Where are we with biosimilars: An update

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Development of a biosimilar

McCamish. MAbs. 2011;3(2): 209-17
Biosimilars in Europe

53 MAAs submitted to EMA

40 MAAs reviewed

2 negative
- Interferon alfa-2a
- Human insulin

29 positive

2 withdrawn post-approval
- Filgrastim
- Somatropin

9 withdrawn
- Epoetin (1)
- Insulin (7)
- Pegfilgrastim (2)

27 valid MA’s
- Enoxaparin (2)
- Epoetin (5)
- Etanercept (1)
- Filgrastim (8)
- Follitropin (2)
- Infliximab (3)
- Insulin glargine (2)*
- Rituximab (1)*
- Somatropin (1)
- Teriparatide (2)*

13 MAAs under review
- Adalimumab (4)
- Etanercept (2)
- Insulin lispro (1)
- Pegfilgrastim (2)
- Rituximab (1)
- Trastuzumab (3)

* Awaiting EC approval

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01/01/2017
<table>
<thead>
<tr>
<th>FDA approved biosimilars</th>
<th>Date</th>
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<tbody>
<tr>
<td>- Adalimumab</td>
<td>23 September 2016</td>
</tr>
<tr>
<td>- Insulin glargine</td>
<td>16 December 2015</td>
</tr>
<tr>
<td>- Etanercept</td>
<td>30 August 2016</td>
</tr>
<tr>
<td>- Infliximab</td>
<td>5 April 2016</td>
</tr>
<tr>
<td>- Filgrastim</td>
<td>6 March 2015</td>
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Exhibit 6: Biosimilars in the Pipeline

Source: IMS Health, IMS Institute for Healthcare Informatics, Jan 2016
Infliximab biosimilar uptake, %

Infliximab as % of total anti-TNFs

Source: IMS Health, MIDAS, Dec 2015
Position ECCO 2013

- A biosimilar proven effective and safe for one indication may not necessarily be effective and safe for a second indication for which the reference biological has been shown to be safe and effective.
- Specific evidence obtained in patients with IBD should be required to establish efficacy and safety for this specific indication, because experience with currently licensed biological medicines has already shown that clinical efficacy in IBD cannot be predicted by effectiveness in other indications, such as rheumatoid arthritis.

*Journal of Crohn’s and Colitis* 2013, 7, 586-89
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 to be as efficacious as the reference product when used in accordance with the information provided in the Summary of Product Characteristics.
Position ECCO 2016

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.
Similar biological medicinal products* Revised

Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues*

- Follicle-stimulating hormone
- Monoclonal antibodies
- Erythropoietins Revised
- Interferon beta
- Interferon alpha* Revision
- Granulocyte-colony stimulating factor Revision
- Somatropin
- Human insulin and insulin analogues* Revised
- Low-molecular-weight heparins* Revision

Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues*

Revised

Immunogenicity guidelines

- Immunogenicity assessment of biotechnology-derived therapeutic proteins* Revision
- Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use
Product specific guidelines under revision

- Low-Molecular Weight Heparins
  - Revision guideline based on comments received on draft guideline

- (Pegylated) filgrastim
  - Revised guideline under discussion

- (Pegylated) interferon alfa
  - Concept paper published: awaiting comments
Current regulatory thinking

- More and more focus on physicochemical characterisation

- Use a risk based approach during development also with regard to immunogenicity

- Efficacy/ safety trial may be waived based on the evidence provided
  - Risk for immunogenicity/ safety concerns
  - Knowledge obtained with approved biosimilars/ reference product
Future regulatory trends

- Guidance on statistical methodology on quality comparability
- Tailored scientific advice to support step-by-step development
- Traceability
- Switching and substitution
Concluding remarks

- Increasing number of biosimilars approved/ under development

- Better reliance in biosimilar approval process

- Uptake differs greatly between countries

- Regulatory field is continuously moving based on experience and scientific insights