Vienna, March 16, 2016

Introducing Biosimilars into the Hospital Formulary
Tools for the Hospital Pharmacist

Arnold G. Vulto PharmD PhD
Professor of Hospital Pharmacy & Practical Therapeutics
ErasmusMC Hospital Pharmacy
Rotterdam / The Netherlands

Vs16c15

Conflict of Interest

- I declare no personal financial interest in any pharmaceutical business.
- My hospital receives financial compensation for the time I consult / lecture for 3rd parties, like speaking bureaus and pharmaceutical companies.
- I entertain friendly relationschips with all innovative and generic / biosimilar companies and I help them all where I can. I don't receive personally any payment for that.

- Companies / Organisations involved are: AbbVie, Amgen, Biogen, EGA, Mundipharma, Pfizer/Hospira, Roche, Sandoz

Agenda

- The Hospital Formulary
- Drug selection in the hospital
- Three generations of biosimilars
- The information gap
- How to raise trust
- Take home message

3

Erasmus MC

Why do we have a hospital formulary

- To rationalise pharmacotherapy
  - Promote drug effectiviness and safety
- To optimise effciency and cost
  - Reduce stock
  - Increase negotiating power

- The content of a hospital formulary in most instances is decided upon by a multidisciplinary Formulary or Drug & Therapeutics Committee.
- The composition varies, with representatives of medical and pharmacy staff, hospital management, nurses etc.
- Formal decision making varies

4

Criteria for product selection in the hospital

- Pharmaceutical quality
- Effectiveness
- Safety
- Economical aspects
  - More then price alone
    - Ease of Use
      - e.g. RTU vs. freeze dried, SC Vs IV, Administration devices
    - Various strengths and dosage forms
    - Stability, storage conditions, (in)compatibilities
    - Barcode, flag label
    - Additional cost in relation with use (e.g. tests, monitoring)

5

Type of products and choices

- Originator products
  - Branded product (innovative, unique, me-too)
- Copy products
  - Non-branded generic
  - Branded generics, Branded biosimilars

- Hospital pharmacists are looking for the best market opportunities to benefit patients, doctors and hospital (budget)
- Drug choice can be
  - Structured (preferred product in a formulary)
  - Ad Hoc (individualised treatment)

6

Agenda

- The Hospital Formulary
- Drug selection in the hospital
- ***Three generations of biosimilars***
- The information gap
- How to raise trust
- Take home message

7

Erasmus MC

Three generations of therapeutic proteins (biologicals)

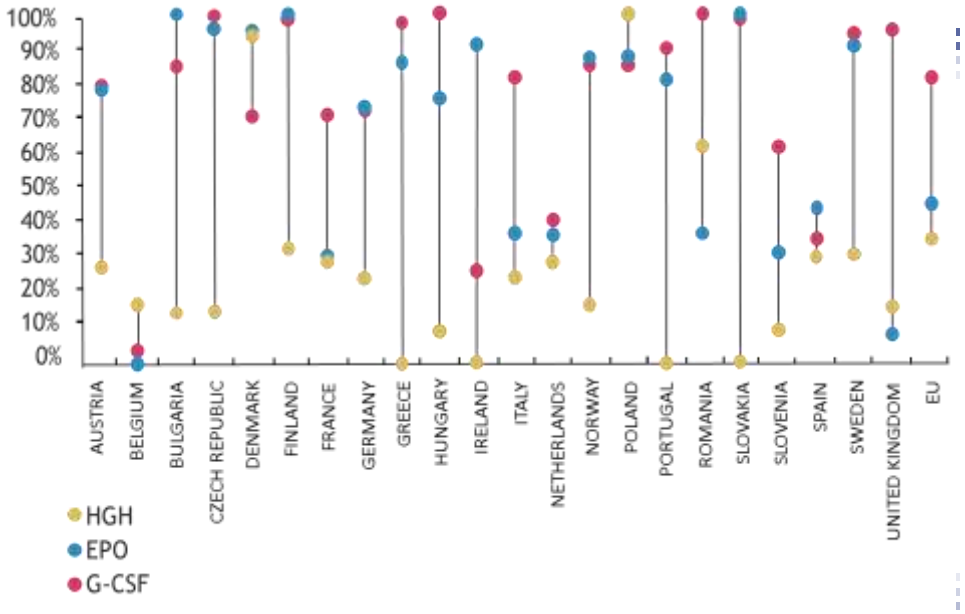
- **Generation 1**: substitution products
  - Hormones like growth factors or insulin
  - Effect visible / measurable in hours or days
- **Generation 2**: proteins with a specific pharmacological effect
  - Like TNF-alfa inhibitors
  - Effect only visible after some time, but not in all patients
- **Generation 3**: proteins with a less concrete clinical effect
  - "Targeted therapies" in oncology
  - The effect is a statistical chance some time in the future (survival)

