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Biosimilars and drug development in allergic and immunologic diseases

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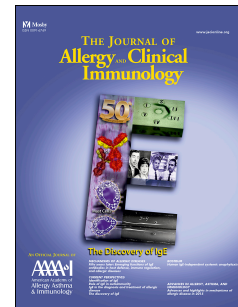
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13 Following the first approval of a recombinant insulin in 1982, the number of biologic drugs has
 14 shown a continuous and exponential increasing trend, which is expected to soon cross-over the
 15 progressive declining trend of the number of chemical drugs. For instance, in the period 2011-
 16 2016, 85 biologics were approved by the Food and Drug Administration (FDA) and 109 by the
 17 European Medicines Agency (EMA), 14 (12.8%) among these lasts having a single (9) or multiple
 18 (5) indications in allergic and immunologic diseases^{1,2}.

19 This changing attitude in drug development is having relevant effects on health care,
 20 pharmaceutical industry, regulators and payers^{3,4}. In fact, the higher costs for the development of
 21 biologics and their indication frequently confined to selected small populations, have produced a
 22 significant increase in total drug expenditure, often not sustainable for many national health
 23 services. As a consequence, the progress in drug development, instead of increasing the quality of
 24 health care, produced the paradoxical effect of reducing it, due to an impaired access of patients
 25 to safe and effective - but expensive - medicines. This also led to an increased risk for
 26 pharmaceutical companies to embark in huge investments without any certainty for financial
 27 return.

28 Biosimilars have been considered a remedy to this phenomenon, because of their potential of
 29 significantly reducing the costs of the many biologics with an expired patent, including most of
 30 those at the top of the lists for sales and costs, well over the one billion of dollars of the "old style"
 31 blockbusters⁵. However, the hope to produce a global saving ranging from 11.8 to 33.4 billions of
 32 Euro in 8 EU countries by 2020 (<http://www.medicinesforeurope.com/2016/02/22/test-article-t/>),
 33 is at present not fully realized.

Biosimilars (also known as Similar Biological Medicinal Products or Follow-on Biologics) are in fact defined by EMA as biological medicinal products that contain a version of the active substance of an already authorised original biological medicinal product (reference medicinal product). Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf).

Biosimilars include products derived from recombinant DNA technology (i.e. monoclonal antibodies) and potentially all biologics such as vaccines, cytokines, hormones, clotting factors, monoclonal antibodies, tissue engineered products, gene and cell therapies. Biosimilars cannot be considered as generics since they have a high molecular weight and a complex heterogeneous structure, are produced through processes strongly dependent on specific experimental conditions and are usually immunogenic (Figure 1). Therefore, the comparison of biosimilars with their reference products is more complex than that required for chemical drugs and implies an accurate comparative assessment of their quality and clinical features, known as “comparability exercise”.

Europe has led the pace for the development of biosimilars, 31 products having received a positive opinion from EMA (26 with a valid marketing authorizations, 2 products waiting for the European Commission (EC) decision and 3 withdrawn by the manufacturers). Omnitrope (somatropin) was the first product approved as a biosimilar in 2006, while the first monoclonal antibody (Infliximab, Remsima, Inflectra) was authorized in 2013¹.

Biosimilars represent an argument of high interest for allergists and clinical immunologists since 7/31 (22%) of the products that received a positive opinion by the EMA Committee on Medicinal Products for Human Use (CHMP) have an indication for allergic and immune diseases (Table 1). Furthermore, in view of the upcoming expiration of patents and intellectual property rights of several biologics of interest in allergy and clinical immunology, a high number of biosimilars is at present under development or review. For instance a Phase II/III trial was completed in May 2016 by Sorrento Therapeutics/Mabtech for omalizumab, whose patents will expire in June 2017 in US and in August 2017 in Europe.

The marketing authorization of biosimilars in Europe is granted through a centralized procedure by the EC, following the opinion of the EMA CHMP supported by the Biosimilar Medicine Working Party and the Biologics Working Party. The EMA has published several documents to regulate the

requirements for approval of biosimilars including an *overarching guideline* defining principles, *general guidelines on quality and non-clinical and clinical aspects* to define safety and efficacy, and *guidelines for specific products* such as insulin, somatotropin, G-CSF, epoetin, IFN-alfa, Low Molecular-Weight Heparins and monoclonal antibodies¹. The EMA also provides Scientific Advice that has been shown extremely useful for a correct implementation of the guidelines and a successful outcome of the applications.

