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Biological agents and biosimilars: Essential information for the internist

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ABSTRACT

Biologics embrace a wide range of substances synthesized by cells or living organisms by means of different biological processes, including recombinant DNA technology, controlled gene expression, or antibody technologies. A biosimilar establishes similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise. Minimizing development costs and accelerating their market access create a convergence of interests between health services, worried about sustainability, and generic manufacturers. While the demonstration of bioequivalence is sufficient for small synthetic molecules, this approach is not scientifically applicable to a copy of biological drug constituted by large and complex molecules, which are similar but not identical to the originator and are also subject to different post-translational processes. Internists should be confident that the development process of biosimilars ensures a comparable risk-to-benefit balance with the originators. On the basis of available evidence and pharmacovigilance network, there are no grounds to believe that the use of a biosimilar carries more risks for the patient than the use of an originator. Since the first biosimilar was authorized in Europe in 2006, no clinical alerts have raised red flags about the established EMA biosimilar pathway. In this article, we discuss some of the most frequent concerns raised by clinicians about biosimilars and try to explains the scientific principles underlying the biosimilar concept established in the EU in order to license biosimilar drugs.

1. Introduction

Biological medicines have revolutionized the treatment of many acute and chronic conditions including neutropenia, enzyme or hormone deficiency, a wide range of inflammatory and autoimmune diseases, and cancer [1]. They have improved the management of diseases, including a more effective control of symptoms, quality of life, productivity and other relevant clinical and social outcomes [2]. By the end of 2009 biological drugs in phase III of clinical development made up to 38% of all pipeline products for the pharmaceutical industry [3]. These shifts in drug development and approval have subsequently been reflected in commercial adoption rates. Most new drugs that receive regulatory approval are under patent protection. Patent life is typically 20 years from the time of filing a submission, which is usually done before clinical testing on humans begins. The forthcoming patent expiries of several, widespread biological drugs open the opportunity to the market for biosimilars, which should be able to improve the sustainability of health services especially in therapeutic areas such as oncology, where demand and costs of new therapies are consistently high [4].

In the last decade, the health authorities have established specific guidelines to demonstrate clinical comparability between biosimilars and their originators [5]. Recently, the European Medicines Agency (EMA) received the first marketing authorization application (MAA) for the biosimilar monoclonal antibody (mAb) infliximab. The intrinsic complexity of antibody structure, the heterogeneity introduced by subtle changes in product manufacturing, and the potential complications associated with the introduction of biosimilars to the marketplace must be brought to the forefront of critical discussion [1].

In this article, we discuss some of the most frequent concerns raised by clinicians about biosimilars and try to explain the scientific principles underlying the biosimilar concept as established in the EU community in order to allow the licensing of biosimilars.

2. What is a biological agent? How are they manufactured?

Biologics embrace a wide range of substances synthesized by cells or living organisms by means of different biological processes, including recombinant DNA technology, controlled gene expression, or antibody technologies. The *biopharmaceutical era* began in the early 1980s and currently represents one of the fastest growing sectors of the drug industry worldwide. Monoclonal antibodies (e.g. infliximab, etanercept,

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adalimumab, golimumab, trastuzumab, rituximab), recombinant hormones (e.g. somatropine, human erythropoietins, glargine insulin), and blood growth factors (e.g. filgrastim) are commonly used in Western countries to treat rare diseases as well as high prevalence illnesses, such as cancer and diabetes. Several advanced medicinal products based on gene and cell therapy are expected to become available in the next decade.

Compared with chemically synthesized drugs, biologics have 100- to 1000-fold larger molecular weight and are relatively heterogeneous. Hence, their physiochemical structure is much more complex and difficult to characterize. Table 1 summarizes the different characteristics of chemically synthesized drugs and biosimilars. The biopharmaceutical manufacturing process is more complex, requiring several steps (Fig. 1) [6], each of which is subject to variations affecting the biological characteristics and the clinical properties of the drug.

Changes in qualitative and quantitative biological parameters can result from unknown deviations (*drift*) and known changes (*evolution*) in the manufacturing process. Although some variability is normal, some product attributes may fall outside intended target values [7]. Discussions on the issues related to manufacturing biologics are often summarized stating that "*the process is the product*." Because the manufacturing process is the basis for the characterization of biologics, there will never be two identical biopharmaceuticals.