8

Biosimilars licensed in the EU (1/1/2016)

Molecule	Company	Approval Date	Reference Product	Brand Name
Somatropin	Sandoz	Apr-06	Genotropin [PFE]	Omnitrope
Somatropin	Biopartners	Apr-06	Humatrope [LLY]	Valtropin
EPO-alfa	Sandoz	Aug-07	Epogen [AMGN]	Binocrit
EPO-alfa	Hexal	Aug-07	Epogen [AMGN]	EPO-alfa Hexal
EPO-alfa	Medice	Aug-07	Epogen [AMGN]	Abseamed
EPO-zeta	Stada	Dec-07	Epogen [AMGN]	Silapo
EPO-zeta	Hospira	Dec-07	Epogen [AMGN]	Retacrit
Filgrastim	Ratiopharm	Sep-08	Neupogen [AMGN]	Filgrastim Ratiopharm
Filgrastim	Teva Pharma	Sep-08	Neupogen [AMGN]	TevaGrastim
Filgrastim	AbZ-Pharma GmbH	Sep-08	Neupogen [AMGN]	Biograstim
Filgrastim	Ratiopharm	Sep-08	Neupogen [AMGN]	Ratiograstim
Filgrastim	Hexal	Feb-09	Neupogen [AMGN]	Filgrastim Hexal
Filgrastim	Sandoz	Feb-09	Neupogen [AMGN]	Zarzio
Filgrastim	Hospira	Jun-10	Neupogen [AMGN]	Nivestim
Infliximab	Celltrion	Sep-13	Remicade [JNJ]	Remsima
Infliximab	Hospira	Sep-13	Remicade [JNJ]	Inflectra
FSH	Teva Pharma	Sep-13	Gonal-f [MRK-GR]	Ovaleap
Filgrastim	Apotex Europe BV	Oct-13	Neupogen [AMGN]	Grastofil
FSH	Finox AG	Mar-14	Gonal-f [MRK-GR]	Bemfola
Insulin glargine	Eli Lilly	Sep-14	Lantus [SNY]	Abasaglar
Filgrastim	Accord Healthcare	Sep-14	Neupogen [AMGN]	Accofil

Biosimilar uptake as % of accesible market (2014; IMS)



Second Generation: Therapeutic proteins with a pharmacological action

- These proteins do not mimic a biological function, but act mostly as an pharmacologcial antagonist e.g. binding a circulating protein or blocking a receptor
- The clinical effect may be visible and measurable within days or weeks
  - In a proportion of patients
- Currently licensed biosimilars (March 2016) infliximab and etanercept

11

Savings can be considerable: The case of infliximab-biosimilar in Norway

- As of February 2014, Norway negotiated a 39% discount on the innovator list price on exclusivity basis: all *new* patients will start on infliximab biosimilar
- Renegotiation 2015: 69% discount; no switching
- Market uptake
  - March 2014 12,7 %
  - March 2015 >50 %

(Steinar Madsen, EGA Biosimilar Meeting London, 2015)

12

Infliximab biosimilar in Norway

Patient	Tender year	Remicade	Remsima	Savings	Savings (%)
Rheumatoid arthritis, 70 kg, one year treatment	2014	84 000 NOK 10 500 EUR 14 000 USD	51 000 NOK 6 400 EUR 8 500 USD	33 000 NOK 4 100 EUR 5 500 USD	39%
	2015	83 400 NOK 9 700 EUR 11 000 USD	26 000 NOK 3 000 EUR 3 400 USD	57 400 NOK 6 700 EUR 7 600 USD	69%

Steinar Madsen, EGA Biosimilar Meeting 2015

13

Third generation: therapeutic proteins with a remote clinical effect

- These protein drugs provide a statistical chance on benefit some time in the future (e.g. trastuzumab, rituximab).
- For these we need deep trust in the principles of similarity.
- On what is the purported clinical effect based?
- Can we expand the use in other types of cancer?
- Doctors may be very reluctant to accept clinical similarity of these molecules ("You can't gamble with patients' lives")

- As yet, these are theoretical questions, as no biosimilar of this type has been granted marketing authorisation yet.

