Biosimilar Medicines

Joan O’Callaghan
Research Scientist for Regulatory Science Ireland

Parenteral Drug Association Ireland Chapter
Radisson Blu, Little Island, Cork
25th Nov 2016
Overview

- Regulatory Science Ireland
- What is a biosimilar medicine?
- Manufacturing process changes – biological medicines
- Regulation of biosimilar medicines in Europe
- Impact of biosimilar competition
- Interchangeability
Regulatory Science Ireland
Regulatory Science Ireland
The increasing complexity of healthcare products requires a data-driven, evidence-based approach to their regulation. This realization has driven the development of the discipline of Regulatory Science.

Regulatory Science Ireland (RSI) is a national response to these developments.

Further information on RSI: joan.ocallaghan@hpra.ie

Regulatory Science

“Develop new tools, standards & approaches to assess the safety, efficacy, quality & performance of regulated products”

“Defined as a range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision making throughout the lifecycle of a medicine.”

1 Advancing Regulatory Science at FDA: A strategic plan (August 2011)
2 European Medicines Agency’s contribution to science, medicines and health Road map to 2015
Regulatory Science Ireland

• RSI is committed to the development of an integrated Irish response to the Global Regulatory Science effort.
RSI Biosimilar Research Project

- **Research activities**: Health Products Regulatory Authority (HPRA) and University College Cork (UCC)
- **Supported by**: Irish Pharmaceutical Healthcare Association (IPHA), HPRA and UCC
- **Project Advisory Panel includes**: Industry representatives, National Institutes for Bioprocessing Research and Training (NIBRT), IPHA, Biopharmachem Ireland, IDA Ireland and a patient representative
Biosimilar Research Project Objectives

• Peer reviewed scientific publications on Biosimilars – Practical considerations for Healthcare Professionals
• Design, execute and report on a survey of HCPs perspectives and understanding of issues relating to biosimilar medicines
• Development of training materials and online resources to support effective knowledge transfer
• Outreach activities
What is a biosimilar medicine?
What is a biosimilar?

A biological medicinal product which contains a version of the active substance of an already authorised original biological medicinal product (reference)

What are the differences between chemical generics and biosimilars?

- Biologicals are large complex molecules
- They are derived from living cells which makes them inherently variable ... this microheterogeneity is present even between different batches of the same product
- Manufacturing an exact copy of a biological medicine is not possible and therefore additional data are required to demonstrate safety and efficacy before approval
- Direct unequivocal demonstration of identical structure is not possible, even with today’s sophisticated analytical technology.
# Complexity of biological medicines

<table>
<thead>
<tr>
<th>Conventional ‘small molecule’ pharmaceuticals</th>
<th>Biotechnology derived biopharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Mw &lt; 1kDa</td>
<td>High Mw (&gt;50kDa)</td>
</tr>
<tr>
<td>Usually organic chemical synthesis</td>
<td>Produced from live cells/organisms</td>
</tr>
<tr>
<td>Single chemical entity, high homogeneity/purity</td>
<td>Complex heterogeneous mixtures, broad specifications</td>
</tr>
<tr>
<td>Parenteral and non parenteral routes</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Non-antigenic (predominantly)</td>
<td>Often immunogenic</td>
</tr>
</tbody>
</table>
Reasons for microheterogeneity

- Amino acid substitution
- N- and C- terminal changes
- Mismatched S-S bonds
- Altered folding
- Truncation
- Aggregation
- Multimer dissociation
- Denaturation

- O- linked glycosylation
- N-linked glycosylation
- Methylation
- Oxidation
- Acetylation
- Deamidation
- Carboxylation
Biological products are naturally variable

- Biologics are derived from living cells with inherent variability - a biosimilar will never be “identical” to the reference product

- Variability in biological products is the norm! Each new batch is never truly "identical" to the previous ones
Manufacture of recombinant proteins

Manufacturing of recombinant Proteins is complex

- DNA Vector
- Cloning into DNA Vector
- Transfer into Host Cell
  - Expression
  - Cell Development
- e.g., bacterial or mammalian cell
- Large-Scale Fermentation
- Downstreaming
- Formulation