3. What is a biosimilar?

A biosimilar is defined by the European Medicines Agency (EMA) as "a biological medicinal product that contains a (copy) version of the active substance of an already authorized original biological medicinal product (reference medicinal product). A biosimilar establishes similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise." This requires a full qualitative documentation, appropriate preclinical pharmacokinetic and pharmacodynamic studies, and ultimately comparative studies with the originator to determine the relative efficacy and safety [8]. Similarly, the Food and Drug Administration (FDA) defines biosimilar as "a product that is highly similar to a US-licensed reference biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product." Both EMA and FDA require that a biosimilar product deliver the same dosage and strength as the reference product and that it can be used for the same indications as the reference product [8,9].

4. Manufacturing process of biological agents and biosimilars

Biological agents and biosimilars are essentially similar, thus the statement "*the process is the product*" is sometimes used to emphasize the differences between an originator and biosimilar(s). However, it applies to several manufacturing changes of any biologics, including an originator. Any originator is actually characterized by *micro-heterogeneity* between different batches of the same product, due to the inherent variability of the expression of biological systems and production process. It reasonable to affirm that most of the marketed originators are no longer equal to the molecule initially tested in pre-marketing development (see "Is the comparability exercise also applied to the reference product?").

Is it possible to manage this variability in order to comply with the quality standards and the parameters of safety and efficacy? Quality by Design (QbD), introduced in 2004, is a systematic approach to define a range of variations that do not modify quality, safety, and therapeutic properties of a biotechnology drug [10]. Identifications of the Quality Target Product Profile (QTTP) and Critical Quality Attributes (CQAs) are the cornerstones of the roadmap for QbD (Fig. 2). The purpose is to identify all key characteristics and properties determining quality, safety, and efficacy of a specific biological product and to establish their acceptable variability. These assessments should be revised over time as soon as new stability, non-clinical and clinical data become available. Subsequently, all variables and their multidimensional combination and interaction are evaluated in order to design product and process spaces, complying with quality requirements of a specific product. In addition, a planned set of controls is established. Both product and process designs are reviewed and approved by regulatory bodies. At any time, any movement outside the approved space is considered as a post-approval change requiring further regulatory assessment. Then, production process validation is performed to demonstrate its effectiveness and capability of delivering a product complying with quality parameters. Once the product is marketed, compliance with CQAs must be monitored constantly and continuous improvements are implemented through risk assessment, raw material management, enhancement of analytic techniques, and development of stochastic models to predict potential risks. Starting from the wide initial variability related to the different cell lines developed to produce a biosimilar, QbD allows to progressively control key variables of subsequent manufacturing steps,—cell culture, purification, and product formulation—in order

Table 1
Main differences between chemically synthesized drugs and biosimilars.

Characteristics	*Chemical drugs*	Biosimilars
Type of molecule (molecular weight)	*Mostly small chemical molecules* (*molecular weight usually less than 1 kDa*)	Large polypeptide chains (usually more than 10 kDa)
Structure	*Usually fully known*	Complex, frequently partially unknown
Synthesis	*Standard chemical synthesis*	By living systems (using recombinant DNA technology)
Physico-chemicals	*Well-defined*, *stable structures*	Complex, heterogeneous, and labile structures
Impurities	*Very rare*	Measures required to prevent viral, bacterial, or fungal impurities
Stability	*Typically stable molecules*	Measures required to monitor and maintain stability
Characterization	*Easy to fully characterize*	Complex molecular composition and heterogeneity make it almost impossible to characterize
Immunogenicity	*Very rare*; *non-antigenic* (*generally*)	Potentially immunogenic: immunologic tests and pharmacovigilance needed to monitor immunogenicity and antigenicity
ADME (absorption, distribution, metabolism, and excretion)		
- Absorption	*More rapid*	Slower (subcutaneous or intramuscular)
- Distribution	*High*	Low or limited
- Metabolism	*Metabolized to active and non-active metabolites*	Catabolism to amino-acids similar to endogenous ones
- Disposition	*Often target-mediated*	Rarely target-mediated
Pharmacokinetic profile	*Non-linear* (*often*)	Frequently linear
Half-life	*Short or shorter*; *variable*	Long
Safety		Exaggerated pharmacology; immunogenicity

