12 Regulatory Framework for Biosimilars

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INTRODUCTION

The term "biopharmaceuticals" is used to describe biotechnologically derived drug products. Biopharmaceuticals are protein-based macromolecules and include insulin, human growth hormone, the families of the cytokines and of the monoclonal antibodies, antibody fragments, and nucleotide-based systems such as antisense oligonucleotides, siRNA, and DNA preparations for gene delivery. A "generic" version of a biopharmaceutical may be introduced after patent expiration of the innovator's product. However, the generic paradigm as it has developed for low molecular weight actives over the years cannot be used for biopharmaceuticals. In the European Union and the US regulatory systems, the term "biosimilar" was coined for copies of brand name, new biopharmaceuticals. Different than for small molecule generic versions, in most cases, comparative clinical testing of the biosimilar product must include a robust evaluation of safety and confirmation of efficacy in appropriate patient populations.

The aim of this chapter is to provide a comprehensive view on current regulatory policies related to the approval of a biosimilar product in the EU and USA. Table 12.1 provides definitions of terms relevant to this chapter.

BACKGROUND

The mission of a regulatory authority is to "Assure that safe, effective, and high-quality drugs are marketed in the country and are available to the people." Safety of an innovator's drug product, be it a small molecule or biopharmaceutical, is established through preclinical studies in vitro and in animals and through controlled clinical studies in humans. Efficacy is established through clinical studies in patients. A description of drug quality is also part of the submitted dossier. In order to have a better understanding of the regulatory process involved, it is essential to appreciate the basic difference between small molecule drugs and macromolecular biopharmaceuticals (cf. Tables 12.2 and 12.3). Small molecules are chemically synthesized and can be fully characterized. On the other hand, most biopharmaceuticals are produced in a living system such as a microorganism, plant or animal cells and are difficult to fully characterize. The proteins are typically complex molecules and are unlikely to be shown to be structurally identical to a reference product. Differences in a manufacturing process may lead to alteration in the protein structure (Crommelin et al. 2003). Protein structures can differ in at least three ways: in their primary amino acid sequence, in (posttranslational) modification to those amino acids sequences (e.g., glycosylation), and in higher-order structure (folding patterns and (unwanted) aggregate formation. Advances in analytical sciences enable protein products to be extensively characterized with respect to their physicochemical and biological properties. However, current methodology may not detect all relevant structural and functional differences between two proteins and the interpretation of the impact of these differences is often unclear (Chaps. 2 and 3).

For the approval of a (small molecule) generic product, it must be pharmaceutically equivalent (same dosage form, strength of active, route of administration, and labeling as brand-name drug) and bioequivalent. Depending on the active, it should have the same in vitro dissolution, pharmacokinetic, pharmacodynamic, and clinical outcome profile as the brand name, innovation drug. For the more complex biological products, such a simple assessment of pharmaceutical equivalence and bioequivalence alone is not an option.

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FDA	US Food and Drug Administration
EMA	European Medicines Agency
Low molecular weight drug	Classical medicinal product prepared by chemical synthesis
Generic product	Non-patented medicinal product of low molecular weight and therapeutically equivalent
Biopharmaceutical drug	The term "biopharmaceuticals" is used to describe biotechnologically derived drug products. Biopharmaceuticals are protein-based macromolecules and include insulin, human growth hormone, the families of the cytokines and of the monoclonal antibodies, antibody fragments, and nucleotide-based systems such as antisense oligonucleotides, siRNA, and DNA preparations for gene delivery[a]
Biosimilar product	A biosimilar is a biopharmaceutical product that is highly similar to an already approved biopharmaceutical product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biosimilar and the approved biopharmaceutical product in terms of safety, purity, and potency
Second-generation biopharmaceuticals	A second-generation biopharmaceutical product is derived from an approved biopharmaceutical product which has been deliberately modified to change one or more of the product's characteristics

[a]For the FDA, "biopharmaceuticals" are part of the "biological product" group, which also include viruses, sera, vaccines, and blood products

