Naming, tracing, switching and other safety issues after 10 years learning

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Disclosures

- Speaker's fee for lectures for pharmaceutical companies, i.e. Roche, Sanofi
- Honoraria for advisory board meetings run by various pharmaceutical companies, i.e. Abbvie, Amgen, Boehringer Ingelheim

Agenda and Learning Objectives

Gain insight in safety aspects of biosimilars

- Pharmacovigilance
- Naming
- Tracing
- Interchangeability
- Switching
- Substitution

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse reactions and other medicine-related problems.

Benefit-risk balance

Medicines may affect the body in unintended, harmful ways. These effects, called side effects or adverse reactions, represent risks of medicines.

At the time when a new medicine obtains a marketing authorisation, the active substance has been tested and the data have allowed a conclusion to be drawn that the benefits of the medicine outweigh its risks.

However, once the medicine has obtained a marketing authorisation, it will be used in normal healthcare settings for many patients who may differ from the study population, for example by age or additional diseases.

It is therefore important to identify any new or changing risk of a medicine as quickly as possible, and to take measures to minimise risk and promote safe and effective use.

Safety studies for Biosimilars

- Pre-marketing safety data
  to be obtained in a sufficient number of patients
  - Immunogenicity must be investigated
- Risk management programme/pharmacovigilance plan
  to be presented according to the EU-Pharmacovigilance Guideline
- Post-marketing Pharmacovigilance
  to determine the benefit–risk profile in patients of individual biosimilars throughout the life cycle

Source: EMEA Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: Non-clinical and clinical issues 2005: EMEA/CHMP/BMWP/428232/2005

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Aspects of the Risk Management Plan

- Safety in indications claimed based on extrapolation,
  including long-term safety data
- Occurrence of rare and particularly serious adverse events described and predicted for the reference product
- Detection of novel safety signals (like other biologicals)
- Obtaining additional long-term immunogenicity data
- Periodic safety update reports (PSURs)
- Pro-active activities, e.g. drug/disease based registries, Phase IV studies
- Black triangle labeling

EMA Guideline on Similar Biological Medicinal Products containing monoclonal Antibodies CHMP/403543 2012

EMA Guideline on good pharmacovigilance practices (GVP). Product- or Population-Specific Consideration II: Biological medicinal products. August 2016

Pharmacovigilance and Immunogenicity

- **Uncertainty in the knowledge about beneficial effects**
  There is a slightly higher level of aggregates in the CT-P13 product than in Remicade, which could potentially increase immunogenicity. However, the risk is considered to be negligible given the very low level and is not reflected in the clinical data.
- **Risks**
  There were no marked differences in the immunogenicity profile of CT-P13 and Remicade up to 54 weeks and the impact of antibodies on efficacy and safety was comparable

Remsima Assessment report EMA/CHMP/589317/2013

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Pharmacovigilance and Immunogenicity

Divergent opinion of CHMP members

Flixabi (SB2) appears to be associated with a higher incidence of ADA than the originator, Remicade. ….

The proposal of the Applicant to resolve the concerns related to immunogenicity in the post-marketing setting by initiating a prospective observational cohort study in the indications of ankylosing spondylitis and Crohn's disease is considered inadequate. ……

Flixabi Assessment report EMA/CHMP/272283/2016

Naming of EMA approved Biosimilars

Biosimilar name	Active substance	Therapeutic area	Authorization date	Sponsor
Abseamed	Epoetin alfa	Anaemia, cancer, chronic kidney failure	28 Aug 2007	Medice Arzneimittel Putter
Epoetin alfa Hexal				Hexal
Binocrit		Anaemia, chronic kidney failure		Sandoz
Inflectra	Infliximab 13	Ankylosing spondylitis, Crohn's disease, psoriatic arthritis, psoriasis, rheumatoid arthritis, ulcerative colitis	10 Sept 2013	Hospira / Celltrion
Flixabi	Infliximab SB2	Ankylosing spondylitis, Crohn's disease, psoriatic arthritis, psoriasis, rheumatoid arthritis, ulcerative colitis	26 May 2016	Biogen
Valtropin	Somatropin	Pituitary dwarfism, Turner syndrome	24 Apr 2006 (withdrawn 2012)	BioPartners
Somatropin Biopartners		Growth hormone deficiency	5 Aug 2013	
LY2963016 (Abasaglar/ previously Abasria)	Insulin glargine	Type 1 diabetes, Type 2 diabetes	September 2014	Eli-Lilly/ Boehringer Ingelheim

