Report

Biosimilars

Regulatory Frameworks for Marketing Authorisation of Biosimilars: Where Do We Go From Here?

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Over the last years, marketing authorisation applications for biosimilars have been reviewed and approved via specific marketing authorisation procedures that vary between jurisdictions. The European Medicines Agency has more than ten years of experience with approval of biosimilars for use in the European Union, allowing us to identify challenges in the marketing authorisation procedures of biosimilars in practice and how these procedures might be improved. This report discusses the current European framework for approval of biosimilars, perspectives on this process from healthcare professionals and patients, and ongoing initiatives and developments to enhance efficiency of the process and involvement of all stakeholders. For shaping biosimilars guidelines, a multi-stakeholder approach is considered appropriate. Challenges associated with the marketing authorisation procedure for biosimilars might not be directly related to the procedure itself, but to concerns that the clinical community does not thoroughly understand the biosimilar development pathway. Education of healthcare professionals and patients will be essen-

tial to ensure uptake. Further convergence of guidelines and sharing of information will also be necessary.

1. Introduction

Biological medicines, i.e., medicines containing an active substance produced by or extracted from a biological source,¹ have revolutionized treatment of many life-threatening and chronic diseases, e.g., autoimmune diseases and cancer, by their specificity to key mediators of the disease.² Since the advent of recombinant DNA technology in the 1980s, the biological market has grown to global sales of US\$ 228 billion in 2016.³ Many of these novel biological medicines have lost, or will lose, patent protection and other exclusivity rights, opening this multi-billion dollar market for competition with non-innovator versions of these molecules, often lower cost alternatives, that offer healthcare systems a tool to control expenses and increase patient access to treatment.

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- 1 Commission Directive 2003/63/EC amending Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [2003] OJ L 159/46.
- 2 D M Geynisman et al, 'Biosimilar biologic drugs: a new frontier in medical care' (2017) 129 Postgraduate Medicine 4, 460 - 470.
- 3 Per Troein, 'Market development in Europe and Globally - A perspective on biologicals and biosimilars' (15th Biosimilar Medicines Conference, London, March 2017).

In terms of evidence development for quality, safety and efficacy, duplication of the full clinical development program of the reference biological product by the biosimilar is scientifically deemed unnecessary and even unethical. However, given the nature of biological medicines, including biosimilars, the simplified marketing authorisation procedure for generic medicines with sole reference to originator's data is not appropriate for biosimilars. Therefore, there was a need for new regulations to make clear what data are needed to file for approval of a biosimilar and ensure similar quality, safety and efficacy to the reference product.

In the European Union (EU), the legal basis for a specific marketing authorisation procedure for biosimilars was established in 2004, with an amendment to Directive 2001/83/EC, which entered into force in 2005.⁴ As for all biotechnology-derived medicines, marketing authorisation applications of biosimilars are reviewed via the mandatory centralised procedure.⁵

The European Medicines Agency (EMA) pioneered the development of a regulatory framework for biosimilars in 2005.⁶ They define a biosimilar as follows: 'A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product) in the European Economic Area (EEA). 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.'⁷ The comprehensive comparability exercise consists of a full physicochemical characterization of the molecule and comparison of these characteristics as well as the biological activity with the reference product. Non-clinical tests in animals, if any, are very limited. In most cases two types of clinical trials occur, i.e. a phase 1 PK/PD study followed by a phase 3 confirmatory efficacy study in the most sensitive indication. The chosen indication is not intended to demonstrate efficacy per se, but to elicit any possible differences between the two molecules. The basis of the biosimilarity exercise is thus the extensive comparative physicochemical and biological characterization. In June 2018, 43 biosimilars were authorized for use in the European Union.⁸

The EMA inspired many other jurisdictions in the publication of guidance on biosimilar development. In 2009, the World Health Organization (WHO) pub-

lished their guidance on evaluating 'similar biotherapeutic products', to help countries develop guidance on biosimilars and increase global harmonization.⁹ Since then, many jurisdictions have established biosimilar guidelines, whether or not based on principles of the EMA or WHO guidance. An overview of a selection of medicines agencies that have issued guidance on biosimilars is given in Table 1. The major variations in biosimilar guidelines issued in Canada, the EU, Japan, Korea and guidance of WHO have previously been described.^{–fnref:11}