Table 12.1 ■ Definitions

Small, low molecular weight drugs	Biopharmaceuticals
Low molecular weight	High molecular weight
Simple chemical structure	Complex three-dimensional structure
Chemically synthesized	Produced by living organism
Easy characterization	Difficult to impossible to fully characterize
Synthetically pure	Often heterogeneous
Rarely produce immune response	Prone to eliciting an immune response

Table 12.2 ■ Difference between small, low molecular weight drugs and biopharmaceuticals

Generic (small molecule) product	Biosimilar product
Drug Price Competition and Patent Restoration Act of 1984	The Biologics Price Competition and Innovation Act of 2009 (BPCI Act)
Food Drug, and Cosmetic Act 505(j)	Public Health Service Act 351(k)
Pharmaceutical equivalent	Pharmaceutical equivalent
Bioequivalent	Non-clinical comparison (animal studies)
Pharmacokinetics	Physicochemical analysis
Pharmacodynamics	Clinical comparison (in humans)
Clinical comparison (not standard)	
In vitro analysis	

Table 12.3 ■ Drug approval for generic product and biosimilar product (FDA)

Both for a generic and for a biosimilar product, a complete set of information on Chemistry, Manufacturing, and Controls (CMC)section) is needed in the dossier submitted for approval to ensure that the drug substance and the drug product are pure, potent, and of high quality. The CMC section should include full analytical characterization, a description of the manufacturing process and test methods, and stability data. In addition to the establishment of safety and efficacy of the drug product, the approval process requires manufacturing of the drug product under controlled current good manufacturing practice (cGMP) conditions. The cGMP requirement ensures identity, potency, purity, and quality of the final product.

■ Characterization of Biosimilar Product (Details)

For biosimilars, a full comparison with the innovator's product characteristics (e.g., the primary, secondary, tertiary and quaternary structure, posttranslational modifications) and functional activity(ies) should be considered. A comprehensive understanding of all steps in the manufacturing process, process controls, and the use of a Quality-by-Design (cf. Chap. 4) approach will facilitate consistent manufacturing of a high-quality product.

As stated before, for complex proteins, the full characterization and assessment of equality of the biosimilar and innovator's product may not be possible with our present arsenal of analytical techniques

(see Chap. 3). This means that for establishing biosimilarity, as a rule, clinical studies are required in the regulatory protocols described later on in this chapter.

Characterization of the active moiety and impurity/contaminant profiling plays an important role in the development process of a biosimilar drug product. The technological advances in instrumentation significantly improved identification and characterization of biotech products (Table 12.4 and Chap. 3). It is acknowledged that no one analytical method can fully characterize the biotech product. A collection of orthogonal analytical methods (Chap. 5) is needed to piece together a complete picture of a biotech product. Determining how a small, homogeneous protein is folded in absolute terms can be accomplished using crystal X-ray diffraction. This can be difficult, expensive, and nonrealistic to perform in the formulated drug product and on a routine basis. Moreover, X-ray diffraction analysis does not pick up low levels of conformational contaminants. The most basic aspect of assessing its identity is to determine its covalent, primary structure using liquid chromatography tandem mass spectrometry (LC/MS/MS), peptide mapping/amino acid sequencing (e.g., via the Edman-degradation protocol), and disulfide bond-locating methods. Through circular dichroism, Fourier transform infrared and fluorescence spectroscopy, immunological methods, chromatographic techniques, etc., differences in secondary and higher-order structures can be monitored. Selective analytical methods are used to determine the purity as well as impurities of the biotech product. Methods here include again chromatographic techniques and gel electrophoresis, capillary electrophoresis, isoelectric focusing, static and dynamic light scattering, and ultracentrifugation. Inadequate characterization can result in failure to detect product changes that can impact the safety and efficacy of a product. The characterization factors that impact safety and efficacy of the product should be identified in the product development process (cf. Chap. 3)

