June 26, 2019

Principles of Biosimilars Approach

1. Definition and Concepts of Biosimilars

Biosimilars are also known as “biosimilar products”, “biosimilar medicines”, “similar biotherapeutic products (SBPs)”, “similar biological medicinal products” or “follow-on-Biologics”.

1) **EMA (European Medicines Agency): *Biosimilar medicines: Overview***

https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview

2) **FDA: *Biosimilar and Interchangeable Products***

https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

3) **Health Canada: *Biosimilar biologic drugs***

https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/biosimilar-biologic-drugs.html

4) **MFDS: *Biosimilar***

https://www.mfds.go.kr/eng/wpge/m_37/de011024l001.do

5) **PMDA**: ***Follow-on biologics (Biosimilar)*** is a biotechnological drug product developed to be comparable in regard to quality, safety and efficacy to an already approved biotechnology-derived product (“original biologic”) of a different company.

6) **Swissmedic**: ***Biosimilars***

https://www.swissmedic.ch/swissmedic/en/home/suche.html?searchField=biosimilar#biosimilar

7) **Therapeutic Goods Administration**: ***Biosimilar medicines***

https://www.tga.gov.au/publication/biosimilar-medicines-regulation

8) **WHO: *Similar biotherapeutic products*** https://www.who.int/biologicals/biotherapeutics/similar_biotherapeutic_products/en/

2. Approval Process for Biosimilars

1) EMA (EU)

• All medicines produced using biotechnology and those for specific indications (e.g. for cancer, neurodegeneration and auto-immune diseases) must be approved in the EU through EMA (via the so-called 'centralized procedure'). Nearly all biosimilars approved for use in the EU have been approved centrally, as they use biotechnology for their production.

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• When a company applies for marketing authorization through EMA, data are evaluated by EMA's scientific committees on human medicines and on safety (the CHMP and PRAC), as well as by EU experts on biological medicines (Biologics Working Party) and specialists in biosimilars (Biosimilar Working Party).

• The review by EMA results in a scientific opinion, which is then sent to the European

Commission, which ultimately grants an EU-wide marketing authorization.

2) FDA (US)

• All FDA-approved biological products, including reference products and biosimilar products, undergo a rigorous evaluation so that patients can be assured of the efficacy, safety, and quality of these products.

• A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared. A reference product is approved in a “standalone” application that must contain all data and information necessary to demonstrate its safety and effectiveness. Generally, the data and information necessary to demonstrate the safety and effectiveness of a reference product will include clinical trials for the disease indications being sought by the manufacturer.

• A biosimilar is highly similar to, and has no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) from, an existing FDA-approved reference product. The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar product and the reference product, not to independently establish the safety and effectiveness of the proposed product.

• The manufacturer of a proposed biosimilar product generates an array of data comparing the proposed product to the FDA-approved reference product in order to demonstrate biosimilarity. The comparative data are generated and evaluated in a stepwise fashion that begins with a foundation of detailed analytical (structural and functional) characterization and comparison of the products, moving on to animal studies if necessary and then to comparative clinical studies.

• Consequently, rather than generating the same full profile of nonclinical and clinical data as the reference product, a manufacturer that shows its proposed biosimilar product is highly similar to and has no clinically meaningful differences from the FDA-approved reference product may rely in part on FDA’s previous determination of safety and effectiveness for the reference product for approval. This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional

therapeutic options, and reduced costs for patients.

3) Health Canada (Canada)

• Biosimilars are regulated as new drugs under the Food and Drugs Act and the Food and Drug Regulations. Health Canada's Biologics and Genetic Therapies Directorate (BGTD) regulates biosimilars in collaboration with the Regulatory Operations and Regions Branch (RORB) and the Marketed Health Products Directorate (MHPD).

• Health Canada's Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs communicates the regulatory framework for biosimilars.

• Biosimilar manufacturers must provide information to Health Canada comparing the biosimilar with the reference biologic drug. Similarity is demonstrated using a step-wise approach beginning with structural and functional studies and continuing with human clinical studies.

• Health Canada evaluates all the information provided to confirm that the biosimilar and the reference biologic drug are similar and that there are no clinically meaningful differences in safety and efficacy between them.

• Once Health Canada authorizes a biosimilar for sale, a Notice of Compliance (NOC) and a unique Drug Identification Number (DIN) are issued.