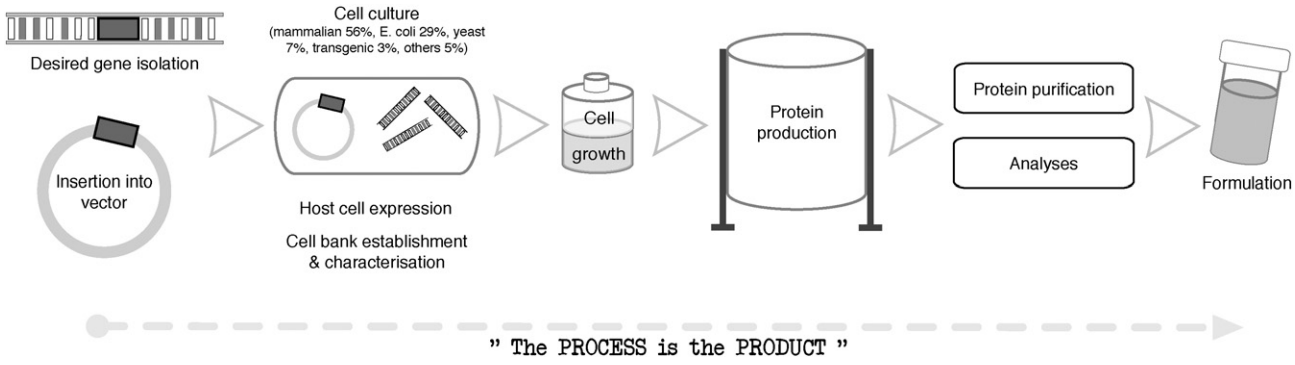

Fig. 1. Biotech manufacturing.

to establish a targeted variability range of quality, safety, and therapeutic properties comparable to the reference biologic.

5. How are biosimilars approved in Europe?

Current worldwide regulations [4] provide for an abbreviated path for granting the marketing authorization of copies of out-of-patent reference medicinal products. Minimizing development costs and accelerating their market access create a convergence of interests between healthcare services, worried about sustainability, and generic manufacturers. While the demonstration of bioequivalence is sufficient for small synthetic molecules, this approach is not scientifically applicable to a copy of biologic drug, constituted by large and complex molecules which are similar but not identical to the originator and are also subject to different post-translational processes.

In 2003–2005, the EMA has addressed this issue by stating that biosimilars must meet the so-called comparability exercise, which has not been specifically developed for biosimilar but had already been introduced earlier by the FDA [11] and EMA [12,13] in order to allow manufacturers to implement changes in the production process of biological originators.

Over the years, EMA has developed and updated several guidelines on the development of biosimilars, divided into three categories (Fig. 3): [9]

- overarching biosimilar guidelines, which expand the comparability exercise to biologics produced by different manufacturers;
- product-specific guidelines for alpha- and beta-interferons, erythropoietins, follicle-stimulant hormone (FSH), granulocyte-colony-stimulating factor (G-CSF), human insulin, low-molecular-weight heparins (LMWH), monoclonal antibodies, and somatropin;
- other guidelines relevant to biosimilars, including comparative assessment of immunogenicity.

A biosimilar is expected to be highly purified and extensively characterized. Quality is the determining factor and the success of any biosimilar is closely related to the progress of analytical techniques in order to provide comprehensive physicochemical and biological characterizations able to prove that it is similar to the reference medicinal product: the Quality Target Product Profile (QTPP). Any differences should be properly explained, considering also the potential clinical impact. The goal that regulatory authorities and scientists are actively pursuing is to compare the fingerprints of biosimilars with the reference originators, so as to establish comparability.

The additional general principles are as follows:

- The reference product must be authorized in the European Union (EU). However, it is possible to conduct comparative studies with a non-EU product, if it is representative of the product approved by the EMA.
- The pharmaceutical form, dosage, and route of administration must be the same.
- The performance and consistency of the manufacturing process should be extensively documented and detailed.

In contrast to the perception by clinicians, under a regulatory perspective, clinical studies play a limited role. In fact, the aim of

