Data requirements to demonstrate biosimilarity in the EU

How has the European Medicines Agency (EMA) changed its requirements for biosimilars since it first approved biosimilars in 2006? This is the question Dr Martina Weise, Head of Licensing Division at the Federal Institute for Drugs and Medical Devices (BfArM), discussed at the 14th Annual Biosimilar Medicines Group Conference.

Keywords: Biosimilar, biosimilarity, data requirements, extrapolation

The European Union (EU) was the first to establish a legal framework and guidance for biosimilars. The legal framework for approving biosimilars in the EU was established in 2003. This framework means that biosimilars can only be approved centrally via the European Medicines Agency (EMA) and not nationally [1]. The agency first developed guidelines for the approval of biosimilars via an abbreviated registration process during 2005 to 2006, and since then has developed many general and specific guidelines for biosimilars [2]. The initial approach by the agency was science-driven, but with no practical experience a cautious, conservative approach to biosimilars was adopted.

Since those early days EMA has issued new guidelines and updated its existing guidelines based on new evidence and rapid advances in analytical sciences. For example, the sensitivity of mass spectrometry methods to detect peptides has increased rapidly over the past two decades. The detection limit for peptides back in 1990 was only 100 pmol compared to 0.00001 pmol in 2011; representing a 10 million-fold increase in sensitivity in 20 years. The agency has also incorporated learning from both manufacturing process changes and biosimilar product reviews.

In her presentation [3], at the 14th Annual European Biosimilars Group Conference, Dr Martina Weise, Head of Licensing Division at the Federal Institute for Drugs and Medical Devices (BfArM), discussed biosimilars applications reviewed by EMA and the evolving landscape on data requirements to demonstrate biosimilarity in the European Union.

Since EMA started reviewing applications for biosimilars, and up to April 2016, the agency had received 44 marketing authorization applications (MAAs). Of these, 13 were still under review and seven had been withdrawn (six for insulin biosimilars and one for an epoetin biosimilar). Up to April 2016 the agency had given a positive opinion for 22 MAAs [of which two were later withdrawn (filgrastim and somatropin)] and a negative opinion for two MAAs (interferon alfa and insulin), see Figure 1.

In May 2016, the infliximab biosimilar Flixabi received approval in the EU [1]. In November 2016, EMA's Committee for Medicinal Products for Human (CHMP) gave a positive opinion for the teriparatide biosimilars, Terrosa and Movymia, and for the insulin glargine biosimilar Lusunda [4].

Major changes in data requirements, according to Dr Weise, include the choice of the reference product, clearer requirements on quality data, changes in the focus for non-clinical studies, use of a tailored clinical programme, reduced clinical programme, extrapolation and pharmacovigilance.

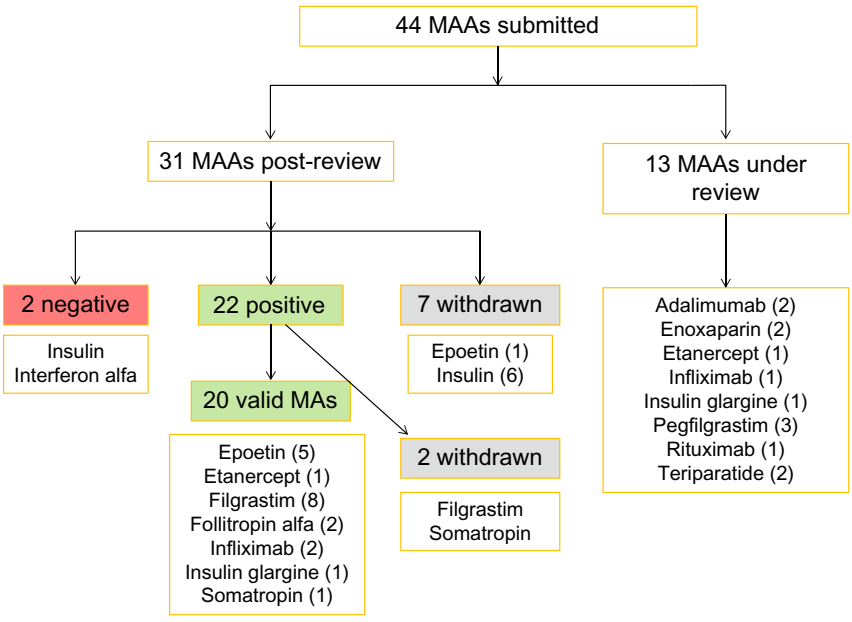
Reference product

One major change with respect to reference products is that a reference product not authorized in the European Economic Area[1] (EEA) may be used for certain clinical and *in vivo* non-clinical studies if it was authorized based on similar scientific and regulatory standards as those used by EMA and if it is representative of the reference product in the EEA [5]. This is outlined in EMA's Guideline on similar biological medicinal products (CHMP/437/04 Rev 1. Effective date: 30 April 2015) [2].

The only catch is that applicants have to prove that batches sourced from outside the EEA are representative of the reference medicine authorized in the EEA through an extensive analytical comparison. Bridging data must include a 3-way analytical comparison (structural and functional data) and may include a 3-way pharmacokinetic (PK) and/or pharmacodynamic (PD) comparison.

[1]EEA: European Economic Area, this area includes the 28 EU Member States, plus Iceland, Liechtenstein and Norway.

Figure 1: Biosimilars review by EMA (until April 2016)



EMA: European Medicines Agency; MAAs: marketing authorization applications.

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Requirements for reference products in the EU and US are comparable.

Quality data

No factual changes have been made, but the guidance, which was updated in December 2014 [2], has been made clearer.