• Health Canada monitors the safety of all drugs on the market, including biosimilars. Each manufacturer must do its part for drug safety:

• Set up a system to monitor reported side effects

- ✓ Report any new information received about serious side effects to Health Canada
- ✓ Notify Health Canada about any studies with new safety information
- ✓ Request authorization for any major changes to
  - the manufacturing process, dose regimen, or recommended uses of the drug

4) MFDS (Korea)

• Biosimilar product should be demonstrated to be biosimilar to already marketed reference product in terms of quality, safety and efficacy under Regulation on Approval

and Review of Biological Products, MFDS Notification.

• Comprehensive comparability assessment should be carried out between the biosimilar product and the reference product based on all the data obtained from comparative quality, nonclinical and clinical studies.

• After demonstration of biosimilarity, extrapolation of other indications is acceptable with appropriate scientific evidence and justification.

• In approval of a biosimilar product, a totality of evidence approach should be considered, i.e. all data generated during the comparability assessment.

5) PMDA (Japan)

• Biosimilar products" were established as a new application category for prescription drugs (Notification No. 0304004 of the Evaluation and Licensing Division, PFSB dated March 4, 2009).

• Documents on points to consider in approval applications (Notification No. 0304015 of the Evaluation and Licensing Division, PFSB dated March 4, 2009) and handling of non-proprietary and brand names (Notification Nos. 0304011 and 0214-(1) of the Evaluation and Licensing Division, PFSB dated March 4, 2009 and February 14, 2013, respectively) were also issued. In March 2010, ”Questions and answers on policies to verify the quality, efficacy, and safety of biosimilar products” was issued (Office Communication of the Evaluation and Licensing Division, PFSB dated March 31, 2010.

• To prove the comparability, appropriate studies are necessary based on the concepts in the ICH Q5E guidelines “Comparability of Biotechnological/ Biological Products Subject to Changes in their Manufacturing Process.” It is also necessary to evaluate the comparability of biosimilars using clinical studies.

• The application for a biosimilar product is required to contain detailed procedures and programs of postmarketing surveillance and risk management as directed in Appendix 9 of the Guidelines on the Assurance of Quality, Efficacy, and Safety of Biosimilar Products (Notification No. 0304007 of the Evaluation and Licensing Division, PFSB dated March 4, 2009). However, the Guidelines on the Risk Management Plan (RMP) issued later (Notification No. 0426-(2) of the Evaluation and Licensing Division, PFSB dated April 26, 2012) requires to attach an RMP, in place of post-marketing

surveillance plan, to be included in the biosimilar product application submitted on or after April 1, 2013.

6) Swissmedic (Switzerland)

• Full quality documentation on the biosimilar including analytical comparability studies using the comparator product (or the reference and the comparator product if these are not the same) is required for the authorization of a biosimilar.

• Concerning the preclinical and clinical study results, Swissmedic may accept reduced documentation. In such cases, the type of the biosimilar, the documentation submitted, the analysis process available, the manufacturing process used, and experience with the comparator product from clinical, preclinical and pharmacovigilance perspectives are also taken into account.

• The Agency reviews and decides on a case-by-case basis the extent and components of the validation and the authorization application that are eligible for submission of reduced documentation. A limited study programme for preclinical and clinical studies is possible.

• Studies on the quality, biological activity, safety and efficacy of the biosimilar in comparison to the corresponding properties of the comparator product (or of the reference and comparator product if these are not the same) must be coherent, and provide conclusive proof of comparability.

• In addition to the results from preclinical and clinical comparability studies that provide sufficient proof of the similarity of the biosimilar to the comparator product (or to the reference product and the comparator product if these are not the same), applicants may also use published scientific data on the safety and efficacy of the reference or comparator product as a basis.

3. Benefits of Biosimilars

For many diseases such as cancer, anemia, inflammatory bowel disease and autoimmune disorders, biological medicines provide better long-term outcomes with fewer

side effects than chemical medicines. However, biological medicines are expensive, and are often the only treatments available to patients suffering from the most severe diseases.

The introduction of biosimilars is expected to drive significant costs savings for healthcare systems and expand earlier, more consistent access to biological medicines. By competing with original biologic medicines across a growing range of therapy areas, biosimilars enable stakeholders – including payers, physicians, and patients – to benefit from greater choice when it comes to treatment options.

1) Benefits for providers

The biologics market is growing rapidly. According to the EvaluatePharma World Review 2017, Outlook to 2022 report (2017), in 2022 52% of the value of the top 100 products will come from biologics as established chemical products drop off the patent cliff and new breakthrough biologics get approved. Patent expiry of blockbuster biologics, such as Humira, Enbrel and Remicade, globally, present a significant opportunity biosimlar market.