With more than ten years of experience with approval of biosimilars in Europe, the aim of this report is to discuss: i) the current European regulatory framework for approval of biosimilars and associated scientific and regulatory challenges, ii) perspectives on existing guidelines of stakeholders not directly involved in the marketing authorisation process (external stakeholders), and iii) future developments and possible improvements to this system. References are also made to other jurisdictions. The genesis of this report originated in a master's thesis project involving stakeholder interviews,¹¹ in addition to the observations of the research team and the literature.

4 Directive 2004/27/EC of the European parliament and of the council amending Directive 2001/83/EC on the Community code relating to medicinal products for human use [2004] OJ L 136, 34.

5 Regulation (EC) 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency' [2004] OJ L 136/1.

6 EMA, 'European Medicines Agency - Multidisciplinary: biosimilar' (2018) <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp> accessed 12 January 2018.

7 EMA, 'Guideline on similar biological medicinal products' (2014) <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf> accessed 22 January 2016.

8 EMA, 'European Medicines Agency - Find medicine - European public assessment reports' (2018) <http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&keyword=Enter%20keywords&searchType=name&alreadyLoaded=true&status=Authorised&jsenabled=false&searchGenericType=biosimilars&orderBy=authDate&pageNo=1> accessed 1 June 2018.

9 WHO, 'Guidelines on evaluation of similar biotherapeutic products (SBPs)' (2013) WHO Technical Report Series No 977, Annex 2.

11 M Geybels et al, 'Experiences of stakeholders with the registration procedure for biosimilars' (KU Leuven 2017).

Table 1: Medicines Agencies for a Selection of Jurisdictions and Date of First Guidance on Biosimilars

Jurisdiction	Medicines agency	Biosimilar guidelines since
European Union	EMA	2005 ^a
United States	FDA	2015 ^b
Canada	Health Canada	2010 ^c
South Korea	MFSO	2010 ^d
India	CDSCO	2012 ^e
Japan	PMDA	2009 ^f
CDSCO: Central drugs standard control organization, EMA: European medicines agency, FDA: US Food and drug administration, MFSO: Ministry of food and drug safety, PMDA: Pharmaceuticals and medical devices agency		

a (n 6).

b FDA, 'Guidances (Drugs) > Biosimilars' (2018) <<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm>> accessed 6 February 2018.

c Government of Canada, 'Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs' (2018) <<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/information-submission-requirements-biosimilar-biologic-drugs-1.html>> accessed 9 February 2018.

d Generics and Biosimilars Initiative, 'South Korean guidelines for biosimilars' (2012) <<http://www.gabionline.net/Guidelines/South-Korean-guidelines-for-biosimilars>> accessed 6 February 2018.

e Central Drugs Standard Control Organization, 'Guidelines on similar biologics: Regulatory requirements for marketing authorization in India, 2016' (2016) <<http://www.cdscn.org.in/writereaddata/Proposed%20Guidelines%20for%20Similar%20Biologic%202016.pdf>> accessed 9 February 2018.

f Daisaku Sato, 'Surfing the wave in Japan for Regulatory Convergence of Biosimilar' (2016) <http://www.egaevents.org/presentations/2016bios/Daisaku_Sato.pdf> accessed 1 February 2018.

II. Current EU Regulatory Framework for Approval of Biosimilars

More than ten years of safety data on biosimilars indicate no occurrence of adverse effects different from those with the reference biological product,¹² confirming the stringency of the marketing authorisation procedure for biosimilars in Europe and demonstrating that it is suitable to assess evidence on the

safety and efficacy of the biosimilar. A specific procedure for biosimilars guarantees their quality, safety and efficacy, while also ensuring to lower development costs for companies and possible increase of patient access to treatment.