Source: Slide by Nanna Aaby Kruse, Mediacademy, Oct 2011
"The process is the product"

- fluctuations in the manufacturing process
  (e.g., pH, temperature, culture media):

- changes in the manufacturing process

  • "One process – one product" paradigm

  Biotechnological medicinal products are "individuals"

  Biotechnological medicinal products are more than the drug substance

  Small changes can have high impact

  How does this fit with biosimilar products???
Manufacturing process changes
– biological medicines
Changes in manufacturing processes after approval

All mAbs and –cept fusion proteins used in rheumatology have had changes in their manufacturing processes after initial approval.

Changes range from change in supplier of cell culture media to new purification methods or new manufacturing sites.

Changes in manufacturing processes after approval

ICH Harmonised Tripartite Guideline
Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process
Q5E

New version will have the same efficacy and safety in all therapeutic indications.

Pre v’s post change product

Regulators have extensive experience in the assessment and judgement of manufacturing process changes.
Changes in manufacturing processes after approval

Manufacture of recombinant proteins

Manufacturing of recombinant Proteins is complex

A second manufacturer uses...

- Transfer into Host Cell Expression Cell Development
- Cloning into DNA Vector
- (Probably) a different DNA vector
- The same amino acid sequence (maybe the same genetic sequence)
- A different down-streaming protocol
- A different fermentation process
- Different in-process controls
- Large-Scale Fermentation
- Formulation
- Maybe a different formulation

A different recombinant cell expression system

Different Process → different product
Similar but not identical

- Not a new concept for biological medicines
- Even consecutive batches of originator products are not identical – modified throughout lifecycle
- Comparability exercise of pre- and post-change batches is a well established regulatory process - ICH Q5E
Regulation of biosimilars in Europe
Legal basis of biosimilars

• 2003 – amendment to EU 2001/83/EC introduced term ‘similar biological medicinal product’
• 2005 - Guideline on similar biological medicinal products published by EMA – introduced the term ‘biosimilar’
• Continued publication of guidelines by EMA
GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS (CHMP/437/2004)
Overarching Guideline

GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY- DERIVED PROTEINS AS ACTIVE SUBSTANCE:


"Product Specific Guidelines"

- Erythropoietins
- Monoclonal antibodies
- G-CSF
- Low molecular weight heparins
- Somatotropins
- Interferon beta
- Insulins
- Interferon alpha
- Interferon alpha
- Follicle stimulating hormone
Biosimilar MAAs submitted to EMA (Nov 2016)

33 MAAs reviewed
- 2 negative
  - Interferon alfa (1)
  - Insulin human (1)
- 23 positive
  - Enoxaparin sodium (2)
  - Somatropin (1)
  - Epoetin (5)
  - Etanercept (1)
  - Filgrastim (8)
  - Follitropin (2)
  - Infliximab (3)
  - Insulin glargine (1)

7 Withdrawn Pre-authorisation
- Insulin (6)
- Epoetin (1)

2 Withdrawn post-authorisation
- Filgrastim (1)
- Somatropin (1)

17 MAAs under review
- Adalimumab (3)
- Etanercept (2)
- Insulin glargine (1)
- Insulin lispro (1)
- Pegfilgrasim (4)
- Rituximab (2)
- Teriparatide (1)
- Trastuzumab (3)

Pending EC decision
- Teriparatide (1)
- Insulin glargine (1)
# Biosimilars: 23 approved in Europe

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Name of reference product</th>
<th>Name of biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin sodium</td>
<td>Clexane</td>
<td>Inhixa, Thorinane</td>
</tr>
<tr>
<td>Epoetins</td>
<td>Eprex</td>
<td>Absamed, Epoetin Alfa Hexal, Binocrit, Retacrit, Silapo</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Enbrel</td>
<td>Benepali</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Neupogen</td>
<td>Filgrastim Hexal, Biograstim, Ratiograstim, Grastofil, Tevagrastim, Nivestim, Zarzio, Accofil</td>
</tr>
<tr>
<td>Follitropin</td>
<td>GONAL-f</td>
<td>Ovaleap, Bemfola</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
<td>Remsima, Inflectra, Flixabi</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Lantus</td>
<td>Absaglar</td>
</tr>
<tr>
<td>Somatropin</td>
<td>Genotropin</td>
<td>Omnitrope</td>
</tr>
</tbody>
</table>
It’s the loss of exclusivity that drives biosimilar interest