14

All large companies are now on the biosimilar bandwagon

- Amgen: 8 molecules
- Baxalta / Momenta
- Biogen / Samsung-Bioepis: “big five”
- Boehringer Ingelheim (big five, but dropped rituximab)
- Merck – Serono
- MSD
- Pfizer / Hospira: “big five”
- Sandoz: “big five”
- TEVA

“Big Five”: adalimumab, etanercept, infliximab, rituximab, trastuzumab

15

For a decision to include a drug in the formulary, information is needed

- Biosimilars are not *identical* but *similar*
- What are then the differences, and what could be the consequence?
- A deep understanding of bioequivalence and “biosimilarity” is not easy
- We have to accept – as with every other drug – that at the time of licensing there is always a certain degree of uncertainty

Physicians don’t like uncertainty

In doubt do not cross!

16

Biosimilars create uncertainty with prescribers

- **Innovative medicines**
  - Offer a clear advantage – whether real or not
  - Marketeers promise a solution for a therapeutic problem
  - And hence, the physician is prepared to take a certain risk
- **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

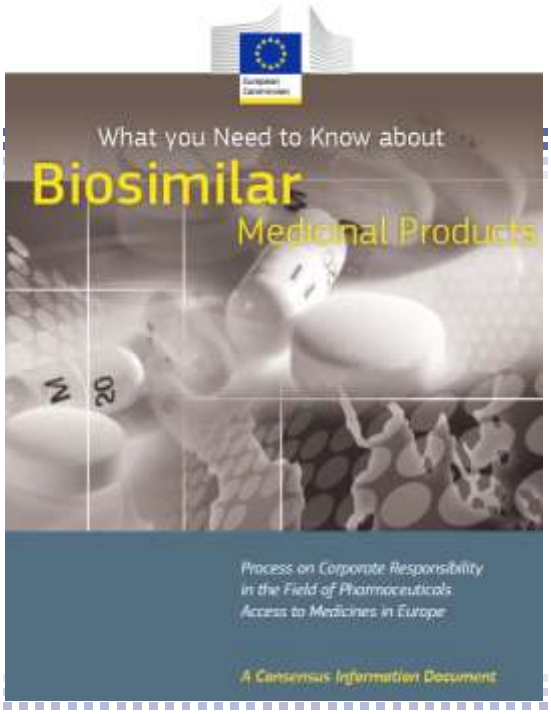
Doctors and patients don't like hassle with their medicines

17

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"
- **Avoid "hassle" around changing to biosimilars**
  - Convince prescribers on the (financial) advantages for the society, without compromising quality of treatment.

18



EU commission published consensus paper (April 2013), very useful for Drug & Therapeutic Committees

Quote:

"Biosimilar medicinal products have been used safely in clinical practice in the European Union since 2006 …. "

19

Agenda

- Introduction and Perspective
- The Hospital Formulary
- Drug selection in the hospital
- Three generations of biosimilars
- ***The information gap***
- How to raise trust
- Take home message

20

We perceive an information gap

- EMA's EPAR (50+ pages) is difficult to read / understand for a healthcare professional
  - Need support to understand the comparability excercise
  - Is 3% antibodies in a Nivestim comparative trial a problem?
  - No access to risk management information / PSUR's
- Research findings should be published and made accesible
  - With 2nd generation, all research data are early available
- Clinical trials scattered and not always easily accesible