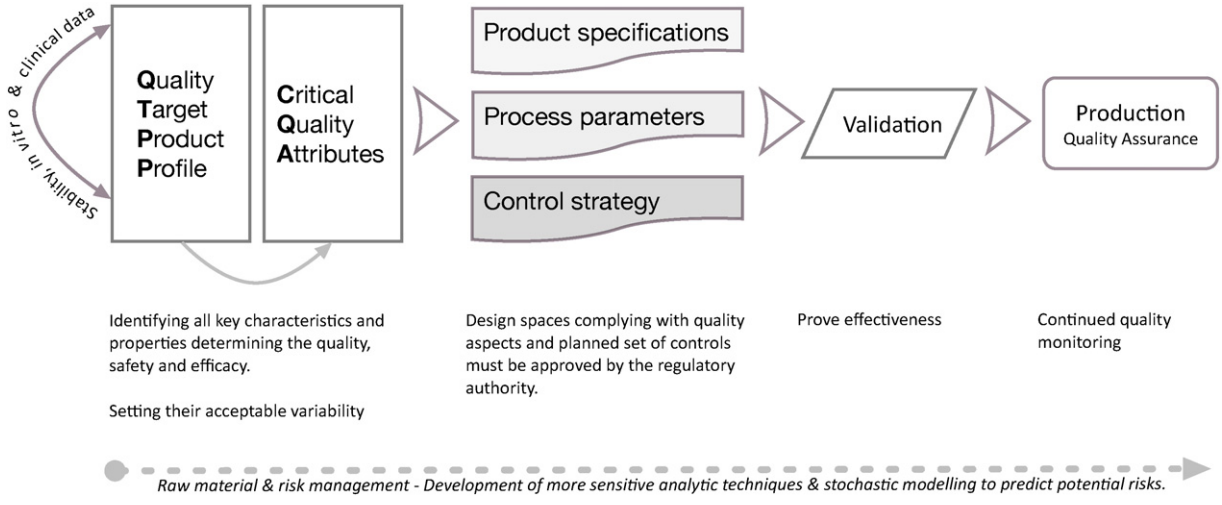

Fig. 2. Quality by design.

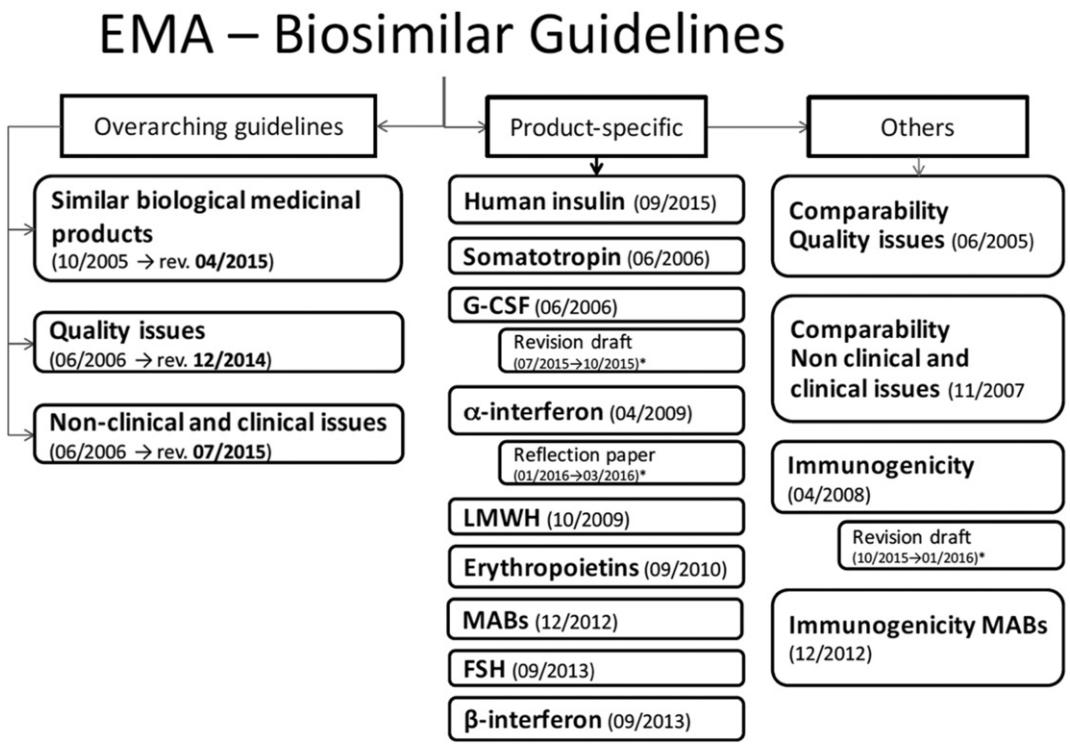

Fig. 3. Biosimilar guidelines scheme of the European Medicines Agency for biosimilars approval.

comparative clinical trials is to address slight physicochemical, biological, and in-vitro dissimilarities. Hence, clinical studies should be specifically designed to detect such differences. Clinical data cannot be used to justify substantial modifications in quality attributes. The goal of studies on biosimilar is not to demonstrate safety and efficacy per se, but rather to prove that safety and efficacy are comparable to those of the originator. Hence, the clinical trials needed in the light of a biosimilar development may differ substantially from those requested for an innovative product. For instance, the number of phase III patients recruited, the clinical endpoints assessed, or the indications tested may vary from those needed for the reference product (Table 2) [14].