UV absorption spectroscopy
Circular dichroism spectroscopy
Fourier transform infrared spectroscopy (FTIR)
Fluorescence spectroscopy
Nuclead magnetic resonance spectroscopy (NMR)
Calorimetric approaches
Bio-assays
Immunochemical assays
Enzyme linked immunosorbent assay (ELISA)
Immunoprecipitation
Biosensor (Surface plasma resonance, SPR; quartz crystal microbalance, QCM)
Potency testing
In cell lines
In animals
Chromatographic techniques
Reverse phase high performance liquid chromatography, RP-HPLC
Size exclusion chromatography (SEC)
Hydrophobic interaction chromatography (HIC)
Ion-exchange chromatography (IEC)
Peptide mapping
Electrophoretic techniques
Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)
Isoelectric focusing electrophoresis (IEF)
Capillary zone electrophoresis (CZE)
Field flow fractionaction (FFF) or asymmetrical flow field-flow fractionation (AF4)
Ultracentrifugation
Static and dynamic light scattering (SLS and DLS)
Electron microscopy
X-ray techniques
Mass spectrometry (MS)
Adapted from Crommelin et al. (2003)

Table 12.4 ■ Analytical techniques for monitoring protein structure

REGULATORY FRAMEWORK IN THE USA

FDA defines a generic drug as a copy that is the same as a brand-name drug in dosage form, strength, route of administration, quality, purity, safety, performance, and intended use. A generic product is a copy of the brand name, innovator's product, except for the inactive ingredients and/or formulations. The required dossier for market authorization focuses on only two aspects. The generic (small molecule) drug product should be pharmaceutically equivalent and bioequivalent to the brand-name product and is therefore therapeutically equivalent and interchangeable with the brand-name drug product. A generic product has the same active ingredient, and therefore, the safety and efficacy of the active ingredient is already established. The only question is the efficacy of the generic formulation, and this is assured by the bioequivalence study in healthy volunteers or patients.

In the case of small molecules, the identity of the active substance is established through a validated chemical synthesis route, full analysis of the active agent, impurity profiling, etc. In the case of biopharmaceuticals, this is, generally speaking, not possible. This biopharmaceutical product contains the active ingredient which is similar (but not necessarily equal) in characteristics to the reference product. For this reason, the generic biopharmaceutical products are referred to as biosimilar products (cf. Table 12.1).

■ Regulatory Pathway for Biosimilar Legal Framework

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was enacted as part of the Affordable Care Act on March 23, 2010. The BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological referenced product. The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act that established abbreviated pathways for the approval of drug products under the Federal Food, Drug, and Cosmetic (FDC) Act. Section 351(k) of the Public Health Service (PHS) Act, added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. A 351(k) application must contain information demonstrating that the biological product is biosimilar to a reference product based upon the data derived from analytical studies, animal studies, and clinical studies. To meet the *higher* standard of interchangeability, sufficient information must be provided to demonstrate biosimilarity. Interchangeable products may be substituted for the reference product without intervention of the prescribing health-care provider (note: this is the US interpretation of the term "interchangeable." It is interpreted differently in other parts of the world, e.g., in European countries). The BPCI Act also includes several exclusivity terms.

■ Biosimilar Drug Approval Process: the Principles

Approval of the biosimilar product is based on scientific considerations in demonstrating biosimilarity to a reference product. The scientific considerations will be on the basis of a risk-based "totality-of-the evidence" approach in comparing the proposed biosimilar (test) and the reference product. The term "totality-of-evidence" includes all data and information submitted in the application, including structural and functional characterization, nonclinical evaluation, human PK and PD data, clinical immunogenicity data, and comparative clinical study(ies) data.

Analytical studies serve as a foundation of a biosimilar development program. The reference product should be adequately characterized with respect to the critical quality attributes, clinically active components, mechanism of action and structure-function relationships. In addition, biochemical characterization, and functional characterization should be carried out. Once the reference product is characterized in detail, comparative tests between the reference product and the biosimilar product should be done.

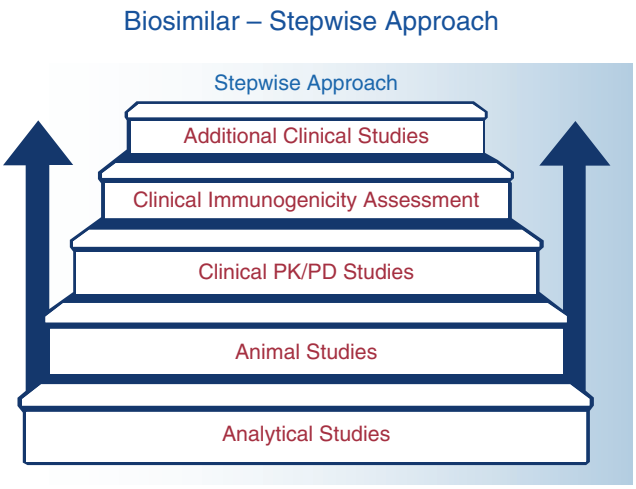

Figure 12.1 ■ (FDA/CDER Learn Program. FDA Continuing Education Course on Biosimilars. February 18, 2016) New figure-redraw