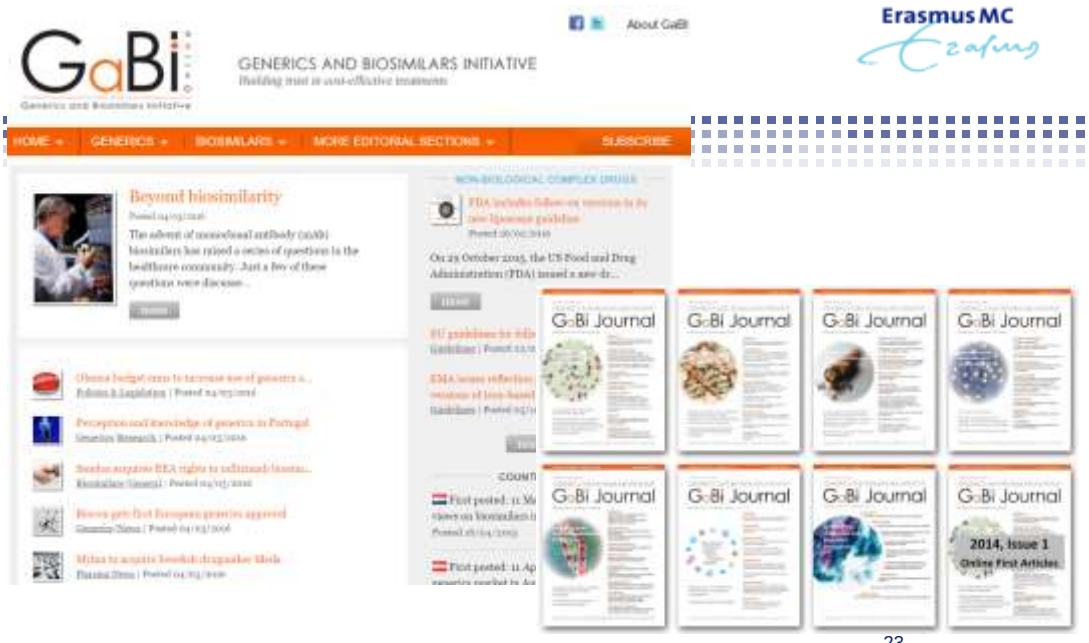
21

2008:
Closing the information gap (www.gabionline.net)

- Umbrella initiative to build trust in cost-effective treatments:
  - One-stop website with comprehensive information on generics and biosimilars
  - Peer reviewed open access scientific journal
  - Scientific symposia
  - Educational meetings
  - Patient information

GaBi
Generics and Biosimilars Initiative
Building trust in cost-effective treatments
www.gabionline.net

22



www.gabionline.net (16c04) www.gabi-journal.net

Agenda

- Introduction and Perspective
- The Hospital Formulary
- Drug selection in the hospital
- Three generations of biosimilars
- The information gap
- ***How to raise trust***
- Take home message

Inclusion of a drug in the formulary depends on trust

- How to raise trust and decrease uncertainty on the new drug?
- Desk research: collect information
  - Whether a product is licensed does not imply it is automatic the product of choice to prescribe
- The information collection should be systematic
  - For that we developed a comprehensive set of questions to help you with the decision process

25

ORIGINAL ARTICLE

Eur J Hosp Pharm 2013

How to select a biosimilar

Niels Boone,[1] Hugo van der Kuy,[1] Mike Scott,[2] Jill Mairs,[2] Irene Krämer,[3] Arnold Vulto,[4] Rob Janknegt[1]

[1]Department of Clinical Pharmacy and Toxicology, Orbis Medical Center, Sittard-Geleen, The Netherlands
[2]Department of Clinical Pharmacy, Antrim Area Hospital, Antrim, UK
[3]University Medical Center, Johannes Gutenberg University, Mainz, Germany
[4]Department of Clinical Pharmacy and Toxicology, Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence to
Niels Boone, Orbis Medical Center, Department of Clinical Pharmacy and Toxicology, PO Box 5500, Sittard-Geleen NL 6130 MB, The Netherlands; nwboone@gmail.com

Received 1 August 2013
Accepted 6 August 2013
Published Online First 28 August 2013

ABSTRACT
In the past few years biosimilars have penetrated the market following the expiry of patents of originator variants. This offers the opportunity to apply high-tech protein products at a lower cost. In contrast to small-molecule generics, clinicians and pharmacists have found it difficult to judge the efficacy and safety profiles of complex protein products. In recent years, the European Medicines Agency (EMA) has gained knowledge on assessing comparability between biosimilars and originator products in scientific and legal areas. This article provides an overview of an extensive set of 31 previously drawn biosimilar selection criteria and describes how several of these criteria are covered by EMA regulations and guidelines. A panel of experts (authors) reviewed the criteria and produced a shortlist of 10 criteria relevant for clinicians and pharmacists.

A different generic approach

Non-protein drugs are typically organic molecules of low molecular mass and well defined molecular structure. Because the molecular structure of such a small-molecule drug can be fully analytically characterised, it is fairly easy for a generic drug manufacturer to produce a bio-equivalent medicinal product with the same drug usage form containing the same active ingredient as the innovator's drug product.