6. Is the comparability exercise also applied to the reference product?

Consecutive batches of originator products are never identical to each other and adequate controls on batch-to-batch consistency are normally imposed. All originator products have undergone changes after their approval and this is what regulators call the "life cycle" of a medicine. Because small differences may have an impact on efficacy, these would normally be picked up early on in product development, in the frame of the extensive physicochemical and functional characterization required for all biological agents [14,15]. Analyses of the quality profiles of the glycosylated recombinant therapeutic proteins darbepoetin alfa, rituximab, and etanercept introduced in the market between 2007 and 2010 provided examples of acceptable variations for products that have remained on the market with unchanged product labels. The analyses suggested that licensed biologics undergo changes in relevant molecular attributes over time. Substantial alterations of the glycosylation profile were found for all tested products, reflecting changes in the production cell line, growth conditions, and the purification sequence [16]. Several changes in manufacturing processes after their initial approval are also reported for all licensed biological agents [15].

A recent study evaluated the number and types of manufacturing changes for originator monoclonal antibodies (mAbs) according to European Public Assessment Report (EPAR) documentation and ascertained the level of risk that these changes might impart. The study found 404 manufacturing changes authorized by EMA for a total of 29 mAbs with publicly available EPAR reports. Among the manufacturing changes authorized, 22 were categorized as high risk, 286 as moderate risk, and 96 as low risk [17]. Changes in the manufacturing processes often require extensive comparability exercises, which are registered and available on the EMA website. As for all biologicals, structural differences between biosimilars and reference products are only acceptable within the heterogeneity pattern of the molecule, and any differences found will need to be explained and justified with regard to the potential impact on the clinical performance of the actual biosimilar [14].

Table 2
Main approval process for generic drugs and biosimilars.

Generic drugs	*Biosimilars*
Quality assessment and comparison with reference product	*Quality assessment and comparison with reference product*
No preclinical data	*Abbreviated preclinical program (tolerance, pharmacokinetic, and pharmacodynamic)*
Bioequivalence study	*Phase I (pharmacokinetic and pharmacodynamic) study* *Phase III study in a representative indication* *Risk management plan*

7. What is the extrapolation of indications?

It is the regulatory and scientific process of granting a clinical indication to a medicine without own/new clinical efficacy and safety data to support that indication. Extrapolation of data is already an established scientific and regulatory principle that has been exercised for many years. For example, in the case of major changes in the manufacturing process of originator biological agents, although it have just recently become the focus of heightened interest since the introduction of biosimilar products on the EU market.

Many biological drugs can be indicated for more than one illness due to similarities between the diseases and the way the drug acts on the disease. For example, rheumatoid arthritis and Crohn's disease are both autoimmune disorders affecting different parts of the body that in many cases can be treated by the same biologic drug (e.g. infliximab,

adalimumab). To avoid unnecessary studies in the target population for ethical reasons, for efficiency and to allocate resources to areas where studies are the most needed [18], extrapolation of indications is thus applied during the approval process of biosimilars.

The EMA uses three scientific criteria to evaluate and approve indication extrapolation. For this purpose, drug developers are required to evaluate the biosimilar in a representative disease condition and provide

- scientific information supporting the biosimilar as having the same or a highly similar mode of action as its originator biological agent;
- comparability testing showing the biosimilar and the originator to be alike at the quality and biological level;
- conclusive evidence proving similar safety and efficacy in at least one indication of the originator.

Much emphasis has been put on the mechanism of action in different indications. Although it is acknowledged that binding of the biologic to the same receptor may have different effects in different target cells depending on differences in intracellular signaling pathways, this situation is not considered an argument to request additional clinical studies. Conversely, if different active sites or different receptors of the target cells are involved in different therapeutic indications, or if the historical safety profile of the reference product differs qualitatively between the different therapeutic indications, additional data may be needed to justify the extrapolation of safety and efficacy data.

The underlying scientific consideration is that the mechanism of action is mediated by the functional moieties of the molecule in a disease-specific manner, which can usually be characterized much more accurately by performing suitable assays than clinical studies [9]. Key principles for extrapolation of indications are summarized in Table 3.