All these products will lose patent protection by 2020 (except Enbrel, US patent extended until 2028)

Global Sales (MAT 06/2014), US$ billion

- Adalimumab (Humira)
- Insulin Glargine (Lantus)
- Etanercept (Enbrel)
- Infliximab (Remicade)
- Rituximab (Mabthera)
- Insulin Aspart (Novomix, Novorapid)
- Bevacizumab (Avastin)
- Interferon Beta-1A (Avonex, Rebif)
- Trastuzumab (Herceptin)
- Glatiramer Acetate (Copaxone)
- Pegfilgrastim (Neulasta)
- Ranibizumab (Lucentis)

Total ~ US$ 79 billion

EU expiry date | US expiry date
---|---
2018 | 2016
2015 | 2016
2015 | 2028 (extended)
2015 | 2018
Expired | 2018
Expired | Expired
2019 | 2019
2015 | 2016
Expired | 2019
2017 | 2015
2015 | 2015
2016 | 2016

Not considered existing biosimilars such as Epoetin Alfa expired in EU, but still patent protected in the US

Source: IMS MIDAS, 06/2014, Rx bound, IMS Patent focus
Biosimilars in the pipeline!
Principles of biosimilar medicines (CHMP/437/04)

- Concept applicable to any biological medicine
- Concept suited to products that are highly purified and thoroughly characterised (e.g. biotechnological medicines)
- **Comparability exercise**: demonstrates similarity to reference in terms of quality characteristics, biological activity, safety and efficacy
- Same posology and route of administration as reference
- Deviations in strength, form, excipients and presentation require justification
Principles of biosimilar medicines (CHMP/437/04)

• Similar efficacy
• Differences that enhance safety can be justified
• Must satisfy all quality requirements for a new biological medicine
• Safety and efficacy requirements outlined in product specific guidelines
• Indication extrapolation if justified
• Once approved no need to repeat demonstration of biosimilarity to reference (e.g. manufacturing process change)
• Pharmacovigilance requirements – Art 102(e) of Directive 2001/83/EC
Stepwise approach for demonstration of biosimilarity

• The manufacturer of the biosimilar will not have access to the manufacturing process of the originator and it is therefore impossible to produce an “identical” product.

• Stepwise **head to head comparison** is needed to demonstrate that the biosimilar and reference product have **highly similar profiles** in terms of quality, safety and efficacy.

There should be no **clinically meaningful differences** between the two products.
Biosimilarity is based on the ‘totality of evidence’

Physiochemical and functional assays are the most sensitive to reveal subtle differences.
There has been a shift toward greater emphasis on the quality package to demonstrate biosimilarity.
EU Regulatory approval pathway for Biosimilars

- Manufacturer needs to demonstrate that there are no clinically meaningful differences between the biosimilar and the Reference i.e. Integrated Compatibility exercise on Q, S, E versus Originator

**CTD Modules**

- Clinical
- Non-clinical
- Quality

**Originator Application**

**Biosimilar Application**

- Clinical + Comparability
- Non-clinical + Comparability
- + Comparability exercise

* a step by step approach, the extent of the Non-clinical and clinical testing can be decided depending on the similarity on the quality profile

**Integrated Comparability Exercise***
Development pathway for biosimilars

Tailoring
  – Analysis of several batches of the reference product for key characteristics. Range of variation defines the target ranges for the biosimilar product (QTPP)

Fitting
  – The manufacturing process is adjusted to produce a protein that fits into the desired target ranges

Comparison
  – Extensive head-to-head comparison to the reference product by physicochemical and *in vitro* biological tests

Confirmation
  – Comparable pharmacokinetics
  – Comparable safety and efficacy

QTPP: A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.
Assessing biosimilarity – protein structure

Primary amino acid sequence should be the same as the reference. Comparable higher order structure.