One of the strengths of the European system is the collaboration with several European experts affiliated with EMA and other stakeholder groups. Regarding biosimilars, the biosimilar working party is at the forefront when it comes to drafting and setting up guidelines¹³ but also other working parties, e.g., the scientific advice working party that is involved in discussions with companies on challenges of biosimilar development, give input. When a guideline is proposed, it is first placed on the website for public consultation,¹⁴ usually for six months. Afterwards, comments are discussed again in the biosimilar working party. Involvement of all stakeholders in developing the regulatory framework may increase acceptance

12 Paul Cornes, 'The economic pressures for biosimilar drug use in cancer medicine' (2012) 7 Suppl 1 Target Oncol S57.

13 EMA, 'CHMP - Biosimilar Medicinal Products Working Party' (2018) <http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000024.jsp&mid=WC0b01ac0580028d97> accessed 1 June 2018.

14 European Medicines Agency, 'News and Events - Open consultations' (2018) <http://www.ema.europa.eu/ema/index.jsp?curl=pages/document_library/landing/landing_page.jsp&mid=WC0b01ac05807a4176> accessed 1 June 2018.

of biosimilar use. As biosimilars of different active substances are already in development, a remark can be made on how useful it is to start drafting new product specific guidelines for these molecules.

The European system can thus be seen as fairly transparent. Together with the final version of a guideline, a list of the comments received during the consultation phase is published, along with justification when a comment has not been included, for example the 'Overview of comments received on Draft guideline on similar biological medicinal products'.¹⁵ Names of substances that are under review are also publicly available.¹⁶ Furthermore, for each product a European public assessment report (EPAR) is published with information on the product and how the data were evaluated and the conclusion was reached. An important point is the observation that healthcare professionals do not tend to be aware of the existence of the EPAR, or availability of other public information on the biosimilar development pathway and approval process. In response, EMA published summaries of the EPAR¹⁷ (now named the 'public friendly overviews')¹⁸ and the European Commission generated information documents for patients and healthcare professionals.¹⁹

III. Perspectives of External Stakeholders

For stakeholders not involved in the development of regulatory guidelines and approval of biosimilars, such as healthcare professionals and patients, it is often difficult to understand the biosimilar pathway,

since it differs from traditional drug development in regard to the emphasis on physicochemical characterisation instead of clinical data. This challenge has been identified and studied in earlier research.²⁰ To increase acceptance of biosimilars and ensure uptake, programs to increase awareness and knowledge on biosimilars are needed. Preferably, this information should come from an unbiased third party, and should take into account the comprehensibility of the information. The European Commission and EMA are collaborating on the development of Q&A documents on biosimilars targeting healthcare professionals and patients.²¹ Recently, and in line with European Commission rules, the information document for patients was translated to different languages.²² The physician is still in the best position to choose an appropriate treatment, but they should be well-informed on the treatment options. The challenge will be to get physicians to understand the abbreviated approval process (focussing on physicochemical characterisations) and to communicate with the clinical community that adequate pharmacovigilance programs are in place.

Although there is already information available, it seems that the target audience is not always reached. The general public is not aware of existing information and perceives the decision-making process to be opaque. This implies that the limited knowledge on biosimilars of external stakeholders may be primarily due to communication problems rather than a lack of information. Therefore, education of physicians on the science behind the biosimilarity exercise will be key to improve uptake.

15 EMA, 'Overview of comments received on 'Guideline on similar biological medicinal products containing biotechnology - derived proteins as active substance: non-clinical and clinical issues Overview of comments received on 'Draft guideline on similar biological medicinal products' (2018) EMA/CHMP/772616/2013.

16 EMA, 'Human medicines - Medicines under evaluation' (2018) <http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/document_listing/document_listing_000349.jsp&mid=WC0b01ac05805083eb> accessed 1 June 2018.

17 EMA, 'European public assessment reports - European public assessment reports: background and context' (2018) <http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000433.jsp> accessed 1 July 2018.

18 EMA, 'Reflection paper on European public assessment report summary for the public' (2006) <http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004173.pdf> accessed 15 September 2018.

