Clinical experience with biosimilar medicines (EAHP 2017 Cannes)

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Disclosures

Name:

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Commercial Interests & Nature of Relationships:

- Sandoz, Roche, Novartis, Astellas, Siemens, Thermo-Fischer, Teva, Chiesi: Consultant/Speaker received honoraria
- Chiesi, Astellas: Research Grant Support, study on transplant related diseases

Program

Teun van Gelder (MD, Erasmus MC, the Netherlands)

Clinical experience with biosimilar medicines

Benedicte Lunddhal (DKMA, Denmark)

Role of regulators to increase trust and confidence in biosimilar medicines?

Barbara Claus (University Hospital Ghent, Belgium)

Considerations for hospital pharmacists when biosimilar medicines enter the hospital

Expert discussion

At present I am:

- chairman of the Dutch Society for Clinical Pharmacology

Personal viewpoint

Acknowledgement: Professor Arnold Vulto – PharmD at Erasmus MC

Elections in The Netherlands (March 15)

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Goals :

Focus on the perspective of the Medical Doctor

Evaluate the concerns behind the use of biosimilars as an alternative to biologics.

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To be discussed:

Perception of Medical Doctor on generic substitution.

Early experience with biosimilars (epo).

Perspectives of different stakeholders on biosimilars.

Generic drugs in The Netherlands (2015)

Volume : 72.4% generic

Cost: 16.5% generic

Criteria for Demonstrating Bioequivalence

Two drug products are considered bioequivalent if 90% Confidence Intervals for both AUC and Cmax mean ratios fall entirely within the acceptance limits of 80–125%

Source: The European Agency for the Evaluation of Medicinal Products (CPMP). Note for guidance on the investigation of bioavailability and bioequivalence.

Available at http://www.emea.europa.eu/pdfs/human/qwp/140198enfin.pdf.

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Are drugs which are bioequivalent also interchangeable?

Perspective of health insurance companies.

Perspective of MDs.

Perspective of PharmDs.

Perspective of patients.

Confusion and mistakes

In The Netherlands the tendering strategy has resulted in too many substitutions from generic A, to generic B, to generic C, to generic D..

Successively providing patients with different generic formulations will lead to irritation, confusion, errors and to reduced adherence.

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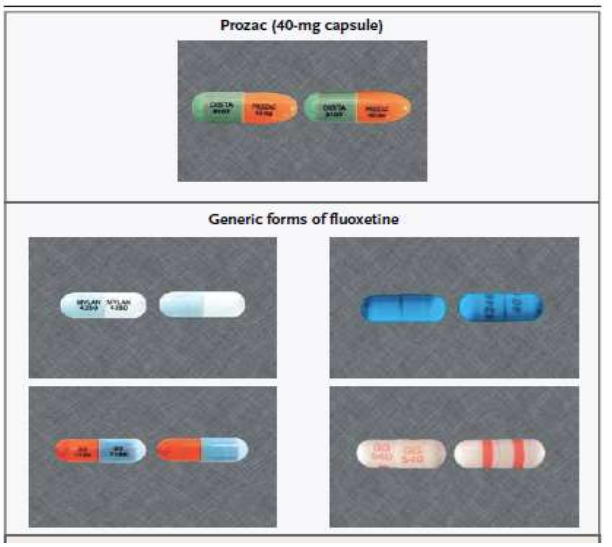
Differences in appearance of innovator and 4 generic versions of fluoxetine.



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JAMA Intern Med. 2013;173(3):202-208.

ORIGINAL INVESTIGATION

Variations in Pill Appearance of Antiepileptic Drugs and the Risk of Nonadherence

Aaron S. Kesselheim, MD, JD, MPH; Alexander S. Misono, MD, MBA; William H. Shrank, MD, MSHS; Jeremy A. Greene, MD, PhD; Michael Doherty; Jerry Avorn, MD; Niteesh K. Choudhry, MD, PhD

Sorting out drugs on the kitchen table.

Visual cues paramount to identification of pills.

Changes in appearance will confuse patients.