FDA recommends the use of a stepwise approach for the development of a biosimilar product: (1) Analytical Studies (2) Animal Studies (3) Clinical PK/PD Studies (4) Clinical Immunogenicity Assessment and (5) Additional Clinical Studies as necessary. This is shown schematically in Fig. 12.1. At each step, the sponsor should evaluate the level of residual uncertainty about the biosimilarity of the proposed biosimilar product to the reference product and identify the next step to address uncertainty. If there is a residual uncertainty about biosimilarity after conducting structural analyses, functional assays, animal testing, human PK and PD studies, and a clinical immunogenicity assessment, then additional clinical data may be needed to adequately address that uncertainty. A clinical study should be designed to investigate whether there are clinically meaningful differences between the biosimilar product and its reference product.

The requirements for approval of biosimilar products are based on the structural complexity and clinical knowledge of and experience with the reference biopharmaceutical product. For example, protein products such as growth hormone have known and relatively simple chemical structures. In addition, extensive manufacturing and clinical experience is available for these products. On the other hand, recFactor VIII is a large, highly complex molecule with several isoforms. Because of the varying complexity of biotech-derived products, the requirements for the approval process should be structured on a case-by-case basis. The following information is required for product approval:

- Structural information—primary, secondary, tertiary, and, if relevant, quaternary structure

information, including information regarding the glycosylation pattern, if relevant.
- Manufacturing process
- Quality attributes and clinical activities
- Pharmacokinetic-pharmacodynamic information, mechanism of drug action
- Clinical experience, efficacy and toxicity information

FDA prefers US-reference listed drug (RLD) for comparability studies—analytical, clinical and PK/PD, to demonstrate biosimilarity. For a PK/PD clinical study the most sensitive dose to detect and evaluate differences in the PK and PD profiles is suggested. FDA is encouraging a two-step process: approval of the biosimilar first and then interchangeability designation. To achieve designation of interchangeability, a special study should be designed in patients. The term interchangeable or interchangeability, in reference to a biological product means that in the USA—dependent on state laws- the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. The proposed interchangeable product "can be expected to produce the same clinical result as the reference product in a given patient." To support a demonstration of interchangeability, the sponsor must first show that the proposed product is biosimilar to the reference product. A dedicated switching study design and analysis is proposed for interchangeability designation (FDA 2017a). Up until March 2018 no biosimilar product has been designated as interchangeable.

Biosimilar products are different from second-generation biopharmaceuticals, e.g., pegylated G-CSF and interferon-alpha, and darbepoetin. The second-generation biopharmaceuticals have improved pharmacological properties/biological activity compared to an already approved biopharmaceutical product which has been deliberately modified. The second-generation products are marketed with the claim of clinical superiority. The second-generation biopharmaceuticals require a full New Drug Application (NDA) and are not interchangeable with the brand-name product.

■ FDA Guidance Documents on Biosimilars

The regulatory process for biosimilars is an evolutionary process. In April 2015 the FDA released two final guidance documents on biosimilar product development: (1) Scientific considerations in demonstrating biosimilarity to a reference product, (2) Quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference product (FDA 2015). In addition, FDA has published the guidance on Clinical pharmacology data to support a demonstration of biosimilarity to a reference product (FDA 2016a), draft guidance on Considerations in demonstrating interchangeability with a reference product (FDA 2017a), draft guidance on Labeling for biosimilar products (FDA 2016b) and guidance on Nonproprietary naming of biological products (FDA 2017b). These guidances are intended to assist sponsors in demonstrating that the proposed therapeutic protein product is biosimilar to a reference product under section 351(k) of the PHS Act.

