Biosimilar costs 39% less than Remicade in Norway**
  - **Budget impact if 50% of patients switched = 1.2 Million Euros**
    - 250 x 12226 x 0.39 = 1192035
- **Most patients take infliximab for 2 years, after 2 years, savings should be 2.4 M Euros/year recurring**
- **Why not invest that 2.4 M Euros / 20 M Norwegian Krone in a trial to switch 50% of patients on infliximab to a biosimilar that is 39% cheaper for 1 year?**

Ref: Spotlight On: Norway unveils near 40 percent discounting for biosimilarinfliximab – can it pave the way for a broader European trend?. FirstWordPharma. URL: http://www.firstwordpharma.com/footer/benefits?tsid=17#axzz3G7Hs6Q99. Accessed oct 14, 2014


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Biosimilars - Interchangeability and substitution

- Questions

- Why have we been worried?
- Terminology
- Rules
- Evidence for safety
  - Regulatory
- Observational studies of substitution & switching
  - Originator to Originator
  - Originator to Biosimilar
- RCTs of switching

- Questions Revisited

Question 1

- **You are part way through a course of treatment with infliximab for rheumatoid disease - The patient is responding without serious toxicity**
- **Your pharmacy colleagues tell you that the next treatment is likely to come from a new purchase of biosimilar infliximab (approved for use by the EMEA)**

- **Do you?**

1. **Refuse – as the patient is part way through treatment and switching is not advised by Malaysian Guidelines**
2. **Agree – but worry there is no data to support this change**
3. **Agree to the switch – as no excess adverse events are expected**

Question 2

- **You are part way through a course of dose dense chemotherapy for breast cancer – supported by Filgrastim GCSF to prevent neutropaenia. The patient is responding without serious toxicity**
- **The patient will transfer mid-way through treatment to stay with her family in another area. Your colleague tells you that in their hospital, they use only biosimilar Filgrastim (approved for use by the EMEA and Malaysian Regulators)**

- **Do you?**

1. **Refuse – the patient is part way through treatment and switching is not advised by Malaysian Guidelines**
2. **Agree – but worry there is no data to support this change**
3. **Agree to the switch – as no excess adverse events are expected**


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