According to EMA Guidelines, quality assessment is the primary fundamental step in the evaluation of biosimilars. The reference product should be approved in the European Union even if pivotal data from comparison with comparators authorized in regulated countries may be accepted, under certain conditions. Non-clinical tests are usually based on in vitro assays that are preferred to studies in animal models.

With reference to clinical aspects, a biosimilar is intended to be used at the same posology and dosing regimen(s) as those of the reference products to treat the same disease(s). Endpoints for clinical comparability may be different from those used to show efficacy of the originator. However, Phase III studies of biosimilars should contain common end-points with the pivotal studies of the originator. If justified by a common mechanism, indications for a biosimilar can be extended to all those of the originator, even if not tested in authorization studies. Equivalence designs should be preferred, but non-inferiority designs may be acceptable. Interestingly, superiority of the biosimilar vs the originator is not acceptable.

Immunogenicity is a major safety concern for products that can elicit specific antibodies potentially responsible for hypersensitivity reactions and severe adverse events (as in the case of the pure red cell aplasia induced by epoietin alfa)⁶, as well as for inhibition of the drug effect. Different methods are available for testing the production of antibodies against biosimilars. However, there is no evidence of a higher risk of immunogenicity for biosimilars compared to that of the reference products.

Pharmacovigilance for biosimilars should not be less than for the originator. A risk management plan is therefore requested and traceability should be guaranteed. The same registry used for the originator can be used. Up-to-now however, in ten years of experience, EMA has not identified any safety signal or adverse drug reaction which is new, more frequent or more severe for biosimilar products compared with their reference medicines.

The drug development of biosimilars is not confined to Europe but represents a world-wide phenomenon. Biosimilar products are available to patients in over 60 countries around the world.

98 At the end of 2014 we counted 53 biosimilars approved in all world countries. However, it is very
99 difficult to keep up-dated this number since it increases almost on a daily basis.

100 In the United States the first biosimilar (Zarxio, filgrastim-sdnz, clinically comparable to Amgen's
101 Neupogen and with the same 5 indications) was approved by the FDA in March 2015 following the
102 Biologics Price Competition and Innovation Act passed by the Congress in 2009, as a part of the
103 Affordable Care Act⁷. This authorized the FDA to oversee an "abbreviated pathway" for approval
104 of biosimilars which stimulated a high number of applications currently at different stages of the
105 marketing authorization process. One of the major topics of debate in US at the moment is
106 whether biosimilars should have the same International Non-proprietary Name (INN) of the
107 originator and criteria for an interchangeable designation. Substitution of the originators with the
108 biosimilar products (interchangeability) is in fact a general matter of extensive discussion that
109 mainly depends on national decisions⁸.

110 Regulatory and clinical guidelines of biosimilars – named as subsequent entry biologics (SEB) -
111 have been recently reviewed in Canada, also focusing on requirements for extrapolation⁹ (the
112 granting of indication approved for the reference biological to the SEB without conducting clinical
113 trials for that indication).

114 In Argentina, Cuba and Mexico copies of biologics were not originally registered as biosimilars,
115 since in the 80's there were no patent laws in Latin American countries. When Venezuela and
116 Brazil first - and then other countries (Mexico in 2011) - adapted, at least in part, to the WHO
117 guidelines for biosimilars, over 100 products were already on the market and over 100,000 doses
118 were administered in Mexico without the availability of adequate pharmacovigilance data. Despite
119 recommendation of the PanAmerican Network For Drug Regulatory Harmonization (PANDRH),
120 harmonization in Latin America is still difficult. Nevertheless, improved pharmacovigilance and a
121 re-evaluation of drugs on the market have been recommended¹⁰.