The Basics of General, Organic, and Biological Chemistry. David W. Ball
Typical physiochemical biosimilarity exercise

**Primary Structure**
- Peptide map
- Amino acid sequence
- Total mass analysis
- Disulfide bonds
- Free sulfhydryls

**Higher order Structure**
- FTIR
- CD Near and Far UV
- DSC
- MALS
- X-Ray crystallography

**Purity**
- SE-HPLC
- CE-SDS
- SDS-PAGE
- AUC MALS
- Deamidation
- Oxidation,

**Aggregation**
- MALS
- SEC
- TFF
- DLS
- SDS-PAGE

**Glycosylation**
- N and O-linked oligosaccharides
- Oligosaccharide profile
- Monosaccharide analysis
- Sialic acid analysis

**Impurities**
- Product related substances
- Host cell proteins
- Host cell DNA
- Downstream impurities
  - e.g. Protein A

**Charge variants**
- Cation exchange HPLC
- Ion exchange HPLC
Physicochemical biosimilarity exercise

- Comprehensive analysis of the biosimilar and the reference product
  - Designed to show similarities and potential differences in quality
  - Side by side analysis using sensitive and orthogonal methods
  - Final commercial product

- Not expected that all quality attributes of biosimilar will be identical to reference product but:
  - Minor differences in microheterogeneity pattern may be acceptable
  - No impact on clinical performance
  - Particular attention to attributes that impact potency and immunogenicity

Ultimate objective: demonstrate similarity to the reference product
Variation due to glycosylation

- Different glycoforms can influence binding to effector cells, potency, PK and immunogenicity
- Very heterogeneous even within the originator, therefore individual glycoforms may not be completely within the reference range
- Where this occurs, additional in vitro assays are required

Variation due to charge

- Relatively common to see differences, can be due to many factors e.g. deamidation, oxidation, fragments, aggregates, C-terminal lysine etc.
- Source of charge variation is identified and justified
Biological activity

• Variety of different assays should be used
• Complementary or orthogonal approaches to overcome limitations of single bioassay
• Assays – sensitive, specific and discriminatory
• If product has more than one mechanism of action all functional activities should be evaluated e.g. receptor binding and activation

Biological assays confirm
Quality of product
Integrity of higher order structure
Mechanisms of action
(Presence of expected functions, absence of new functions)
Potential effects of post-translational modifications

Receptor binding
(ELISA/SPR)

Cell based assays
Functional assays
Apoptosis
ADCC
C1q binding
CDC
FcyRI binding
FcyRII binding
FcyRIII binding
FcRn binding
Biological activity (comparative assays) – Biosimilar infliximab

- Receptor binding assays
- Human tissue cross reactivity using immunohistochemistry
- hTNFα neutralisation assay
- Apoptosis
- Reverse signalling
- Effect of blocking soluble TNFα in *in vitro* IBD model
- Complement-dependent cytotoxicity (CDC)
- Antibody dependent cytotoxicity (ADCC)
- Evaluation of regulatory macrophage function