19 EMA and the European Commission, 'Biosimilars in the EU - Information guide for healthcare professionals' (2017) <http://www.ema.europa.eu/docs/en_GB/document_library/Information_and_communication/2017/05/WC500226648.pdf> accessed 08 June 2017; European Commission, 'What I need to know about biosimilar medicines - Information for patients' (2016) <<http://ec.europa.eu/DocsRoom/documents/20961>> accessed 30 June 2017; European Commission, 'What you need to know about biosimilar medicinal products - A consensus information document' (2013) <<http://ec.europa.eu/DocsRoom/documents/8242>> accessed 24/09/2015.

20 Luca Pasina et al, 'A survey among hospital specialists and pharmacists about biosimilars' (2016) 35 *European Journal of Internal Medicine*, 31 - 35; M Beck et al, 'Knowledge, behaviors and practices of community and hospital pharmacists towards biosimilar medicines: Results of a French web-based survey' (2017) 9 *MAbs*, 383 - 390; I Jacobs et al, 'Patient attitudes and understanding about biosimilars: an international cross-sectional survey' (2016) 10 *Patient Preference Adherence*, 937 - 948; E van Overbeek et al, 'Perception of Originator Biologics and Biosimilars: A Survey Among Belgian Rheumatoid Arthritis Patients and Rheumatologists' (2017) 31 *BioDrugs* 447.

21 European Commission (n 19).

22 *ibid.*

There is especially a need for readily available information, for example on the internet, so that patients can discuss it with their physician. Also national medicines agencies can play a more prominent role in education of stakeholders, e.g., development of a tool for physicians to support informing their patients. Focus of future research on awareness of available information on the approval process for biosimilars and identification of information gaps and specific needs of physicians and patients is necessary.

The role of academia could be to participate in think tanks and advisory committees to help shape guidelines and communicate with regulators about them. Furthermore, researchers can play a role in the education of physicians and patients, for example by developing educational materials and programs.

IV. Future Developments

Regulatory frameworks are dynamic and evolve as more experience with biosimilars is gained. The Central Drugs Standard Control Organization (CDSCO)

released revised guidance on biosimilars in 2016,²³ while the Korean Ministry Of Food And Drug Safety did the same in 2015.²⁴ Since 2016 Health Canada also uses the terminology 'biosimilar' (previously 'subsequent entry biologics'),²⁵ and EMA continues to revise the overarching as well as product-specific guidelines.²⁶

In the development of a biosimilar, clinical trials are less sensitive than analytical techniques to detect differences between the biosimilar and the originator product,²⁷ and as technology evolves and characterisation techniques improve, it has been suggested that phase 3 clinical trials may become unnecessary. In Europe, biosimilars to some of the simpler molecules are already being approved without a phase 3 clinical trial, e.g., teriparatide²⁸ and enoxaparin sodium.²⁹ However, the importance of the need for a PK/PD trial should be stressed.³⁰ Approving a biosimilar without a phase 3 clinical trial might be not really an issue for regulatory agencies, but probably more for market uptake, since healthcare professionals are used to looking at clinical data and might lose confidence in these products when moving too quickly.

European regulators are aware that information about the marketing authorisation procedure for biosimilars might not be sufficiently understandable for physicians, patient organizations, and individual patients, and are working to further improve communication to and education of healthcare professionals and patients to increase confidence in this process.³¹ However, one can argue that there is a wide variation in patients' knowledge on biosimilars. They are either capable of reading the more technical documents (e.g., the EPAR) or else the healthcare professional plays a key role in explaining what a biosimilar is. Efforts should be made to promote the use of the EPAR and make people aware of existing information.

We believe it is worthwhile to discuss guidelines with different medicines agencies and work on convergence. Ongoing initiatives include the biosimilar cluster interactions between EMA, FDA, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and Health Canada, where there is exchange of views on general principles and sometimes on individual products. Also the specific biosimilar working group of the international pharmaceutical regulators forum, IPRF (now International Pharmaceutical Regulators Programme, after consolidation with the Inter-

23 Government of India, 'Guidelines on similar biologics: Regulatory requirements for marketing authorization in India, 2016' (2016) <<http://dbtbiocafety.nic.in/DBT2016-17/CDSCO-DBT2016.pdf>> accessed 9 February 2018.