8. Is extrapolation of the indication only applied to biosimilars?

The approval of a new formulation of an on-patent biological agent is an example of extrapolation of indication applied to originators [14]. This is illustrated by the approval of the subcutaneous (SC) formulation of trastuzumab, firstly approved as a solution for intravenous (IV) infusion for metastatic and early breast cancer. The Marketing Authorisation Holder (MAH) has then developed an SC formulation containing recombinant human hyaluronidase as a permeation enhancer which facilitates subcutaneous delivery. This formulation is considerably different from the IV and a difference of this magnitude would not generally be acceptable for a biosimilar approval. The potential impact of the implemented changes in the manufacturing process on the quality of trastuzumab SC has been addressed by comprehensive comparability studies. Pharmacokinetics, efficacy, and safety of the SC formulation have been evaluate in a phase III, randomized, open-label study (297 patients treated with trastuzumab IV and 294 with trastuzumab SC) in women with HER2-positive early breast cancer. The RCT demonstrated non-inferior efficacy of the fixed dose trastuzumab SC formulation compared with the standard trastuzumab IV formulation at the 20-month follow-up in the neoadjuvant setting. Thus the extrapolation of the efficacy data to the metastatic breast cancer setting was considered acceptable [19].

The approval of darbepoetin alfa, obtained from 2008 with the high throughput (HT) process in place of the previous and less efficient roller bottle (RB) process, is another example. An extensive comparability exercise, including two clinical trials, was requested to the MAH in order to support comparability in terms of quality, safety, and efficacy between darbepoetin alfa HT and RB. The first study assessed the clinical efficacy in 446 patients (222 treated with darbepoetin alfa HT and 224 with darbepoetin alfa RB) with chronic kidney disease receiving hemodialysis during 28 weeks. Because darbepoetin alfa is commonly administered SC (which is also the most immunogenic way of administration for biological agents) but only 35 patients in the HT group and 37 in the RB group were treated with darbepoetin alfa SC, additional safety data were required and an open-label, single–arm safety trial in patients with chronic kidney disease (560 receiving dialysis and 567 not receiving dialysis) was performed. Indication for the treatment of symptomatic anemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy was extrapolated, as well as indication for symptomatic anemia associated with chronic renal failure in pediatric patients [20].

Table 3
Main principles for extrapolation of indications.

- Evidence of biosimilarity between biosimilar and originator from the comparability exercise.
  - Good clinical experience with the originator.
  - Same mechanism(s) of action between biosimilar and originator in each indication (including its degree of certainty).
  - No differences in the safety and immunogenicity profile in each therapeutic indications and patient-related factors (e.g. comorbidities, medication, or immunologic status).
  - Extrapolation of immunogenicity: it is possible only from high- to low-risk patient populations and clinical settings (e.g. from subcutaneous to intravenous route of administration or from immunocompetent to immunocompromised patients).
  - Additional tests or studies including relevant pharmacodynamic parameters and/or specific functional assays reflecting the pharmacologic action(s) of the molecule: in some cases, they may be needed to further support extrapolation of indications.

9. Are biosimilars interchangeable with their reference products?

Interchangeability is of utmost importance for the health care system because most costs of biological products are due to chronic treatments. It has been claimed that the switch from the reference product to the corresponding biosimilar may have an impact on efficacy and safety. In theory, changes in safety and efficacy might be associated with a switch from the reference product to the biosimilar if either product has a higher inter-individual variation in pharmacokinetics, but such a difference has not been observed with current available biosimilars. Development programs of several biosimilars have included studies in which the reference product has been switched to the biosimilar and occasionally back to the reference product. The current position of the Finnish Medicines Agency is that biosimilars are interchangeable with their reference products under the supervision of a health care officer. This view is supported by the fact that switches between reference products and biosimilars have been commonly associated with hospital tendering processes in some EU member states and have not indicated a risk for adverse effects. Yet, there is no safety signal associated with such switches in the European EudraVigilance database for serious adverse effects and [21].

10. Immunogenicity

Human immunogenicity data are generally necessary before licensing a new biological or biosimilar drug to exclude a marked increase in immunogenicity of the biosimilar compared with the reference product. If the incidence of the immune response is known to be rare and thus unlikely to be captured before licensing, additional post-marketing pharmacovigilance programs are required by regulatory agencies.