- Full quality dossier + extensive comparability exercise with the chosen reference product
- Use of state-of-the-art, sensitive and orthogonal analytical tools
- Amino acid sequence must be the same; small differences in micro-heterogeneous part acceptable with justification
- Identify 'Quality Target Product Profile' (QTPP) based on characterization of multiple batches of the reference product
- Select expression system and adjust manufacturing process to achieve the QTPP
- Quality attribute ranges should not be wider than the range of variability of the reference product batches, unless justified

Non-clinical studies

The latest revision to EMA's Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev 1) came into effect on 1 July 2015 [2]. The document includes:

- Focus on comparative *in vitro* studies to extensively characterize and compare the function(s) and activity of the molecule
  - Usually more sensitive to detect differences than *in vivo* studies
  - Target binding, e.g. receptors, antigens, enzymes
  - Signal transduction and functional activity
- Risk-based approach for *in vivo* studies, e.g.
  - Novel (or not widely used) expression system or excipients
  - Quality findings of concern or unclear relevance

Tailored clinical programme

According to Dr Weise, the clinical programme for a biosimilar is not intended to show efficacy and safety *per se*. The endpoints should be sensitive to detect differences in efficacy and may be different from those used in clinical trials with the originator. There has been a clear shift to PD endpoints, examples include:

- Magnetic resonance imaging (MRI) endpoint for drugs in multiple sclerosis
- Overall response rate for anticancer drugs
- Anti-factor Xa (anti-FXa) and anti-FIIa activity for low molecular weight heparin (LMWH)
- Absolute neutrophil count (ANC) for granulocyte colony-stimulating factor (G-CSF)
- Number of oocytes retrieved for follitropin (IVF)
- Glucose infusion rate (in clamp studies) for insulin

Reduced clinical programme

EMA does not require a full clinical dossier for a biosimilar. It is usually possible to carry out one clinical trial in one indication, with the option to extrapolate to other indications of the reference biological.

- Clinical trial not needed, if analytical, PK and PD comparisons allow conclusion of similar efficacy and safety and the impurity profile and the nature of excipients of the biosimilar do not give rise to concern
  - Mentioned in the general guidelines and specifically for insulin and LMWH; planned for filgrastim
  - Also expected for more complex biologicals with increasing characterizability of their physicochemical and functional properties

Extrapolation

Regarding extrapolation[2] of indications for biosimilars, EMA has stated that 'if clinical similarity can be shown in a key indication, extrapolation of efficacy and safety data to other indication(s) of the reference product may be possible' under certain conditions [1].

In her presentation, Dr Weise explained that extrapolation:

- Should be considered in the light of the totality of data supporting biosimilarity
- Changed from 'situations where extrapolation may be considered' to 'situations where additional data may be required':
  - If different active sites of the molecule or different receptors involved in different indications
  - Efficacy and/or safety (immunogenicity) data are not relevant for extrapolated indication(s)

[2]Extrapolation involves extending and applying the data from clinical studies regarding one medical condition to another medical condition.

Pharmacovigilance

New pharmacovigilance legislation was adopted by the European Parliament and European Council in December 2010. EMA is responsible for implementing the legislation. As part of its commitments the agency released draft guidance on pharmacovigilance for biologicals in December 2015 for public consultation. This guideline has since been finalized and came into effect in August 2016.

Guideline on good pharmacovigilance practices (GVP)

Product- or Population-Specific Considerations II: Biological medicinal products
Effective Date: 16 August 2016
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/08/WC500211728.pdf

The guideline outlines the following:

- Risk-management plan obligatory
  - Needs to be in line with the risk-management plan of the reference product
  - Deviations in risk-minimization measures or safety monitoring imposed on the reference product must be justified
  - Encouragement to participate in pharmacoepidemiological studies of the reference product
- Ensure product traceability
  - Product name and batch number should always be recorded
  - Data from EudraVigilance suggest good identification by brand name

Dr Weise concluded that 'EMA has shaped biosimilar development globally', with '10 years of safe and effective use of biosimilars in the EU'. Meanwhile the agency is increasingly 'moving from a science-based concept to a science and experience-based approach'. This, accompanied by the 'increasing armamentarium and sensitivity of analytical tools allows increased tailoring and reduction of clinical programmes'. Finally, she added that global development is 'desirable' but warned that 'complete alignment of scientific thinking and data requirements may not be achievable'.

Disclaimer

The author of the presentation [3] declared that the views and opinions expressed in the presentation were personal views, and may not be understood or quoted as being made on behalf of the CHMP or reflecting the position of the CHMP or any other EMA Committee or Working Party.

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References

1. GaBI Online – Generics and Biosimilars Initiative. Biosimilars approved in Europe [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2016 Dec 8]. Available from: www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe
2. GaBI Online – Generics and Biosimilars Initiative. EU guidelines for biosimilars [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2016 Dec 8]. Available from: www.gabionline.net/Guidelines/EU-guidelines-for-biosimilars
3. Weise M. Evolving landscape on data requirements to demonstrate biosimilarity – the EU perspective. 14th Annual Biosimilar Medicines Group Conference; 28–29 April 2016; London, UK.
4. GaBI Online – Generics and Biosimilars Initiative. EMA approves biosimilars of insulin glargine and teriparatide [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2016 Dec 8]. Available from: www.gabionline.net/Biosimilars/News/EMA-approves-biosimilars-of-insulin-glargine-and-teriparatide
5. GaBI Online – Generics and Biosimilars Initiative. EMA to accept biosimilar reference medicines from outside EEA [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2016 Dec 8]. Available from: www.gabionline.net/Guidelines/EMA-to-accept-biosimilar-reference-medicines-from-outside-EEA

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