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UPDATE ON BIOSIMILAR MEDICINES

- **A biosimilar medicine is a biological medicine that is developed to be highly similar to an approved (reference) biological medicine**
- **A biosimilar medicine must establish similarity to the key characteristics of the molecular and biological activity of the reference medicine**
- **Biosimilar medicines are not the same as generic (chemical-based) medicines; therefore they may not be regarded as interchangeable with the reference biological medicine**
- **Biological and biosimilar medicines should be prescribed by brand name to enable ongoing safety monitoring of individual medicines**

INTRODUCTION

Biological medicines (biologics) have been used in clinical practice for many years in the management of conditions such as diabetes mellitus, blood clotting disorders and in the field of immunisation.[1,2,3] Advances in technological expertise over the last 30 years have enabled the development of more complex biological medicines, and they now play a vital role in the management of many other conditions, including cancer and autoimmune diseases.[2] Since 2006, biosimilar medicines – biologics that are highly similar to approved (reference) biologics[3] – have started to be introduced into the market, due to patent expiry of the reference biologics.[4] It is anticipated that increasing numbers of biosimilars will be available over the next few years, including recombinant proteins and monoclonal antibodies, for the management of certain cancers, autoimmune diseases and diabetes mellitus.[5] **The availability of less-costly biosimilar medicines enhances competition, with the potential to improve patient access to biological medicines.**[6] Therefore, biosimilars offer potential economic benefit to healthcare systems while addressing the issue of new treatment options brought about by advances in medical science.[6]
This bulletin will outline the background to the development of biological and biosimilar medicines and discuss their potential role in current clinical practice. It will also explain why biosimilar medicines cannot be regarded as generic medicines and therefore why they may not be regarded as interchangeable with the reference biologic.[5]

BIOLOGICAL MEDICINES

A biological medicine (biologic) is one that contains one or more active substances made by, or derived from, a biological source, including substances already present in the human body (e.g. proteins such as insulin and erythropoietin).[7] The broad category of biologics includes vaccines, blood and blood components, allergenic agents, somatic cells, gene therapy products, tissues, as well as recombinant therapeutic proteins.[2] In addition, advances in the understanding of the pathogenesis of many diseases have enabled the development of biologics which are aimed at specific cellular and molecular targets of disease (so called "targeted medicines").[8-11] Table 1 lists examples of currently available biologics of varying complexity, from replacement therapy to targeted therapy.

Table 1: Examples of Biological Medicines Used in Clinical Practice[1,2,9-15]

Biologic source	Examples	Mode of Action	Clinical Uses include
Animal-derived products	• Heparin • Vaccines	Prevents clotting process Generate antibody response	Anti-coagulation Immunisation
Blood-derived products	• Clotting factors	Receptor modulators	Blood-clotting disorders (replacement therapy)
Recombinant proteins	• Insulin/analogues • Erythropoietin • Etanercept	Receptor modulator Receptor modulator TNF-α inhibitor	Diabetes mellitus Chronic renal failure Arthritides, psoriasis
Monoclonal antibodies	• Trastuzumab • Infliximab	HER-2 receptor antagonist TNF-α inhibitor	Breast cancer Arthritides, IBD, psoriasis

HER-2= human epidermal growth factor receptor 2; TNF-α=tumour necrosis factor-α; IBD=inflammatory bowel disease

Typically, biologics are large complex molecules, with inherent variability in their structure, unlike classical small molecule (i.e. chemically-based) medicines. Table 2 outlines the main differences between biologics and small molecule medicines.[4]

Table 2: Differences between Biologics and Small Molecule Medicines[4]

Parameter	Biologic agents	Small molecule (chemically-based) medicines
Properties: • Size • Structure • Degradation • Variability	• Large • Complex • Complex mechanism(s) • Heterogeneous product	• Small • Simple • Precise and known • Single, defined structure
Manufacturing	Unique bank of living cells (unlikely to achieve identical copy)	Predictable chemical and reagent reaction (identical copy can be made)
Characterisation	Difficult to fully characterise	Easy to fully characterise
Stability	More sensitive to storage and handling conditions	Less sensitive to storage and handling conditions
Immunogenicity	Higher potential	Lower potential