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ORIGINAL RESEARCH | Annals of Internal Medicine

Burden of Changes in Pill Appearance for Patients Receiving Generic Cardiovascular Medications After Myocardial Infarction

Cohort and Nested Case–Control Studies

Aaron S. Kesselheim, MD, JD, MPH; Katsiaryna Bykov, PharmD, MS; Jerry Avorn, MD; Angela Tong, MS; Michael Doherty, MS; and Niteesh K. Choudhry, MD, PhD

Ann Intern Med. 2014;161:96-103.

Conclusion: Variation in the appearance of generic pills is associated with nonpersistent use of these essential drugs after MI among patients with cardiovascular disease.

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Generic substitution

In Netherlands: reality for majority of drugs.
Electronic prescription: generic name, not trade name.
Save money, but fear for penny wise, pound foolish.

If innovator drug is preferred: specify on prescription!
Insurance company asks for explanation (allergy?)

MD feels he/she has lost control.

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Biosimilars

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Three generations of therapeutic proteins

Generation 1: substitution products

- Hormones like growth factors or insulin
- Effect visible / measurable in hours or days

Generation 2: proteins with a specific pharmacological effect

- Like TNF-alfa inhibitors
- Effect only visible after some time, but not in all patients

Generation 3: proteins with a less concrete clinical effect

- “Targeted therapies” in oncology
- The effect is a statistical chance some time in the future (survival)

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Erythropoeitin

Whereas the pathogenesis of anemia of Chronic Kidney Disease is multifactorial, the decreased production of EPO with declining renal mass is considered the primary etiologic factor.

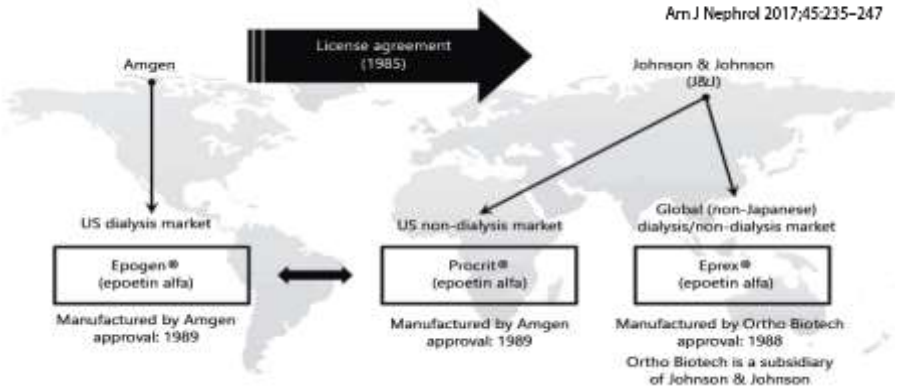
Anemia is associated with fatigue, weakness, and dyspnea, as well as worsening quality of life and performance status

Am J Nephrol 2017;45:235–247

The first rHuEPO: epoetin alfa

Manufactured by Amgen, sold as Epogen ® in US for CIHD pts in 1989.

Amgen transferred rights for all non-dialysis indications in the US and all indications outside the US (excluding Japan) to Johnson & Johnson, and its affiliate Ortho Biotech.



Safety of erythropoiesis stimulating agents (ESAs)

Cardiovascular events

More CV events and more hypertensive episodes when using higher doses of ESAs to achieve higher hemoglobin targets

(FDA: black box warning for all ESAs in 2007)

Pure Red Cell Aplasia

Case reports in mid-1990s

“Epidemic” between 1998-2004

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THE NEW ENGLAND JOURNAL OF MEDICINE March 7, 1996

BRIEF REPORT: AUTOANTIBODIES AGAINST ERYTHROPOIETIN IN A PATIENT WITH PURE RED-CELL APLASIA

NICOLE CASADEVALL, M.D., EVELYNE DUPUY, M.D., PASCALE MOLHO-SABATIER, M.D., GÉRARD TOBELEM, M.D., BRUNO VARET, M.D., AND PATRICK MAYEUX, PH.D.