Immunogenicity is a well known safety concern for biopharmaceuticals, especially for biological drugs for which immune responses have been linked to serious safety issues. These medications are active molecules and are indeed able to induce a noxious immunological response. An example was the development of pure red cell aplasia sustained by cross-reacting neutralizing antibodies against erythropoietin. Immunogenicity may be related to patient, disease, or product characteristics. For biosimilar drugs, data on some patient characteristics and disease-related factors have been already obtained from the experience gained during the development of the originator product and therefore do not need to be further reinvestigated. Thus,

the principal focus for the evaluation of immunogenicity is on potential product-related factors, such as structural alterations/modifications (i.e., aggregation, a factor implicated in the immunogenicity of erythropoietins) or impurities/contaminants (in most cases, these are readily detected by analytical methods). Another factor that may affect immunogenicity is the route of administration of the drug. Generally, intramuscular or subcutaneous administrations are more immunogenic than the intravenous administration, as found for the subcutaneous administration of the originator epoetin alfa, which was associated to pure red cell aplasia caused by tungsten-mediated unfolding and aggregation of the drug [22].

11. Pharmacovigilance

The post-marketing evaluation of the safety profile of biosimilars is a regulatory requirement of EMA as stringent as for any new biological product and requires a comprehensive risk management plan, including a plan for post-authorization safety surveillance which must be submitted to the authorities at the time of the marketing authorization application [12]. This must address identified and potential safety concerns for the biosimilar, the reference product, and/or the substance class. It is aimed not only to track and monitor potential differences in the immunogenicity profile between biosimilar and originator, but also a proactive pharmacovigilance system to minimize and detect already known and unknown potential risks and adverse events. These data are considered important to detect rare adverse drug reactions, such as progressive multifocal leukoencephalopathy in patients with multiple sclerosis treated with natalizumab or in patients with psoriasis treated with efalizumab, and the case of pure red cell aplasia in patients treated with epoetins [23]. As is the case with all biologics and other chemically synthesized medicines, the continuous pharmacovigilance surveillance system is a common feature of all new biosimilar products. Finally, in order to enable better pharmacovigilance on biosimilar products, international regulatory agencies and the World Health Organization [24–25] are discussing to develop a standard nomenclature and product labeling for biosimilars. This is important to make each biosimilar drug readily distinguishable from originators, as well as from other biosimilar products and to help clinicians to report adverse drug reactions. In this way, regulatory agency will be certain that adverse events that occur in post-marketing phase will be readily and adequately associated with a specific product and manufacturer.

12. Biosimilar market and potential benefits for health care providers

In a context of progressive scarcity of healthcare resources, the availability of biosimilars is expected to become an important tool to find out financial means needed to support access of new (or, preferably, innovative) health technologies, particularly in therapeutic areas where demand is increasingly growing (such as cancer, neurodegenerative, psychiatric, and metabolic disorders). It is internationally acknowledged that in Western countries, the success of biosimilars is key to the sustainability of pharmaceutical spending in the next decade. According to the US Federal Trade Commission, the competition for biosimilars is expected to be smaller compared to that for generics, as the number of competitors will be restricted due to the significant investments required for their development and production [26]. In addition, it is emerging that major competitors will be the big pharma, that pursues a strategy of profit maximization by imposing high prices often not value-based. As a result, discounted prices of biosimilars compared to originators are likely to be less than desirable.

As of March 2016, about 50 biosimilars were reported to be under active development. Tables 4 and 5 summarize biosimilars approved by European Medicines Agency and those currently under review. While patent of insulin glargine expired in 2015, additional key biologics scheduled to lose exclusivity in 2016–2020 are etanercept and rituximab in 2016, pegfilgrastim in 2017, and adalimumab and trastuzumab in 2018. According to IMS Health, cumulative spending in the EU on these originator biologics is forecasted to reach €47 billion in 2016–2020. For European payers, this is a significant target to aim to obtain significant savings, which seem to be closely related to the ability of biosimilar to promote competition by defining European rules on substitutability and interchangeability with originators [27].

13. Biosimilars and internists

Although one of the main expected benefit of the introduction of biosimilar drugs is the reductions in costs and consequently to extend the access to new innovative biotherapeutic drugs, the scientific rules used for defining comparability are the same applied for any already approved originator after a significant change in its manufacturing process. Starting from this evidence, internists should only prescribe medicines for which quality, safety, and efficacy have been demonstrated according to state-of-the-art science and technology, irrespective if they are originators or biosimilar products. Based on an extensive developmental program, there is no scientific reason to consider that a biosimilar would behave differently from the originator when used in clinical practice according to the approved indication.