Clinical Studies

As a rule, clinical studies are required to assure safety and efficacy of the biosimilar candidate product. The comparative clinical trial exercise is a stepwise procedure that should begin with pharmacokinetic and pharmacodynamic studies when necessary followed by clinical efficacy and safety trials. The choice of the design of the pharmacokinetic study, i.e., single dose and/or multiple doses, should be justified. Normally, comparative clinical trials are required for demonstration of clinical efficacy and safety. However, in certain cases, comparative pharmacokinetic/pharmacodynamic studies between the biosimilar product and the reference product using biomarkers may prove to be adequate.

Nonproprietary Naming (FDA 2017b)

The proper name for the approved biological product will include a core name (nonproprietary name) and an FDA-designated suffix. A distinguishing suffix that is devoid of meaning and composed of four lower case letters will be attached with a hyphen to the core name of each originator biological product, related biological product or biosimilar product. Use of shared core name will indicate a relationship among products, for example:
- replicamab-cznm,
- replicamab-jhxf.

This naming convention will facilitate pharmacovigilance for biological and biosimilar drug products.

At present the following biosimilars (not-interchangeable) are approved by FDA (see list in the Purple Book, FDA 2018): adalimumab-adbm Cyltezo; adalimumab-atto Amjevita; bevacizumab-awwb Mvasi; etanercept-szzs Erelzi; filgrastim-sndz Zarxio; infliximab-abda Renflexis; infliximab-dyyb Inflectra; infliximab-qbtx Ixifi; trastuzumab-dkst Ogivri

Labeling

- Information and data from a clinical study of a proposed biosimilar product should be described in its labeling only when necessary to inform safe and effective use by a health care practitioner.

EMA REGULATORY FRAMEWORK

The regulatory process for the approval of biopharmaceuticals and biosimilars in the EU follows a centralized (i.e., not a national competence of the member states) route through the European Medicines Agency (EMA). The EMA started issuing guidance documents on the regulatory process for biosimilars in 2004. The overarching guideline for biosimilar drug products is CHMP/437/04, revised in 2014. From 2006 on, EMA published a series of guidance documents on biosimilar medical products containing specific biotechnology-derived proteins as active substance, e.g., on recombinant erythropoietin, somatropin, granulocyte colony-stimulating factor (G-CSF), and human insulin. These guidelines define key concepts/principles of biotechnology-derived proteins and discuss quality issues and non-clinical and clinical issues and are regularly updated (EMA 2018a).

■ Status of Biosimilars in the EU

The EMA (EMA 2017) published an informative brochure on biosimilars explaining in detail its position on different aspects of the approval process and use of biosimilars. It also provides definitions on the terms interchangeability and substitution. It is not EMA but the individual EU countries that decide on interchangeability and substitution rules in their territory. Table 12.5 lists the biosimilars approved by the EMA (2018b)). This list is growing. The market share of biosimilars varies strongly per country and per biosimilar product (QuintilesIMS 2017). The advent of the biosimilars to the market led to questions on what grounds to choose, either for the originator's product or for the biosimilar product. The *European Journal of Hospital Pharmacists* published a document: "*Points to consider in the evaluation of biopharmaceuticals*", followed by '*How to select a biosimilar'* (2013) Health-care providers can use these publications to make a documented choice (Kraemer et al. 2008; Boone et al. 2013).

Nonproprietary Naming

'As required by EU law, every medicine will have an invented name (trade name or brand name) together with the active substance name (i.e., the INTERNATIONAL NONPROPRIETARY NAME, OR INN, which is assigned by WHO). For identifying and tracing biological medicines in the EU, medicines have to be distinguished by the trade name and batch number' (EMA 2017).

THE CHALLENGE AND THE FUTURE

A major problem today is the inadequate definition of the relationship between the complex structure and function of protein pharmaceuticals. Analytical tools are becoming increasingly sensitive and provide more detailed information regarding the molecular structure. This may allow for certain biopharmaceuticals to be shown to be pharmaceutically equivalent, therapeutically equivalent, and interchangeable on the basis of a validated analytical definition alone. For instance, for relatively small protein molecules like insulin, a well-characterized biopharmaceutical product, equivalence may be established using presently available analytical techniques (Table 12.4). But for larger and complex proteins, it is not possible to characterize the molecule in full detail and establish equivalence. In such a scenario, clinical safety and efficacy studies will be needed to establish equivalence.