24 MFDS, 'MFDS - Ministry Of Food And Drug Safety - Bio & Cosmetics > Biosimilar' (2018) <<http://www.mfds.go.kr/eng/index.do?nMenuCode=183>> accessed 6 February 2018.

25 Health Canada, 'Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs' (2018) <<https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/information-submission-requirements-biosimilar-biologic-drugs-1.html>> accessed 9 February 2018.

26 Peter Richardson, 'Biosimilars - EU/International update' (2017) <https://www.edqm.eu/sites/default/files/biosimilars_the_regulatory_framework_by_peter_richardson_ema.pdf> accessed 9 February 2018.

27 Laszlo Endrenyi et al, *Biosimilar Drug Product Development* (Taylor & Francis Group 2017).

28 EMA, 'Movymia: EPAR - Public assessment report' (2016) EMA/88527/2017; EMA, 'Terrosa: EPAR - Public assessment report' (2016) EMA/84371/2017.

29 EMA, 'Inhixa: EPAR - Public assessment report' (2016) EMA/536977/2016; EMA, 'Thorinane: EPAR - Public assessment report' (2016) EMA/536972/2016.

30 E Wolff-Holz, 'Initiatives at a glance: EMA perspective' (16th Biosimilar Medicines Conference – Biosimilar Medicines: unlocking the full potential of biologics, April 2018, London)

31 Klara Tiitso, 'Biosimilar medicines initiatives: an EMA perspective' (16th Biosimilar Medicines Conference – Biosimilar Medicines: unlocking the full potential of biologics, April 2018, London).

national Generic Drug Regulators Programme), tries to converge guidelines and exchanges information, e.g. on extrapolation of Indications and on a common format of public summary reports.³² Collaborations could also increase scientific capacity and reduce timelines for approval.

More harmonization in guidelines could contribute to facilitated global development of biosimilars, by avoiding unnecessary studies, leading to a less expensive biosimilar. Barriers to improve harmonization of guidelines might be political/strategical differences between jurisdictions, the number of regulators involved, the fact that not all countries are equally included in the discussion, and the difficulty to have the same level of discussion between regions that are more experienced and regions in a learning phase.

Initiatives on harmonization involve mainly developed countries. This is a first step, as developing countries may learn from the experience of more advanced countries. However, one framework might not be readily applicable in other jurisdictions. Differences exist in the financial capacity of countries, which raises the question whether scientific standards can be the same for each country. It is also important for developing countries to maintain their autonomy and make decisions with their local policy in mind. Some jurisdictions might accept more uncertainty, if this means patients get access to treatment. Agreement on general principles and sharing of real-world evidence on a global level can help coun-

tries gain experience with biosimilars and may facilitate biosimilar development.

V. Conclusion

Since the biosimilar market is rapidly developing due to patent expiration and loss of market exclusivity of different biological products, it is important to have a clear legal and regulatory framework for marketing authorisation of biosimilars. Today, we have more than ten years of experience in Europe with biosimilars.

To effectively shape biosimilars guidelines, a multi-stakeholder approach should be undertaken. Challenges associated with the marketing authorisation procedure for biosimilars might not be directly related to the procedure itself, but to concerns that the clinical community does not thoroughly understand the biosimilar development pathway. Education of healthcare professionals and patients will be essential to ensure uptake. Further convergence of guidelines and sharing of information will be necessary.

32 International Pharmaceutical Regulators Forum, 'Final Reflection Paper on Extrapolation of Indications in Authorization of Biosimilar Products' (2018) <<https://www.i-p-r-f.org/index.php/en/news/biosimilar-reflection-paper/>> accessed 1 June 2018; International Pharmaceutical Regulators Forum, 'Public Assessment Summary Information for Biosimilar (PASIB) – final documents after consultation' (2018) <<https://www.i-p-r-f.org/index.php/en/news/pasib-final/>> accessed 1 June 2018.