The manufacturing process of a biologic requires multiple complex steps (including changes in temperature, pH, the type of expression systems used for recombinant protein production etc), each of which may have a profound impact on the final structure of the biological product.[16] In addition, complex biologics, such as monoclonal antibodies, (used for medical conditions such as cancer and autoimmune disease) are characterised not only by the amino acid sequence, but also by their three-dimensional (3-D) structure, the degree and location of their glycosylation sites, their isoform profiles and the degree of protein aggregation.[16] **The 3-D structure of the active protein and its aggregation status are important** as these properties will determine tissue distribution and binding, as well as interaction with other factors, such as target receptors. Therefore the structural properties of a biological agent are key determinants that dictate its pharmacology profile, including biological activity, clinical efficacy and safety in patients. It has been said that **for biological agents**, "**the process is the product**".[8]

Every biologic displays a certain degree of variability (micro-heterogeneity), even between different batches of the same product; this is caused by the inherent variability of the biological expression system and the manufacturing process (Table 2).[17] This so-called "**batch-to-batch variation**" is kept within strict acceptable limits (called release specifications), which must be monitored by the manufacturer and approved by the regulatory authority.[3,17,18]

Because they contain biologic material there may be the potential for a biological agent to induce an immune response in the patient, which could potentially affect clinical efficacy or safety (e.g. the development of neutralising antibodies to erythropoietin leading to red cell aplasia; hypersensitivity reactions).[16,18] Therefore all biologics must undergo **immunogenicity testing** prior to approval for use.[18]

In the past, some protein-based therapeutic agents (e.g. blood clotting factors and growth hormone), were harvested from animal or human sources with the associated risk of transmission of previously unknown infectious pathogens.[2] However due to the development of molecular biological techniques, therapeutic proteins are now synthesised in bacteria or other cells, which are transfected with the appropriate human genes, thereby eliminating the risk of transmission of infectious agents.[2,19]

Within the EU, an application for a marketing authorisation (licence) for a biologic must provide extensive evidence of quality (all aspects of manufacture including source materials) and sufficient evidence from clinical, animal and *in vitro* studies to show a positive risk-benefit analysis in the proposed therapeutic indication. All such applications are evaluated at EU level by the European Medicines Agency (EMA), in conjunction with experts from the regulatory agencies of each member state; full details are available on the EMA website (**www.ema.europa.eu**).

BIOSIMILAR MEDICINES

A biosimilar medicine (biosimilar) is defined as a biological medicine that contains a version of the active substance of an already authorised biologic (known as the reference biologic).[20] This means that the **candidate biosimilar must establish similarity to the key characteristics of the molecular and biological activity of the reference product** and will be expected to have similar clinical outcomes in terms of safety and efficacy.[3] However, **a biosimilar is not assumed to be identical to the reference biologic,** due to the inherent variability in the manufacturing of biologics (batch-to-batch variation, see also Table 2) and the complexity of making an exact copy.[19,20,21]

The process of authorisation for a biosimilar is different to that of a generic version of a chemically-based medicine, which is normally authorised for clinical use on the basis that (1) it can be shown that it contains a structurally identical active substance and (2) a bioavailability study, undertaken in humans, shows that the rate and extent to which the active substance reaches the circulation is equivalent to the reference medicine.[22] Although not required to undertake the extensive clinical trial programme that is required for novel biologics, **a biosimilar must show comparative quality, safety and efficacy (with respect to the reference biologic)**, based on a comprehensive comparability exercise, before it receives EU approval.[20,22-24] Table 3 lists the typical requirements for marketing authorisation of a biosimilar. It should be noted that the goal of a biosimilar development programme is not to demonstrate safety and efficacy for the candidate biosimilar *per se*, but rather to prove that its safety and efficacy are comparable to the reference biologic's profile.[22]

Table 3: Typical Requirements for Authorisation of a Biosimilar Medicine[20-25]

Parameter	Requirements
Quality aspects	Thorough head-to-head structural and biological activity studies between the biosimilar candidate and the reference biologic (involving comparison with several batches of the reference biologic) in order to demonstrate identical amino acid sequence as well as a highly comparable structure, glycosylation and full biological activity profile of the biosimilar (i.e. the specific ability or capacity of the agent to achieve a defined biological effect)
Non-clinical aspects	Specific testing in cell culture and in animal studies in order to more fully evaluate the functional aspects of the biosimilar candidate, and in particular to identify possible subtle differences in the functionality of the biosimilar compared with the reference biologic
Clinical aspects	Stepwise "clinical comparability" exercise - pharmacokinetic and pharmacodynamic studies, as well as immunogenicity studies, all normally supplemented by clinical studies (to show comparable safety and efficacy to the reference biologic)