Science-based regulatory policies are being developed. They are dynamic. They have evolved over the years and will continue to do so based on the development of superior analytical techniques to characterize the products, on introducing improved manufacturing practices and controls and on growing clinical and regulatory experience. Rigorous standards of ensuring product safety and efficacy must be maintained and, at the same time, unnecessary and/or unethical duplication trials must be avoided.

The approval of a biosimilar product should depend on the complexity of the molecule. A gradation scheme should be designed for the drug approval process rather than using a "one size fits all" model. From simple chemically synthesized molecules to highly complex molecules, e.g., from a chemically synthesized simple molecule such as acetaminophen to cyclosporine, to insulin, to human growth hormone, to interleukins, to erythropoietin type of growth factors, to albumin, to monoclonal antibodies, and to factor VIII, different regulatory regimens are required.

The regulatory processes for biosimilars are following an evolutionary route. We learn from new information coming in every day; we evaluate the data, adjust the rules, and develop new protocols to make sure that the patient keeps on receiving high-quality, safe and effective biopharmaceuticals.

SELF-ASSESSMENT QUESTIONS

Question 1: Human growth hormone has a molecular weight of around 22 kDa (see Chap. 20) and erythropoietin of 34 kDa (see Chap. 24). Why does the EMA request different clinical protocols for approval of a biosimilar product for these protein drugs?

Question 2: Can the US approved biosimilar product be interchanged with the brand name product?

Answer 1: Human growth hormone is a non-glycosylated protein with a well-established primary sequence; erythropoietin is heavily glycosylated with a

Biosimilar	CHMP positive opinion	Indication	Marketing Authorisation Holder	Authorised
Somatropin (Omnitrope®)	jun-03	Prader-Willi Syndrome, Dwarfism, Pituitary, Turner Syndrome	Sandoz	apr-06
Epoetin alfa (Abseamed®)	okt-08	Anemia, Kidney Failure, Chronic Cancer	Medice	aug-07
Epoetin alfa (Binocrit®)	jun-07	Anemia, Kidney Failure, Chronic Cancer	Sandoz	aug-07
Epoetin alfa (Epoetin Alfa Hexal®)	jun-07	Anemia, Kidney Failure, Chronic Cancer	Hexal	aug-07
Epoetin zeta (Retacrit®)	oct-07	Anemia, Kidney Failure, Chronic Blood Transfusion, Autologous Cancer	Hospira	dec-07
Epoetin zeta (Silapo®)	oct-07	Anemia, Kidney Failure, Chronic Blood Transfusion, Autologous Cancer	Stada	dec-07
Filgrastim (Ratiograstim®)	jul-08	Neutropenia, Hemato poietic Stem Cell Transplantation, Cancer	Ratiopharm	sep-08
Filgrastim (Tevagrastim®)	jul-08	Neutropenia, Hematopoietic Stem Cell Transplantation, Cancer	Teva	sep-08
Filgrastim (Filgrastim Hexal®)	nov-08	Neutropenia, Hematopoietic Stem Cell Transplantati on, Cancer	Hexal	feb-09
Filgrastim (Zarzio®)	nov-08	Neutropenia, Hematopoietic Stem Cell Transplantation, Cancer	Sandoz	feb-09
Filgrastim (Nivestim®)	mrt-10	Neutropenia, Hematopoietic Stem Cell Transplantation, Cancer	Hospira/Pfizer	jun-10
Infliximab (Remsima®)	jun-13	Spondylitis, AnkylosingArthritis, RheumatoidColitis, UlcerativeArthritis, PsoriaticCrohn Disease, Psoriasis	Celltrion	sep-13
Infliximab (Inflectra®)	jun-13	Spondylitis, AnkylosingArthritis, RheumatoidColitis, UlcerativeArthritis, PsoriaticCrohn Disease, Psoriasis	Hospira	sep-13
Follitropin alfa (Ovaleap®)	aug-13	Anovulation	Teva	sep-13
Filgrastim (Grastofil®)	jul-13	Neutropenia	Apotex	oct-13
Follitropin alfa (Bemfola®)	jan-14	Anovulation	Finox	mrt-14
Filgrastim (Accofil®)	jul-14	Neutropenia	Accord Healthcare	sep-14
Insulin glargine (Abasaglar®)	jun-14	Diabetes Mellitus	Eli Lilly	sep-14