A protein product is a heterogeneous mixture of large molecules based on a sequence of amino acids folded in secondary and tertiary three-dimensional structures, which undergo post-translational folding processes to ultimately fold into a complex spatial structure. Post-translational modification is a function of host cells, which are not identical for the biosimilar and the originator medicinal product. This complex process is difficult to reproduce even in the production process of the originator drug. A full chemical characterisation of the product resulting from this process is a challenge using multiple analytical tools. However, it is not easy to decide which battery of chemical tests should be per-

INTRODUCTION

Selection of biosimilars in hospitals is a relatively

26

Practice Research & Innovation

Binocrit: assessment of quality, safety and efficacy of biopharmaceuticals

Carsten Brockmeyer, PhD; Andreas Seidl, PhD

Eur J Hosp Pharm 15(2009)No.2, 34-40

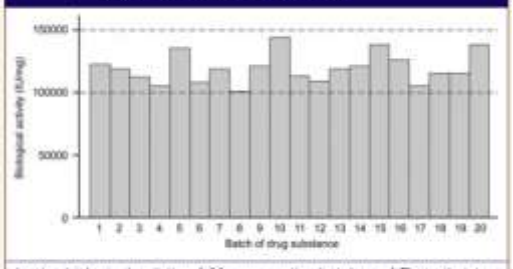
In *EJHP Practice*, 2008, issue 1, published an article titled *Points to consider in the evaluation of biopharmaceuticals* with a detailed checklist. Here, this checklist is used for evaluating an erythropoiesis stimulating agent (ESA), Binocrit, to demonstrate the quality of this ESA.

Table 1: Release specifications relevant for purity, safety and potency of Binocrit drug substance

Parameter	Method	Specification
Host Cell Proteins (HCP)	Specific ELISA	<30 ng/mg rhEPO
Host Cell DNA	Threshold method	<30 pg/mg rhEPO
Endotoxins	LAL-test (Ph. Eur. 2.6.14.)	<20 IU/100,000 IU rhEPO
Bioburden	Membrane filter method (Ph. Eur.)	<10 CFU (colony forming unit)/10 mL
Bioactivity	Normocythaemic mouse assay (Ph. Eur.)	100,000 – 150,000 IU/mg rhEPO

rhEPO: recombinant human erythropoietin

Figure 1: *In vivo* biological activity of 20 consecutive batches of Binocrit



In vivo biological activity of 20 consecutive batches of Binocrit determined with the normocythaemic mouse assay according to the erythropoietin monograph of Ph. Eur. [10]. The method is routinely applied for release of drug substance.

27

Erasmus MC

What were the succes factors in Norway

- An advisory board with most of the (clinical) opinion leaders were involved in deciding on the pre-tender conditions
- To start with, only new patients will receive the biosimilar
- New tender again for NEW patients (existing patients will not be changed)
  - (Based on good experience many patients have been switched)
- Savings will be invested in:
  - Treating more patients for less money
  - Trials in support of unresolved areas like extrapolated indications and controlled switching
- This is a win-win for everybody (Torfinn Aanes, National Procurement Board)

28

Some words of caution on tendering

- Tendering has become complicated, as not all patients may be included
  - Dependent on switch-policy of the hospital: only new patients or all
  - Possibly indication related
  - As such, a low biosimilar price may not be the best outcome
- "Biosimilar" is not a container principle: we need to differentiate
- Some are more immunogenic (rituximab, infliximab) than others (growth hormone, GCSF, etanercept).
  - It seems prudent to be more cautious in switching high immunogenic molecules in the first year of treatment.
  - Check Anti-Drug-Antibody (ADA) + trough level before switching

29

Take home message: All stakeholders need to be educated

- Stakeholders
  - Prescribing doctors
  - Dispensing (procuring) pharmacists
  - Policy makers (government, third-party payers)
  - Patients
- Decision to *change* prescribing by doctors dependent on
  - Incentives (like INN-prescribing systems)
  - Real or perceived advantages (like lower cost, quality of care)
- We as hospital pharmacists can play a key role in this education