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Pure Red-Cell Aplasia and Epoetin Therapy

Charles L. Bennett, M.D., Ph.D., M.P.P., Stefano Luminari, M.D., Allen R. Nissenson, M.D., Martin S. Tallman, M.D., Stephen A. Klinge, B.A., Norene McWilliams, J.D., M.P.H., June M. McKoy, M.D., J.D., M.P.H., Benjamin Kim, M.D., E. Allison Lyons, B.A., Steve M. Trifilio, R.P.H., Dennis W. Raisch, Ph.D., Andrew M. Evens, D.O., Timothy M. Kuzel, M.D., Glen T. Schumock, Pharm.D., M.B.A., Steven M. Belknap, M.D., Francesco Locatelli, M.D., Jerôme Rossert, M.D., Ph.D., and Nicole Casadevall, M.D.

N Engl J Med 2004;351:1403-8.

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PRCA (with innovator biologic!)

January 1998 - April 2004: epoetin-associated pure red-cell aplasia

175 cases for Eprex

11 cases for Neorecormon

5 cases for Epogen

Eprex: polysorbate in stead of human serum albumin, and uncoated rubber stoppers of prefilled syringes?

After procedures were adopted to ensure appropriate storage, handling, and administration of Eprex to patients with chronic kidney disease, the exposure-adjusted incidence decreased by 83% worldwide.

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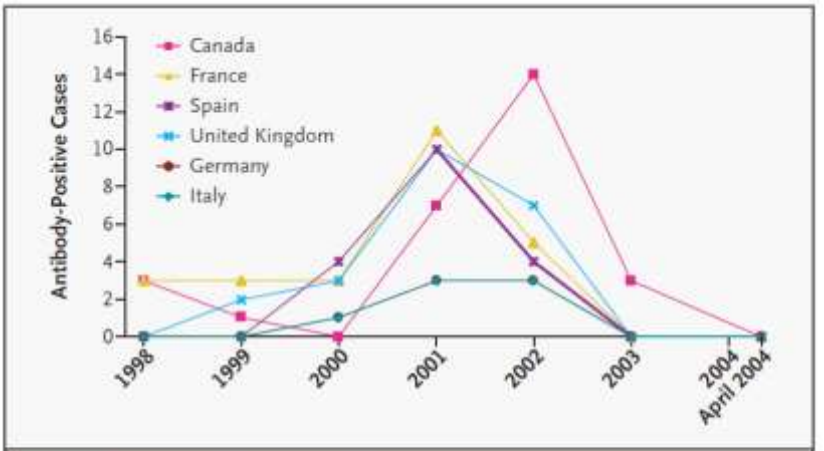

Figure 1. Cases of Antibody-Positive, Eprex-Associated Pure Red-Cell Aplasia Identified in the Database of the Adverse Event Reporting System of the Food and Drug Administration between January 1998 and April 2004.

In Germany and Italy there were the same number of case reports within each year.

Biosimilar ESAs

Currently, there are several biosimilar EPOs marketed in Europe by various license holders.

However, these products represent only 2 biosimilar EPOs:

- epoetin alfa (e.g., Binocrit ® , Sandoz)
- epoetin zeta (e.g., Retacrit ® , Hospira, a Pfizer company)

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Table 1. Summary of erythropoiesis-stimulating agents

INN	Trade name	License holder	Approval	Manufacturing process	Licensed in		
					European Union	United States	Other regions
First generation							
Epoetin alfa	Epogen®	Amgen	1989	Recombinant DNA technology (in CHO cells)		✓	
	Eprex®	Ortho Biotech	1988		✓	✓	✓
	Procrit®	Amgen	1989			✓	
Epoetin beta	Recormon®	Boehringer Mannheim	1990	Recombinant DNA technology (in CHO cells)	✓		
Epoetin omega	Epomax® Hemax®	Elanex/Baxter	1990	Recombinant DNA technology (in hamster kidney cells)			✓
Second generation							
Epoetin beta	NeoRecormon®	Roche	1997	Recombinant DNA technology (in CHO cells)	✓		✓
Darbepoetin alfa	Aranesp®	Amgen	2001	Recombinant DNA technology (in CHO cells)	✓	✓	
Third generation							
Epoetin delta	Dynepo®	Transkaryotic therapies/Shire	2002	Gene activation technology (in HT-1080 cells)	✓	✓	
Methoxy polyethylene glycol epoetin beta	Mircera®	Roche	2007	Recombinant DNA technology (in CHO cells)	✓	✓	
Epoetin alfa (biosimilar)	Binocrit® Abseamed® Epoetin Alfa Hexal®	Sandoz Medice Hexal AG	2007	Recombinant DNA technology (in CHO cells)	✓		
Epoetin zeta (biosimilar)	Retacrit™ Silapo™	Hospira, a Pfizer company Stada	2007	Recombinant DNA technology (in CHO cells)	✓		✓
Epoetin theta	Biopoin® Eporatio®	Teva Ratiopharm	2009	Recombinant DNA technology (in CHO cells)	✓		