Table 12.5 ■ EMA list of approved biosimilars, Jan 2018

Etanercept (Benepali®)	nov-15	Rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis and plaque psoriasis	Samsung Bioepis	jan-16
Infliximab (Flixabi®)	mrt-16	Rheumatoid arthritis, adult and paediatric Crohn's disease, ulcerative colitis, paediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis	Samsung Bioepis	mei-16
Enoxaparin (Inhixa®)	jul-16	Prevention and treatment of various disorders related to blood clots	Techdow	sep-16
Enoxaparin (Thorinane®)	jul-16	Prevention and treatment of various disorders related to blood clots)	Pharmathen	sep-16
Insulin glargine (Lusduna®)	nov-16	Diabetes Mellitus	MSD	jan-17
Teriparatide (Movymia®)	nov-16	Osteoporosis	STADA Arzneimittel	jan-17
Teriparatide (Terrosa®)	nov-16	Osteoporosis	Gedeon Richter	jan-17
Rituximab (Truxima®)	dec-16	Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis	Celltrion	feb-17
Adalimumab (Amgevita®)	jan-17	Rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, paediatric Crohn's disease, ulcerative colitis and uveitis.	Amgen	mrt-17
Adalimumab (Solymbic®)	jan-17	Rheumatoid arthritis, enthesitis-related arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis	Amgen	mrt-17
Etanercept (Erelzi®)	apr-17	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis, paediatric plaque psoriasis.	Sandoz	jun-17
Rituximab (Riximyo®)	apr-17	Non-Hodgkin's lymphoma, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis.	Sandoz	jun-17
Rituximab (Rixathon®)	apr-17	Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis.	Sandoz	jun-17
Rituximab (Blitzima®)	may-17	Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, granulomatosis with polyangiitis and microscopic polyangiitis.	Celltrion	jun-17

Table 12.5 ■ (continued)

Rituximab (Rituzena®)	may-17	Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, granulomatosis with polyangiitis and microscopic polyangiitis.	Celltrion	jun-17
Rituximab (Ritemvia®)	may-17	Non-Hodgkin's lymphoma, granulomatosis with polyangiitis and microscopic polyangiitis.	Celltrion	jun-17
Insulin Lispro (Insulin lispro Sanofi®)	may-17	Diabetes mellitus.	Sanofi	jun-17
Adalimumab (Imraldi®)	jun-17	Rheumatoid Arthritis, Juvenile idiopathic arthritis, Axial spondyloarthritis, Psoriatic arthritis, Psoriasis, Paediatric plaque psoriasis, Hidradenitis suppurativa, Crohn's disease, Paediatric Crohn's disease, Ulcerative colitis, Uveitis.	Samsung Bioepis UK Limited	aug-17
Adalimumab (Cyltezo®)	sep-17	Rheumatoid Arthritis, Juvenile idiopathic arthritis, Axial spondyloarthritis, Psoriatic arthritis, Psoriasis, Paediatric plaque psoriasis, Hidradenitis suppurativa, Crohn's disease, Paediatric Crohn's disease, Ulcerative colitis, Uveitis.	Boehringer Ingelheim	nov-17
Trastuzumab (Ontruzant®)	sep-17	Metastatic breast cancer, Early breast cancer, Metastatic gastric cancer.	Samsung Bioepis UK Limited	Awaiting authorisation
Bevacizumab (Mvasi®)	nov-17	Fallopian Tube Neoplasms, Non-Small-Cell Lung Carcinoma, Ovarian Neoplasms, Renal Cell Carcinoma, Peritoneal Neoplasms, Breast Neoplasms	Amgen	Awaiting authorisation

Table 12.5 ■ (continued)

number of isoforms with more analytical challenges. The EMA guidance documents giving more details can be found on the EMA website.

Answer 2: No, it cannot be interchanged unless they do interchangeability studies and get FDA approval.

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