Even if the candidate biosimilar shows comparable efficacy to the reference biologic, the **safety profile may be different, due to differences in the manufacturing process**.[17] Therefore, the clinical evaluation process must include safety data collection to enable comparison with the safety profile of the reference biologic, before marketing authorisation is granted.[24] In addition, since immune responses have been shown to affect clinical efficacy[15] and safety (and cannot be predicted from animal studies), the **immunogenic potential of each candidate biosimilar must be evaluated** (usually by measuring antibodies specifically generated against the biosimilar).[17,24,26] If the immune response is different to that observed with the reference biologic, further analyses will be required to elucidate the potential impact of the difference(s) noted.[24] Only very minor molecular differences between a biosimilar and its reference biologic are allowed, and then only if such differences have been convincingly demonstrated to be without any impact on efficacy and/or safety (including immunogenicity).[20-26]

Once it receives approval, every biologic (including biosimilars) is subject to additional post-authorisation safety monitoring; **this is identifiable by way of the inverted black triangle on the product information** [▼]; prescribers and patients are actively encouraged to report any safety concerns to the Health Products Regulatory Authority (**www.hpra.ie**).[27]

Extrapolation of Indications: Although the reference biologic may have several authorised therapeutic indications, the candidate biosimilar is not normally required to provide clinical efficacy data for each indication in order to be granted approval for each of these indications.[1,3,20] **The decision as to whether the biosimilar may be authorised for all indications of the reference biologic is taken on a case-by-case basis,** following evaluation of the totality of the data package presented to support the authorisation application. For example, extrapolation would require evidence to show that the mechanism of action of the active substance, in terms of achieving the therapeutic effect, is the same across each indication and that the immunogenic effect of the biosimilar has been adequately demonstrated.[1,3,17]

USE OF BIOSIMILAR MEDICINES IN CLINICAL PRACTICE

Since 2006, biosimilar versions of several reference biologics have been approved for use in the EU and many are available for use in Ireland. However, it would appear that the introduction of biosimilars into clinical practice is not as straightforward as it is with generic medicines.[5] Recent data have reported variable uptake rates for the different biosimilars that are marketed in the UK, while European data have shown that sales of biosimilar products account for a relatively small (albeit showing increasing annual growth) segment of the total EU biologics market.[5,6,28]

Table 4 outlines the list of active ingredients (and the reference biologics) for which biosimilars have been authorised in the EU, and their availability for use in Ireland. It is noteworthy that, with the exception of insulin glargine, the biologics for which biosimilars are currently available require prescription and monitoring by specialist physicians who are expert in management of the relevant disease.

Table 4: List of Active Biological Ingredients for which Biosimilar Medicinal Products have been approved for use in the EU[13-15,29-34]

Active Ingredient [Reference Biologic]	Therapeutic area*	Biosimilar available in Ireland**
Somatropin*** [Genotropin®]	Growth hormone deficiency conditions	Yes*
Epoetin*** [Eprex®]	Symptomatic anaemia associated with specified medical conditions	Yes*
Filgrastim*** [Neupogen®]	Neutropenia associated with cancer therapy / specified medical conditions	Yes*
Follitropin alfa*** [Gonal-F®]	Infertility conditions	Yes*
Infliximab*** [Remicade®]	Arthritides, inflammatory bowel disease, psoriasis	Yes*
Insulin glargine [Lantus®]	Diabetes Mellitus	*Due to be marketed shortly**
Etanercept*** [Enbrel®]	Arthritides, psoriasis	*Received positive opinion from the CHMP 19th November 2015. Awaiting issue of EU marketing authorisation*

**Exact indications approved for each medicine are listed in its Summary of Product Characteristics; **more than one biosimilar may be available; ***under specialist physician prescription and monitoring. CHMP=[EU scientific] Committee for Medicinal Products for Human use.