INN, international nonproprietary name; NCE, new chemical entity; NME, new molecular entity.

CHMP erythropoietin biosimilar application requirements

Assessment type	Requirements	
Nonclinical		
Pharmacodynamic	In vitro (receptor binding, cell proliferation)	In vivo (comparison of erythrogenic effects)
Toxicologic	Repeat dose toxicity in a relevant species, duration of at least 4 weeks	Local tolerance in a relevant species
Clinical		
PK	Single-dose, crossover study for indicated routes of administration selected dose should be in the sensitive part of the dose-response curve	Healthy volunteers
Pharmacodynamic	Evaluated as part of the PK assessments, selected dose should be in the linear ascending part of the dose-response curve	Healthy volunteers
Efficacy	Adequately powered, randomized, double-blind, parallel group assessments for indicated routes of administration	Correction phase (pre-dialysis population) and maintenance phase (hemodialysis population) to target hemoglobin concentration, with primary efficacy endpoints assessed at 5–6 months
Safety	Comparative safety data, adverse events of special interest include hypertension/aggravation of hypertension and thromboembolic events	12-month comparative immunogenicity assessment

Am J Nephrol 2017;45:235–247

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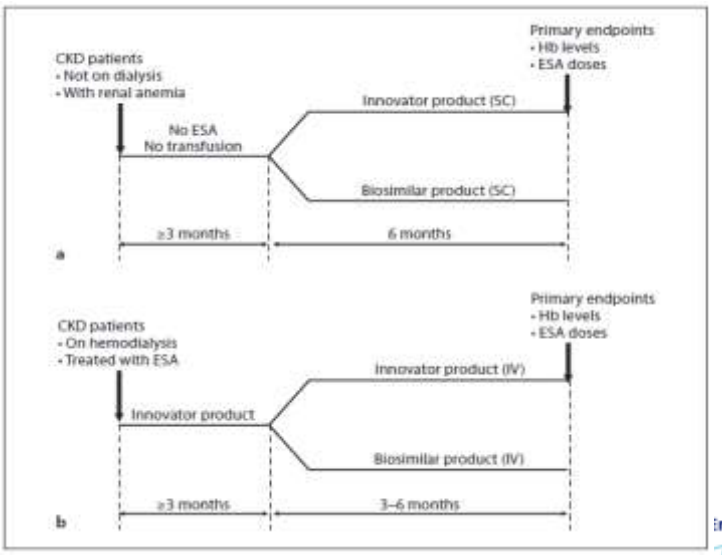
Approval biosimilar epoetin products



Kidney Blood Press Res 2007;30(suppl 1):13–17

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Safety of biosimilar ESAs

To date, no evidence for an increase in PRCA or other untoward adverse events among biosimilar ESAs.

Retacrit (iv/sc) : European data show an extensive treated population of patients without any unexpected adverse events [Michallet 2016] .

Binocrit (iv/sc) : Majority of exposure data are favorable.

But, one confirmed case and another suspected case of PRCA in patients receiving subcutaneous Binocrit [Haag-Weber 2012].

(possibly unfolding of Binocrit protein due to tungsten species in the syringes) .