122 Asiatic countries represent a very active area for biosimilars. Japan published biosimilar guidelines
123 in 2009 and has approved several biosimilars up-to-now under the requirement that subjects of
124 Japanese ethnic origin had been included in the pharmacokinetic and efficacy studies¹¹. Following
125 the approval of guidelines in 2009, South Korea made a massive investment in biosimilars with the
126 expectation of acquiring 20% of the entire market in 2020. In India, biosimilars represent a very
127 active area and the next "big thing" for a country which is expected to become the 8th drug
128 market. Guidelines for biosimilars have been recently revised and approved biosimilars also
129 include products not approved in other countries. Therefore, Singapore looks with great interest

130 to initiatives for attracting Indian companies. In China the guidelines finally released in 2015
131 hopefully will overcome the problems encountered for the poor quality of some products
132 approved in this rapidly growing market.

133 At last, the Australian Therapeutic Goods Administration recently adopted the EMA's guidelines
134 for biosimilars. Among products approved in Australia and New Zealand, infliximab represented
135 the first substitutable biosimilar by pharmacists.

136 Although WHO guidelines are available¹², there are still some differences in the regulations
137 adopted in Europe, US, Japan and India that prompted for a global harmonization for this
138 emerging class of medicines^{13,14}.

139 In conclusion, biosimilars represent a class of drugs of increasing relevance in the next years in
140 view of the high number of expiring patents for expensive products such as biologics. Biosimilars
141 may partially reduce the costs of biologics, with the potential of making them more affordable in
142 all parts of the world. Harmonization of guidelines should however be achieved for this global
143 market. Issues still waiting for a solution include: nomenclature, interchangeability and
144 extrapolation of indications.

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Figure legend

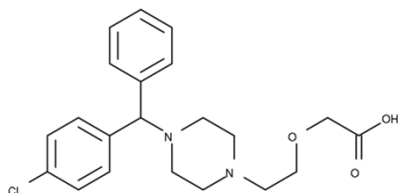
Fig. 1. The figure shows , as an example, the molecular structure of one chemical drug (cetirizine) and one biologic (infliximab) used in the treatment of allergic and immunologic diseases in order to highlight the differences between generics and biosimilars in replicating the reference medicines.

Table 1: Biosimilars with indications in allergic and immunologic diseases which received an approval by the European Commission or a positive opinion by the EMA Committee for Medicinal Products for Human Use (CHMP).

Product name	Active substance	Indication	Authorization date	Manufacturer
Amgevita	Adalimumab	Crohn's disease Psoriasis Psoriatic arthritis Rheumatoid arthritis Spondylarthritis Suppurativa hidradenitis Ulcerative colitis Uveitis	CHMP positive opinion 26 Jan 2017	Amgen
Benepali	Etanercept	Axial spondyloarthritis Psoriatic arthritis Plaque psoriasis Rheumatoid arthritis	14 Jan 2016	Samsung Bioepis
Flixabi	Infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	26 May 2016	Samsung Bioepis
Inflectra	Infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	10 Sep 2013	Hospira
Remsima	Infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	10 Sep 2013	Celltrion
Solymbic	Adalimumab	Ankylosing spondylitis Crohn's disease Psoriasis Psoriatic arthritis Rheumatoid arthritis Suppurativa hidradenitis Ulcerative colitis	CHMP positive opinion 26 Jan 2017	Amgen
Truxima	Rituximab	Chronic lymphocytic leukaemia Granulomatosis with polyangiitis Microscopic polyangiitis Non-Hodgkin's lymphoma Rheumatoid arthritis	CHMP positive opinion 15 Dec 2016	Celltrion

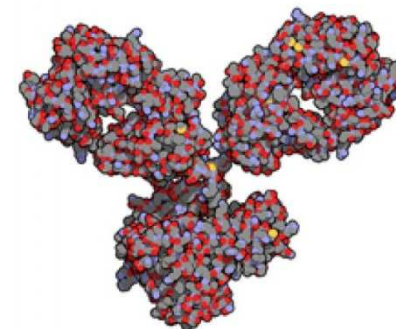
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Chemical drugs/Generics

- Low Molecular weight
- Simple structure
- Chemically produced
- Standardized manufacturing process
- Possible to obtain exactly the same molecule
- Stable
- Non immunogenic
- Bioequivalence based on pharmacokinetic



Biologics/Biosimilars

- High molecular weight
- Complex structure
- Produced by living cells
- Specialized manufacturing process
- Possible variability among different batches (as for biologics)
- Sensitive to storage and handling
- Immunogenic
- Complex comparability exercise (PK-PD studies, CTs)