Bioidenticals

EMA website: http://www.emea.europa.eu/. Accessed 26 March 2015

WHO: INN System and Recent Developments

- WHO (2012–2014) reported that the current INN system for biologics including biosimilars was 'not satisfactory'

  'There needs to be some way of distinguishing between one similar biologic product and another and between the reference product… to ensure clear identification of pharmaceutical substances'[1]

- Proposed addition of a Biological Qualifier (BQ), comprising four random consonants and an optional 2-digit checksum, after the INN
- Proposal for implementation of BQ on a provisional basis and evaluation (October 2016)

1. 56th Consultation on INN for Pharmaceutical Substances, Geneva: WHO, 2013, INN working document 13.335; 2; 3. Proposal for Assignment of Biological Qualifiers (BQ), Geneva: WHO, 2015, INN working document 14.342; 4. 61st Consultation on INN for Pharmaceutical Substances, Executive Summary. Geneva: WHO, 2015, INN working document 15.386, WHO INN meeeting 2016

Traceability and Naming

- ***Physician would be well advised to always document exactly which biological is used for an individual patient. In the ADR report ….INN, brand name, manufacturer, lot number, country of origin to ensure a proper root cause analysis[1]***
- ***For suspected adverse reactions ….. the definite identification of the concerned product with regard to its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to identify clearly any biological medicinal product ….. with due regard to the name … and the batch number***

1. Ehmann, F., Schneider K. HPE 2011;56:32-35,
2. EMA Guideline on Similar Biological Medicinal Products containing monoclonal Antibodies CHMP 403543 2012

Traceability of Biologics in The Netherlands

Reporting of recombinant biologics by product class in ADR reports

Product class	ADRs reported, n	Brand names reported, n (%)	Batch numbers reported, n (%)
Somatropins	4	3 (75)	0
Epoetins	43	40 (93)	0
Filgrastims	19	17 (89)	1 (5)
Follitropins	21	21 (100)	1 (5)
Monoclonal antibodies	797	536 (67)	45 (6)
Insulins	180	164 (91)	18 (10)
Interferons	51	45 (88)	3 (6)
Antihaemophilic factors	52	52 (100)	1 (2)
Fusion proteins	232	178 (77)	5 (2)
Enzymes	2	1 (50)	0
Other	122	95 (78)	0
Total	**1523**	**1152 (76)**	**74 (5)**

Klein et al. Drug Saf 2015; epub ahead of print

Traceability of Biologicals

- In pharmacy-based aseptic preparation units, batch numbers of individual preparations are recorded on a regular basis
  Documentation is supported by electronic systems
- In wards and physician offices batch numbers are recorded on an irregular basis
  Documentation should be facilitated by bar code reading or barcode labels
- When products are administered by the patients themselves batch numbers are poorly recorded
  Documentation should be facilitated by barcode labels and a diary

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Track and Track

My healthcare provider and I are thinking about choosing a biosimilar medicine for my treatment: is it going to be safe and effective?

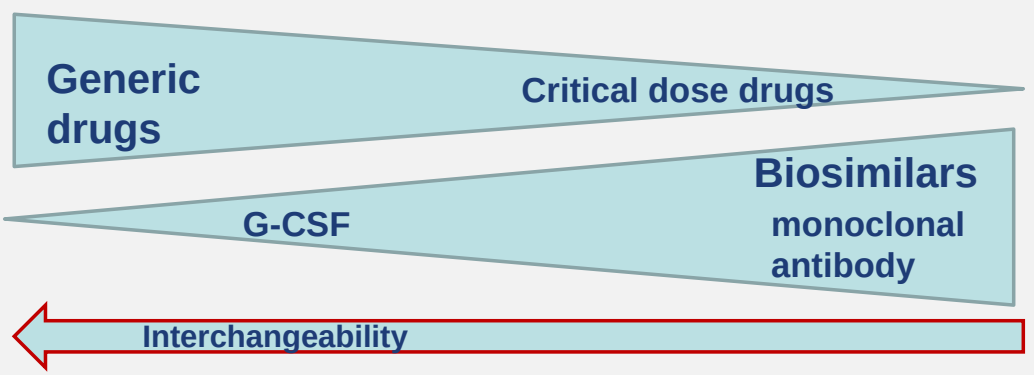
Like any medicine approved in the EU, biosimilar medicines can be expected to be safe and effective treatment options when they are used appropriately in their approved indications. Instructions for

As with any treatment, it is important to have a thorough conversation with your prescribing doctor about all the available therapeutic options, their safety, benefits and risks, and the differences between the medicines, before coming to a decision.