Because biologics are produced from living organisms, manufacturing issues are more important than in the chemical drug market. The barriers to biosimilar entry into the marketplace are much more difficult to overcome than challenges generic manufacturers typically face and are similar to obstacles specialty injectable producers encounter. Therefore, companies with experience in manufacturing, especially in manufacturing biologics, will have a considerable advantage over new companies with no such manufacturing experience.

2) Benefits for patients

Patients need access to safe, effective, high-quality medicines such as biological medicines, particularly as chronic diseases become more common. Biosimilar products provide patients with the same treatment as high-priced Biologics but at more reasonable prices and it also improves patients access to treatment they need. For most classes, there is a significant increase in consumption since biosimilar entry in countries which had low starting volumes. There are also some countries which already had high usage of classes before biosimilar entry, such as Sweden with Anti-TNF’s, which show a significant

increase in consumption (Table 1).

Table 1. Countries with highest change in volume TD (2016/Year before biosimilar entrance)

Anti-TNF	Price per TD 2016/ Year before Biosimilar entrance	Volume TD 2016/ Year before Biosimilar entrance	TD/capita (Year before Biosimilar entrance)
Bulgaria	-23%	190%	0.10
Slovakia	-19%	93%	0.49
Sweden	-39%	74%	0.94
Portugal	-13%	63%	0.26
Czech	-13%	59%	0.24

G-CSF	Price per TD 2016/ Year before Biosimilar entrance	Volume TD 2016/ Year before Biosimilar entrance	TD/capita (Year before Biosimilar entrance)
Romania	-62%	2542%	0.02
Bulgaria	-47%	581%	0.02
Slovakia	-61%	509%	0.05
Slovenia	-57%	178%	0.05
Norway	-31%	164%	0.07

EPO			
Poland	-46%	237%	0.03
Greece	-51%	196%	0.02
Italy	-10%	39%	0.82
Czech	-32%	36%	0.09
Bulgaria	-16%	36%	0.23

HGH			
Romania	-31%	152%	0.02
Poland	-42%	82%	0.04
UK	-16%	79%	0.04
Finland	-52%	70%	0.06
Czech	-25%	68%	0.08

※ Source: QuintilesIMS, The Impact of Biosimilar Competition in Europe, May 2017

※ Definitions

- Price evolution: price per Treatment Day (TD) in 2016 versus year before biosimilar entry
- Volume evolution: number of Treatment Days in 2016 versus year before biosimilar entry
- Anti-TNF: Anti-tumor necrosis factor
- G-CSF: Granulocyte colony-stimulating factor
- EPO: Epotein
- HGH: Human growth hormone

3) Benefits for payers and systems

Biosimilars have the potential to generate savings and efficiencies for health care systems, which can help expand access to biologic medicines or free up resources for other important aspects of health care, including the development and use of new

medicines. By opening markets to biosimilar competition, healthcare systems could realize savings of more than EUR10 billion in the EU5 (France, Germany, Italy, Spain, and the UK) alone between 2016 and 2020, simply based on direct competition for the originator molecule and excluding any indirect competition for other in-class or therapy-area specific product sales. The cumulative savings over the next five years in the EU5 and the U.S. combined could range from EUR49 billion to as much as EUR98 billion (Figure 1).

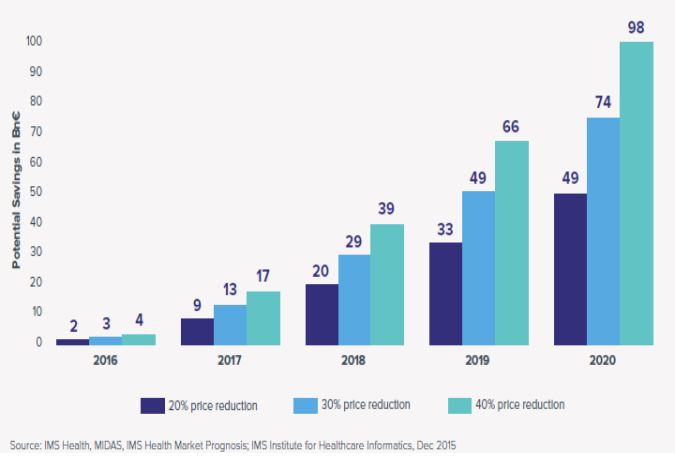

Figure 1. Biosmilar savings potential in the EU5 and U.S., for 8 key products (*) in 2015-2020

※ Source: IMS Health, Delivering on the Potential of Biosimilar Medicines: he Role of Functioning Competitive Markets, March 2016

※ 8 key products: Adalimumab, Isuline glargine, Etanercept, Infliximab, Rituximab, Peg-figratim, Trastuzumab, Follitroplin Alfa