Source: Remsima EPAR
### Quality comparability exercise: case study

<table>
<thead>
<tr>
<th>Quality attribute</th>
<th>Product</th>
<th>Min/max ranges</th>
<th>Bar diagram</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0F-GlcNac</td>
<td>RBP A</td>
<td>0.05 – 0.3%</td>
<td></td>
</tr>
<tr>
<td>G0</td>
<td>RBP A</td>
<td>1.2 – 2.1%</td>
<td></td>
</tr>
<tr>
<td>GOF</td>
<td>RBP A</td>
<td>20.3 – 32.1%</td>
<td></td>
</tr>
<tr>
<td>Man5</td>
<td>RBP A</td>
<td>0.0 – 0.9%</td>
<td></td>
</tr>
<tr>
<td>(1,6)G1F</td>
<td>RBP A</td>
<td>2.5 – 4.1%</td>
<td></td>
</tr>
<tr>
<td>(1,3)G1F</td>
<td>RBP A</td>
<td>1.6 – 2.3%</td>
<td></td>
</tr>
<tr>
<td>G2F</td>
<td>RBP A</td>
<td>10.5 – 25.7%</td>
<td></td>
</tr>
<tr>
<td>G2FS1</td>
<td>RBP A</td>
<td>35.3 – 39.1%</td>
<td></td>
</tr>
<tr>
<td>G2FS2</td>
<td>RBP A</td>
<td>11.4 – 13.2%</td>
<td></td>
</tr>
<tr>
<td>NGN4</td>
<td>RBP A</td>
<td>3.3 – 5.5%</td>
<td></td>
</tr>
<tr>
<td>Deamidation</td>
<td>RBP A</td>
<td>0.9 – 2.4%</td>
<td></td>
</tr>
<tr>
<td>Oxidation</td>
<td>RBP A</td>
<td>1.2 – 4.3%</td>
<td></td>
</tr>
<tr>
<td>Dimer</td>
<td>RBP A</td>
<td>0.0 – 2.1%</td>
<td></td>
</tr>
<tr>
<td>Higher aggregates</td>
<td>RBP A</td>
<td>0.0 – 0.8%</td>
<td></td>
</tr>
<tr>
<td>Binding assay</td>
<td>RBP A</td>
<td>91 – 108%</td>
<td></td>
</tr>
<tr>
<td>CDA activity</td>
<td>RBP A</td>
<td>84 – 110%</td>
<td></td>
</tr>
<tr>
<td>ADCC activity</td>
<td>RBP A</td>
<td>75 – 122%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality attribute</th>
<th>Product</th>
<th>Min/max ranges</th>
<th>Bar diagram</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP candidate 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SBP candidate 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-clinical data requirements

• In vitro tests are the mainstay of the non-clinical comparability exercise – highly important in demonstrating biosimilarity and extrapolation

• Variety of cell types and assays required: consider high sensitivity, but also physiological conditions

• Animal studies – only in rare specific situations
  – E.g. new PTMs, novel excipients, quantitative differences in quality attributes
  – Do relevant species exist?
  – Animal models are poor predictors of PK and immunogenicity in humans
Clinical studies required for Biosimilars

- Tailored clinical testing programme
- Comparative PK studies (PD if possible) are always necessary
- Choice of population for PK/PD studies must be justified
- Comparative PK/PD studies may be sufficient along with immunogenicity data (e.g. surrogate marker)

<table>
<thead>
<tr>
<th>Product</th>
<th>PD surrogate marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim</td>
<td>Absolute neutrophil count (ANC)</td>
</tr>
<tr>
<td>Alpha interferon</td>
<td>Early viral load reduction in chronic hepatitis C</td>
</tr>
<tr>
<td>Insulin</td>
<td>Euglycaemic clamp test</td>
</tr>
</tbody>
</table>
Efficacy trials

- Efficacy trials are designed to investigate if there are no clinically meaningful differences between the biosimilar and reference, they are not designed to establish patient benefit.
- Patient benefit established by reference product, need to demonstrate similar safety and efficacy.
- Equivalence design.
- Target population for efficacy trials: homogenous (not clinically challenging) and most sensitive patient population (in order to detect differences).
- Comparability margins generally represent the largest difference in efficacy that would not matter in clinical practice.
Safety

- Captured during initial PK/PD studies and pivotal efficacy studies
- Immunogenicity of biologicals well known
- Product related causes include protein aggregates, attachment of sugars that are not present in humans, host cell proteins
- Safety data includes immunogenicity testing of biosimilar and reference (up to 1 year in a chronic condition) in order to identify any differences between the biosimilar and reference
- Pharmacovigilance and risk management activities necessary during the post-authorisation phase
Indication extrapolation

- Reference product usually has more than one indication
- When biosimilar comparability has been shown in one indication, extrapolation of clinical data to other indications possible if justified
- Consider in light of ‘totality of data’, mechanism of action and potential risks in patient populations
- Extrapolation of immunogenicity data from studied indication/route of admin must be justified
- HCPs should consult EPAR for details on clinical data provided
Indication extrapolation