In Ireland, biosimilars are subject to a review by the National Centre for Pharmacoeconomics, in order to evaluate their potential cost-effectiveness within the Irish healthcare setting.[35] In addition, **the Health (Pricing and Supply of Medical Goods) Act 2013 in Ireland specifically excludes biological medicines (including biosimilars) from being added to the "list of interchangeable medicinal products"**.[1,36,37] This is in keeping with some regulatory and expert bodies who have recommended that patients are not automatically switched back and forth between biosimilars and reference biologics since, at the present time, the availability of data on the impact of this are limited.[1,3,5,16,38-40]

It is currently **recommended that brand names (as opposed to the active ingredient / non-proprietary names) are used when prescribing all biological medicines**, to facilitate traceability and for safety monitoring purposes. Table 5 summarises potential scenarios for use of a biosimilar in current clinical practice, as outlined by regulatory and expert bodies.

Table 5: Potential Clinical Settings for Use of a Biosimilar[1,3,38-40]

Clinical Scenario	Suitability for biosimilar	Comments
Previously untreated patient	Patient is suitable for biosimilar therapy (in agreement with prescriber and patient)	Prescribing by brand name is recommended to prevent future inadvertent switching to another brand* (and for safety monitoring)
Ongoing treatment with reference biologic / specific branded biosimilar	It is recommended that patient remains on his/her current brand* as switching back and forth between brands* is not recommended	Prescribing by brand name is recommended to prevent inadvertent switching to another brand* (and for safety monitoring)
Ongoing treatment with reference biologic where patient requests change / physician considers change to use of biosimilar	Final decision rests with the prescribing physician and patient, following full evaluation of the individual case and all available information	If a decision is made to change the prescribed brand, the dispensing pharmacist should be alerted to this change to prevent future inadvertent switching to another brand* (and for safety monitoring)

*includes biologic and biosimilar brands

FURTHER SOURCES OF INFORMATION ON BIOSIMILARS

- The **European Medicines Agency** website provides information on all biosimilar medicines that have been submitted for marketing authorisation within the EU. Check out the *European Public Assessment Reports* for human medicines at: **www.ema.europa.eu**
- The **Health Products Regulatory Authority** has published a Guide to Biosimilars for healthcare professionals and patients, which is available to download from its *Publications and Forms* section on its website: **www.hpra.ie**
- The **EU Commission** has issued a consensus document entitled "What you need to know about biosimilars" which provides scientific background to biosimilars and explores early economic data in relation to their use in the EU. It also has very useful Questions & Answers sections on biosimilars for patients and prescribers. It is available to download at: **http://ec.europa.eu/DocsRoom/documents/8242**

List of references available on request. Date of preparation: December 2015

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug.

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References: Update on Biosimilar Medicines

1. Guide to Biosimilars for Healthcare Professionals and Patients. Health Products Regulatory Authority. 14 October 2015 (AUT-GO141-1). Available online at https://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/guide-to-biosimilars-for-healthcare-professionals-and-patients-v1.pdf?sfvrsn=9. Accessed 15th October 2015
2. Hurko O, Target-based drug discovery, genetic diseases and biologics. Neurochemistry International 2012; 61: 892-8
3. What is a biosimilar Medicine? NHS England (2015). Available online at: www.england.nhs.uk/wp-content/uploads/2015/09/biosimilar-guide.pdf. Accessed 5th October 2015
4. Camacho L et al, Biosimilars 101: considerations for US oncologists in clinical practice. Cancer Medicine 2014; 3(4): 889-99
5. What are biosimilars and are they important? Drugs and Therapeutics Bulletin 2013; 51: 57-60
6. What you need to know about biosimilar medicinal products (consensus information document) EU Commission. Available online at: http://ec.europa.eu/DocsRoom/documents/8242. Accessed 5th November 2015
7. Biosimilar Medicines. Similar-biological-product applications Questions 1-43. European Medicines Agency. Available online at: www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jsp&mid=WC0b01ac0580281bf0. Accessed 15th October.
8. Braido F et al, from "blockbusters" to "biosimilars". An opportunity for patients, medical specialists and health care providers. Pulm Pharmacol Therap 2012; 25: 483-6
9. Agarwal SK et al, Biologic agents in rheumatoid arthritis: an update for Managed Care professionals. J Manag Care Pharm. 2011; 17 (9-b): S 14-S18
10. Amiot A and Peyrin-Biroulet L. Current, new and future biological agents on the horizon for the treatment of inflammatory bowel diseases. Ther Adv Gastroenterol 2015; 8(2): 66-82.
11. Rak Tkaczuk K and Jacobs I. Biosimilars in oncology: from development to clinical practice. Semin Oncol 2014; 41: S3-S12.
12. Herceptin® Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 18th November 2015
13. Remicade® Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 18th November 2015
14. Eprex® Summary of Product Characteristics. Available online at: www.hpra.ie. Accessed 19th November 2015
15. Enbrel® Summary of Product Characteristics. Available online at: www.hpra.ie. Accessed 19th November 2015
16. Muller R et al, The advent of biosimilars: challenges and risks. Swiss Medical Weekly 2014; 144:w13980
17. Weise M et al, Biosimilars: the science of extrapolation. Blood 2014; 124 (22): 3191-6