30

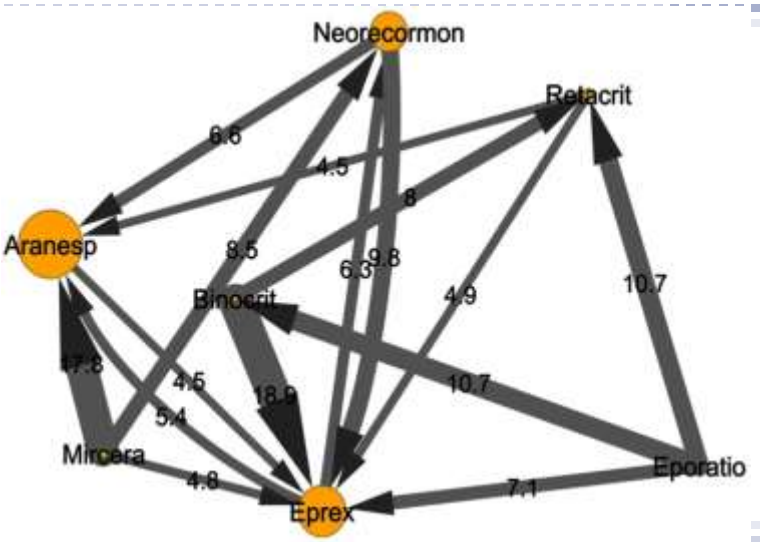
Thank you for your attention

More Facts on Biosimilars
Thursday March 17, 2016
15:00 – 16:30h, Hall K

Contact: a.vulto@erasmusmc.nl

31

Switching of EPO in the first year did not increase immunogenicity (Italy)



Ingrasciotta et al. BioDrugs 29(2015)275

1. Which statement is true?

Once licensed by the EMA biosimilars

A. Can be prescribed for all indications of the reference product
B. Can be dispensed interchangeably for all patients
C. Can only be prescribed / dispensed to new, drug naïve patients
D. Have an increased risk of immunogenicity in patients already treated with the innovative product.

33

1. Which statement is true?

Once licensed by the EMA biosimilars

A. Can be prescribed for all indications of the reference product
B. Can be dispensed interchangeably for all patients
C. Can only be prescribed / dispensed to new, drug naïve patients
D. Have an increased risk of immunogenicity in patients already treated with the innovative product.

Explanation:

- A is on indication extrapolation, which is not automatic
- B is the basis for EMA licensing of biosimilars; there may be local restrictions
- C is not true: patients can be switched (under conditions)
- D there is no evidence for this

34

2. Which statement is true?

Selection of a biosimilar for the drug-formulary

A. Can be solely based on the acquisition cost of the product, as everything else is the same;
B. Is always advantageous for the hospital-budget
C. Should be based on fully powered clinical equivalence trials
D. Is a careful multifactorial process

35

2. Which statement is True?

Selection of a biosimilar for the drug-formulary

A. Can be solely based on the acquisition cost of the product, as everything else is the same;
B. Is always advantageous for the hospital-budget
C. Should be based on fully powered clinical equivalence trials
D. Is a careful multifactorial process

- A: more factors need to be taken into account then just cost
- B: this may be dependent on the conditions: only naive patients or also switching existing patients
- C: false: this would undermine the biosimilarity-principle
- D: as with any formulary decision, it is multifactorial

36

3. Which statement is true?

What information is required for the responsible use of biosimilars?

A. Proof of clinical efficacy in all indications
B. Data on consistency of manufacturing for at least 10 batches
C. Stock position of the manufacturer (> 3 months)
D. A release-certificate of an EU-qualified person
E. A patient-based registry for all dispensed biologicals, including biosimilars

37

3. Which statement is true?

What information is required for the responsible use of biosimilars?

A. Proof of clinical efficacy in all indications
B. Data on consistency of manufacturing for at least 10 batches
C. Stock position of the manufacturer (> 3 months)
D. A release-certificate of an EU-qualified person
E. A patient-based registry for all dispensed biologicals, including biosimilars

- A: false, would undermine biosimilarity principle
- B: this requirement is in principle covered by the licensing process
- C: Nice to have – but no strict requirement - in the light of drug-shortages discussion, but until now we have not seen any problems here.
- D: Not required for a licensed medicine, only for non-licensed medicines
- F: True: this is an EU requirement for all biologicals – including biosimilars – since 2010 (Directive 2010/84/EU, December 15, 2010).
- Interesting question: do you adhere to this directive for all biologicals dispensed by your pharmacy?

38

39