• Clinical experience with reference
• Mechanism(s) of action/active site(s)
• Target receptors
• Differences in safety/immunogenicity profile between indications
• Degree to which functional moieties of molecule can be analytically characterised and compared

Indication extrapolation

Infliximab biosimilar (CT-P13)

- Differences in afucosylated glycan structures, FcγRIIIa binding, and in a highly sensitive antibody-dependent cell mediated toxicity assay (ADCC)
- Clinical studies: patients with RA and AS

EMA concluded assay was not representative of physiological situation and allowed extrapolation to UC, CD, PsA and PsO

Health Canada (2014): ADCC may be an active mechanism in IBD but not in rheumatic diseases - extrapolation not recommended for UC and CD

Health Canada (2016): IE approved for UC and CD. Based on newly submitted data (physicochemical and biological, justifications concerning MOA and observational clinical data in IBD (safety signals)
Extrapolation

Not unique to biosimilars – has been used for many years in originator products which have undergone a manufacturing change

Aranesp line extension for new master cell bank and new manufacturing technology

- Head to head trial in patients with chronic kidney disease using pre- and post-change batches ...extrapolation to anaemia indication accepted

Herceptin new subcutaneous formulation with hyaluronidase

- Clinical study in neoadjuvant setting ...extrapolation to metastatic setting based on totality of evidence

“population was considered more homogenous with fewer confounding factors than patients with MBC” ...Herceptin EPAR, 2013
Pharmacovigilance

- A medicinal product is authorised on the basis that, its benefit-risk balance is considered to be positive at that time for a specified target population within its approved indication(s).

- Not all risks can be identified at the time of initial authorisation.

- Some risks emerge or are further characterised in the post-authorisation phase of the product’s life cycle.
Pharmacovigilance

• All newly authorised biological medicines are subject to additional monitoring after approval
• Biologicals have specific considerations- immunogenicity, stability/cold chain and manufacturing variability
• HCPs play a pivotal role in the surveillance of the safe use of medicines
• Brand name and batch number should be included in reports of suspected adverse reactions for biological medicines

Reference: European Medicines Agency (2016) Guideline on good pharmacovigilance practices (GVP) Product- or Population- specific considerations II: Biological medicinal products
Naming of biosimilars

• In the EU, biosimilars have the same INN as their reference*

Biological medicines can exhibit variability and therefore biological medicines which have the same INN should not be considered to be identical

To facilitate traceability any biological medicine prescribed, dispensed or sold should be clearly identifiable (brand name or INN plus name of MAH). This will also ensure substitution by pharmacists does not inadvertently occur when the medicine is dispensed by a pharmacist

* Except when the core INN is accompanied by a WHO Greek letter designators for glycosylated proteins

Source: HPRA Guide to Biosimilars for Healthcare professionals and Patients
Naming of Biosimilars

WHO - INN biological qualifier proposal

• Voluntary scheme
• Random code follows INN
• Code - differentiate biological drug substances manufactured by different processes
• Aims to aid in the minimisation of errors in prescription, dispensing, pharmacovigilance and international transfer of Rxs
• Will prevent proliferation of national qualifier systems
• Scheme has generated controversy
• Impact assessment on scheme implementation to be carried out

FDA – draft guidance on Nonproprietary naming of biological products

• Shared non-proprietary names not appropriate for all biological products
• Non-proprietary name will include FDA designated suffix
• Aims to identify biological products to prevent inadvertent substitution and improve pharmacovigilance
• ?? if interchangeable products will share same suffix as reference
• Public consultation now closed - no update so far!
Impact of biosimilar competition
IMS Report: The Impact of Biosimilar Competition

• Available on the European Commission website
• Describes effects of biosimilar competition on price, volume and market share
• Data from 2015
• Pricing information based on publically available prices
Potential cost savings from the use of biosimilars

Biosimilar savings potential in the EU5 and U.S., for 8 key products in 2015-2020: EUR49 billion to EUR98 billion