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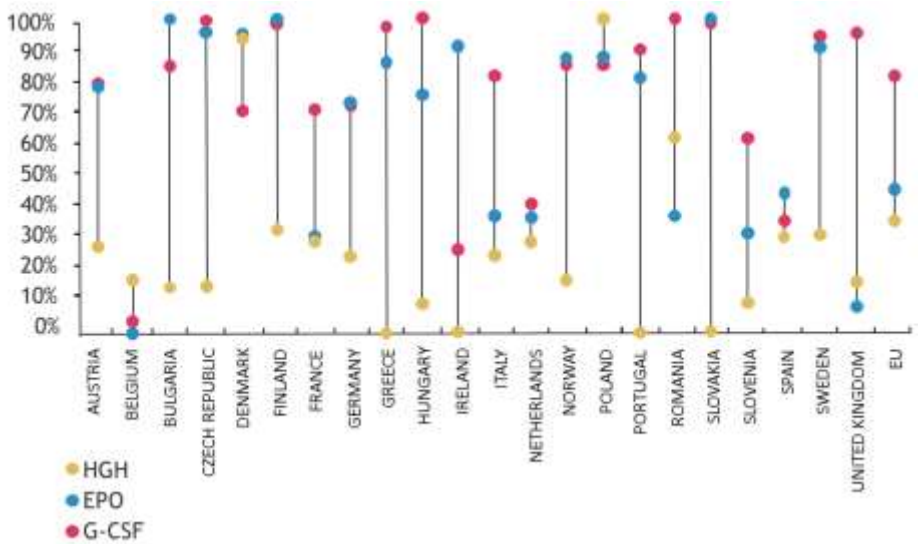
Biosimilar acceptance in 2014



Biotech

Differences in uptake of biosimilars

Between countries

Within one country between specialty groups.

Immunogenicity

Biosimilars : different manufacturing processes and different master cell line, processing and purification, inert ingredients, and packaging.

Need to know : also within the life span of a biologic drug there will be changes in the manufacturing processes, including purification, inert ingredients, and packaging (Eprex).

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Uncertainty

Biosimilars are not *identical* but *similar*

A deep understanding of bioequivalence and “biosimilarity” is not easy (for MDs)

We have to accept – as with every other drug – that at the time of licensing there is always a certain degree of uncertainty

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Biosimilars create uncertainty with prescribers

Biosimilars

- Don't offer prescriber and patient a clear therapeutic advantage
- May offer a modest price advantage for the patient / 3rd party payer
- They may carry – as with any other new drug – some risk

Doctors and patients don't like hassle with their medicines

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How to build trust in biosimilars?

Reduce the information gap

Regulators can communicate their knowledge actively to medical professionals:

"The past 10 year there has not been a single serious incident with biosimilars"

"The assessment system worked as expected"

"Raised mistrust was not justified; we learned better in the meantime"

Convince prescribers on the (financial) advantages for the society, without compromising quality of treatment.

Netherlands

Regulators and Pharmacists: Biosimilars and biologics have the same efficacy and safety, and therefore they can be used interchangeably. Not a problem to change from one formulation to another in maintenance treatment (in close collaboration with prescriber).

MDs: Biosimilars and biologics have the same efficacy and safety, and therefore they can both be used in a new patient. If patient is doing well on maintenance treatment then better not to change.

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Product Category Ownership:

- Involve the key opinion leader in specific area
- Identify push and pull factors: transparency
- Loyalty with producer(s)
- Sponsored projects with producer(s)
- Discuss preference for particular product
- Discuss price differences
- Discuss incentives for prescibers
- Negotiate with producer(s)

Conclusion - 1

Biosimilars are as safe as any other biological licensed in the EU

Reluctance with prescribing biosmilars : no scientific evidence to support this reluctance

Almost 10 years of experience with well-regulated biosimilars did not show a single serious incident

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Conclusion - 2

Medical Doctors may still feel uncertain or reluctant to use biosimilars:

- teach them
- identify push and pull factors (transparency)
- involve them
- avoid repetitive substitutions among biosimilars
- incentives work!

Pharmacists have a key position

- independent educators for prescribers and patients

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Biosimilars in The Netherlands

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