18. Weise M et al, Biosimilars: what clinicians should know. Blood 2012; 120 (26): 5111-7
19. Kinch M, An overview of FDA-approved biologics medicines. Drug Discovery Today 2015; 20(4): 393-8
20. Guideline on similar biological medicinal products (CHMP/437/04 Rev 1, 23 October 2014). Committee for Medicinal Products for Human Use (CHMP). Available online at: www.ema.europa.eu. Accessed 18th November 2015
21. Feagan B et al, The challenge of indication extrapolation for infliximab biosimilars. Biologicals 2-014; 42: 177-183
22. De Mora F, et al, Biosimilar: what it is not. BJCP 2015; 80: 949-56
23. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1) (EMA/CHMP/BWP/247713/2012, 22 May 2014). Committee for Medicinal Products for Human Use (CHMP). Available online at: www.ema.europa.eu. Accessed 18th November 2015
24. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014). Committee for Medicinal Products for Human Use (CHMP). Available online at: www.ema.europa.eu. Accessed 18th November 2015
25. Zuniga L and Calvo B, Biosimilars approval process. Regulatory Toxicology and Pharmacology 2010; 56: 374-7
26. Wadhwa M et al, Immunogenicity assessment of biotherapeutic products: An overview of assays and their utility. Biologicals 2015; 43: 298-306
27. Medicines under additional monitoring. Health Products Regulatory Authority. Available online at: http://www.hpra.ie/homepage/medicines/special-topics/new-eu-pharmacovigilance-legislation/medicines-under-additional-monitoring. Accessed 23rd November 2015
28. Farfan-Portet M-I et al, Are biosimilars the next tool to guarantee cost-containment for pharmaceutical expenditures? Eur J Health Econ 2014; 223-8
29. Genotropin® Summary of Product Characteristics. Available online at: www.hpra.ie. Accessed 19th November 2015
30. Neupogen® Summary of Product Characteristics. Available online at: www.hpra.ie. Accessed 19th November 2015
31. Gonal-F® Summary of Product Characteristics. Available online at: www.ema.europa.eu. Accessed 18th November 2015.
32. Lantus® Summary of Product Characteristics. Available online at: www.ema.europe.eu. Accessed 18th November 2015
33. European Public Assessments Reports: Biosimilars. European Medicines Agency. Available online at : http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars&genericsKeywordSearch=Submit. Accessed 23rd November 2015
34. Benapali® [etanercept] Summary of opinion (initial authorisation). European Medicines Agency 19th November 2015 (EMA/CHMP/693863/2015). Available online at: www.ema.europa.eu. Accessed 26th November 2015

35. Pharmacoeconomic evaluations. National Centre for Pharmacoeconomics. Available online at: http://www.ncpe.ie/pharmacoeconomic-evaluations/. Accessed 23rd November 2015
36. Update on prescribing and dispensing of medicines in Ireland. National Medicines Information Centre. 2014; Volume 20; number 6. Available online at: www.nmic.ie. Accessed 18th November 2015
37. The Health (Pricing and Medical Goods) Act 2013. Number 14 of 2013. Available online at: http://www.oireachtas.ie/documents/bills28/acts/2013/a1413.pdf. Accessed 21 January 2015
38. Position statement – biosimilar insulins. Diabetes UK (October 2013). Available online at: www.diabetes.org.uk/Biosimilar-insulins. Accessed 23rd November 2015
39. Position of Paul-Ehrlich-Institut regarding interchangeability of biosimilars. Available online at: http://www.pei.de/EN/medicinal-products/antibodies-immunoglobulins-fusion-proteins/monoclonal-antibodies/biosimilars/position-pei-interchangebility-biosimilars-content.html. Accessed 1st December 2015
40. Biosimilar medicines. Medicines Evaluation Board (Netherlands). Available online at: : http://english.cbg-meb.nl/human/for-healthcare-providers/contents/biosimilar-medicines. Accessed 1st December 2015