Source: IMS Health, MIDAS, IMS Health Market Prognosis; IMS Institute for Healthcare Informatics, Dec 2015
Biosimilars in Ireland – conclusions from IMS report

• Biosimilars are being used in place of reference product
• Overall market share is relatively low as other medicines from same therapeutic class are dominating the marketplace
• Biosimilar competition affects not just the price of biosimilar/reference product but also impacts total market price
• What will happen as more biosimilars become available?
• Will Infliximab biosimilars be adopted?
Epoetin medicines in Europe: increase in access since introduction of biosimilar

Average increase of volume of treatment days*
+16%

Change of price per treatment day**
-27%

+263%
-50%

Source: IMS Health, MIDAS, The Impact of Biosimilar Competition, Nov 2015
Notes: Pricing and discounts: the report is based on publicly available prices. Discounting occurs, especially in contracting with hospitals and in countries using tenders for biological drug procurement, which can lead to larger price fluctuations than is visible through the reported IMS Health data.
* Change of volume of treatment days in total market between launch and 2014.
**Change of price per treatment day in total market between launch and 2014.
G-CSF in UK: increased access after introduction of biosimilar
Interchangeability
Prescribing and interchangeability?

• Are biosimilars interchangeable with their reference product?

• What about substitution at pharmacy level?

• Decisions on interchangeability are made at a national level
Interchangeability, substitution and switching

• **Interchangeability**: medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient (prescriber is involved)

• **Switching**: decision from treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment

• **Substitution**: practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber
Interchangeability: who decides?

EMA does not make recommendations on interchangeability with the reference medicine

HPRA recommends treating physician should be involved in any decision regarding switching. Multiple switches not recommended.

‘Generic’ substitution of biological medicines currently not allowed under Irish legislation.
HPRA Guideline

- Regulation
- Product information
- Prescribing
- Dispensing
- Traceability
HPRA position on interchangeability and switching

If it is planned to change the medicine a patient receives from a reference to a biosimilar medicine or vice versa, the treating physician should be involved; this should involve discussion between the prescriber/patient and prescriber/dispensing pharmacist.

- Ongoing engagement between prescribers, dispensers and those with responsibility for procurement
- Switching back and forth not recommended as currently availability of data on the impact of this is limited
### EU Regulatory Positions

<table>
<thead>
<tr>
<th>Country</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Netherlands</td>
<td>• New patients can always be treated with biosimilars</td>
</tr>
<tr>
<td>(MEB)</td>
<td>• Switching is permitted once adequate clinical monitoring and patient is informed</td>
</tr>
<tr>
<td></td>
<td>• Uncontrolled exchange to be avoided</td>
</tr>
<tr>
<td>Finland (FIMEA)</td>
<td>• Switches are common and not usually problematic</td>
</tr>
<tr>
<td></td>
<td>• Biosimilars are interchangeable with reference under HCP supervision</td>
</tr>
<tr>
<td>Germany (PEI)</td>
<td>• No evidence in scientific literature that safety problems occur when switching from an originator to biosimilar</td>
</tr>
</tbody>
</table>


Substitution policies

Pharmacist substitution on treatment initiation
- Substitution policy under restricted conditions legally adopted but not implemented

Pharmacist substitution permitted
- ‘a’ flag awarded by reimbursement body (PBAC)
- Caveats apply

Interchangeable biological products
- Biosimilars shown to be ‘interchangeable’
- Substitution allowed in some states if legislation has been passed
Uptake of infliximab biosimilars in Nordic countries

• Hospital tendering processes in Norway and Denmark have resulted in high uptake
• Large scale switching
• Norwegian Health Authorities sponsoring ‘Nor-Switch’ in order to promote use of biosimilars
• DK- increased focus in agency on monitoring ADRs associated with switching

Norway: http://gabi-journal.net/norway-biosimilars-in-different-funding-systems-what-works.html
Denmark: http://gabi-journal.net/pharmacovigilance-on-biologicals-and-biosimilars-a-danish-perspective.html
Switching studies - Infliximab