European Commission Question & Answer Document for Patients Builds Trust and Understanding on Biosimilar Medicines across Europe
Brussels - 25 October 2016

Interchangeability

- Practice of switching one medicine for another provided that medicines are equivalent in a given setting



Switching and Substitution

- **Switching = physician's action**
  - Medical switching because of efficacy, tolerability
  - Non-medical switching because of convenience, cost
- **Substitution = pharmacist's action**
  - Refers to a national policy which permits the switch from one to another medicine
  - Automatic substitution without physician's involvement

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Interchangeable Bioidenticals

Co-marketed Biosimilars = Bioidenticals

- Same expression system
- Same marketing authorisation
- Same formulation
- Different brand names

Likelihood of Switching

Refe… One … Two …
pro…

Further facts to consider in switching

- Chronic or short-term use
- Single switching or multiple switching
- Treatment naive patients or adapted patients
- Co-medication like immunosuppressants

ECCO Position Statement

October 2016

6. ECCO Statements

A consensus meeting was held on October 15, 2016 in Vienna. Based on the current regulatory guidance form the European Medicines Agency and the evidence about efficacy and safety of biosimilars in IBD patients, the attendees agreed on the following statements:

1. Biosimilarity is more sensitively characterised by performing suitable *in vitro* assays than clinical studies.
2. Clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation. Therefore data for the usage of biosimilars in IBD can be extrapolated from another sensitive indication.
3. When a biosimilar product is registered in the EU, it is considered

7. Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients
8. Switching from originator to a biosimilar should be performed following appropriate discussion between physicians, nurses, pharmacists, and patients, and according to national recommendation. The IBD nurse can play a key role in communicating the importance and equivalence of biosimilar therapy.

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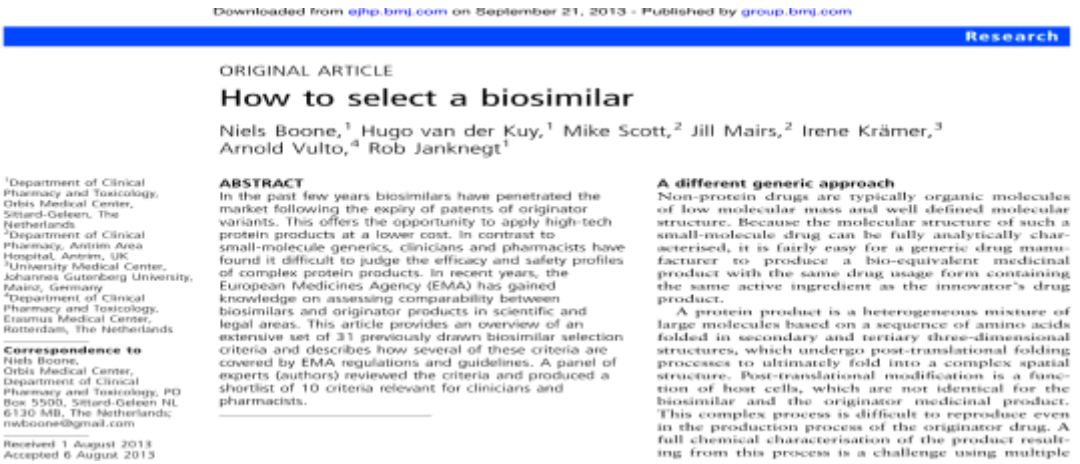
Selection of a biosimilar by a matrix system

- Ten selection criteria were judged as relevant for clinical practice
- MD and pharmacist can give own weight to criteria



ORIGINAL ARTICLE

How to select a biosimilar

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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

Boone N et al. Eur J Hosp Pharm. 2013;20:275-286. doi:10.1136/ejhpharm-2013-000370

Risk management of Biosimilars in hospital practice

Substitution/switching should be combined with

- Close monitoring of the patients
- Ensured traceability
- Decision making by a qualified healthcare professional