• Infliximab was first biosimilar monoclonal antibody to gain approval in Europe (2013)

• Examples of clinical studies to evaluate safety and efficacy of switching from originator to biosimilar
  – PLANETRA and PLANETAS – Switching in RA\(^1\) and AS\(^2\) (Extension of studies used for biosimilar MA)
  – BIO-SWITCH study (NL, rheumatology)
  – PROSIT-BIO (IT, IBD\(^3\))
  – NOR-SWITCH: switching in all indications

Rheumatoid arthritis, \(^2\) Ankylosing spondylitis, \(^3\) Inflammatory bowel disease
NOR-SWITCH

• Aim of study to examine switching from originator to biosimilar infliximab (CT-P13)
• 52 week randomized, double blind, non-inferiority, phase IV trial
• All indications were included - CD, UC, SpA, RA, PsA, Ps
• N= 481, non-inferiority margin: 15%
• Primary endpoint – disease worsening
• Conclusion: switch from originator to biosimilar was not inferior to continued treatment with originator
NOR-SWITCH study design

- Exploring switching for non-medical reasons
- Primary endpoint: Effectiveness (disease worsening)

A randomized, double-blind, parallel-group study to evaluate the safety and efficacy of switching from innovator infliximab to biosimilar infliximab compared with continued treatment with innovator infliximab in patients with rheumatoid arthritis, spondylarthropathy, psoriatic arthritis, ulcerative colitis,Crohn’s disease and Chronic plaque psoriasis.

Assumption: 30% worsening in 52 weeks
Non-inferiority margin: 15%

Source: Presentation by Guro Lovik Goll, available online: https://www.nsf.no/Content/2929566/Nor-Switch%20av%20Guro%20Goll.pdf
1. Infliximab must be prescribed by brand name (i.e., Remicade, Remsima or Inflectra) and not by International Non-proprietary Name (INN).

2. For patients starting infliximab: Remicade, Remsima or Inflectra can be prescribed, taking into account the evidence showing similar clinical effectiveness. There is evidence that monitoring of patients, including measurement of drug and anti-drug antibody levels, is no different for the biosimilar drugs compared to Remicade. The choice of preparation should take into account the cost of the drug and its administration.

3. There is sufficient evidence to recommend that patients who are in a stable clinical response or remission on Remicade therapy can be switched to Remsima or Inflectra at the same dose and dose interval. This should be done after discussion with individual patients, with explanation of the reason for switching (which is usually on the grounds of benefit to the overall service by reduction in costs of the drug and its administration).

4. Automatic substitution, (dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber), is not appropriate.

5. Pharmacovigilance is essential for any new biological medicine, and patients prescribed Remsima or Inflectra should be followed for safety, in a registry such as the UK National IBD Registry.


Recommendation 2: Prescription for clinical reasons
Clinical effectiveness and patient safety should be the overriding principles for prescribing any biologic agent. Prescribing should therefore be made on a case by case basis, based on clinical reasons and not solely as a measure to save money. In all cases, physicians should consider the efficacy, safety and cost-effectiveness profile when making these prescribing decisions.

The BSR supports the inclusion of biosimilars as a biologic therapy choice for patients initiating a new biologic therapy but does not support a universal mandate that all patients should start a biosimilar purely to save costs. The BSR advises against summarily switching all patients currently receiving a reference product that is effective and well tolerated to a biosimilar. The decision to switch should be on a case-by-case basis and until further data are available to support safe switching, strong safeguards are required to ensure that patients who have responded well to existing medicine are not switched for non-clinical reasons.
Summary

• Biosimilar medicines contain a version of the active substance of an already authorised biological medicine
• Biosimilars must undergo a head to head comparability exercise against the reference to show that both medicines have similar quality, safety and efficacy such that there is no clinically meaningful differences between the two
• In Europe biosimilars share the same INN as their reference medicine but WHO and FDA have proposed ‘qualifier systems’ for the INNs of biological substances
• The EMA does not make recommendations on interchangeability but decisions are left to Member States
• Policies on switching and substitution vary globally
Any questions????????????
joan.ocallaghan@hpра.ie