Internists should be also reassured with regard to immunogenicity and safety issues. It is well known that the problem of epoetin antibody-induced pure red cell aplasia was first recognized after a major change in the manufacturing process used for an originator epoetin. However, when an adverse drug reaction occurs or is suspected during the use of a biosimilar, the report should include, in addition to the international non-proprietary name, such other indicators as brand name, manufacturer's name, lot number, and country of origin of the batch used. Finally, clear information about existing guidelines, access to unbiased information, and educational interventions regarding the clinical utility of biosimilars will help to improve the knowledge and to implement the use of this medications in the internists practice.

14. Conclusions

No biopharmaceutical product—whether original or biosimilar—is risk free. However, internists should be confident that current development processes and regulatory requirements for biosimilars allow to achieve a comparable risk-to-benefit balance with the originator. On the available evidences and pharmacovigilance network, there are no grounds to believe that the use of a biosimilar carries more risks for the patient than the use of an originator. In fact, since the first biosimilar was authorized in 2006 by the European Union, no clinical alerts have raised red flags about the established EMA biosimilar pathway. The future development of biosimilars will depend on the definition of reliable parameters of interchangeability and will require further advances in knowledge on the characterization of the molecules. Internists, other clinicians and healthcare providers and patients will play a key role in determining how biosimilars will be integrated into clinical practice.

Learning points

- Biologics embrace a wide range of substances synthesized by cells or living organisms by means of different biological processes, including recombinant DNA technology, controlled gene expression, or antibody technologies.
- A biosimilar is defined by the European Medicines Agency as "*a biological medicinal product that contains a* (*copy*) *version of the active substance of an already authorized original biological medicinal product* (*reference medicinal product*). *A biosimilar establishes similarity to the reference medicinal product in terms of quality characteristics*, *biological activity*, *safety and efficacy based on a comprehensive comparability exercise*".
- While the demonstration of bioequivalence is sufficient for small synthetic molecules, this approach is not applicable to a copy of a

Table 4
Biosimilars approved by European Medicines Agency.*

Active substance	Product name	Therapeutic area	Authorization date
Epoetin alfa	Abseamed	*Anemia* *Cancer* *Chronic kidney failure*	August 28, 2007
	Binocrit	*Anemia* *Chronic kidney failure*	August 28, 2007
	Epoetin alfa Hexal	*Anemia* *Cancer* *Chronic kidney failure*	August 28, 2007
	Retacrit	*Anemia* *Autologous blood transfusion* *Cancer* *Chronic kidney failure*	December 18, 2007
	Silapo	*Anemia* *Autologous blood transfusion* *Cancer* *Chronic kidney failure*	December 18, 2007
Etanercept	Benepali	*Axial spondyloarthritis* *Psoriatic arthritis* *Plaque psoriasis* *Rheumatoid arthritis*	January 14, 2016
Filgrastim	Accofil	*Neutropenia*	September 18, 2014
	Biograstim	*Cancer* *Hematopoietic stem cell transplantation* *Neutropenia*	September 15, 2008
	Filgrastim Hexal	*Cancer* *Hematopoietic stem cell transplantation* *Neutropenia*	February 6, 2009
	Filgrastim ratiopharm	*Cancer* *Hematopoietic stem cell transplantation* *Neutropenia*	September 15, 2008 Withdrawn on April 20, 2011
	Grastofil	*Neutropenia*	October 18, 2013
	Nivestim	*Cancer* *Hematopoietic stem cell transplantation* *Neutropenia*	Jun 8, 2010
	Ratiograstim	*Cancer* *Hematopoietic stem cell transplantation* *Neutropenia*	September 15, 2008
	Tevagrastim	*Cancer* *Hematopoietic stem cell transplantation* *Neutropenia*	September 15, 2008
	Zarzio	*Cancer* *Hematopoietic stem cell transplantation* *Neutropenia*	February 6, 2009
Follitropin alfa	Bemfola	*Anovulation (IVF)*	March 24, 2014
	Ovaleap	*Anovulation (IVF)*	September 27, 2013
Infliximab	Flixabi	*Ankylosing spondylitis* *Crohn's disease* *Psoriatic arthritis* *Psoriasis* *Rheumatoid arthritis* *Ulcerative colitis*	CHMP positive opinion on April 1, 2016
	Inflectra	*Ankylosing spondylitis* *Crohn's disease* *Psoriatic arthritis* *Psoriasis* *Rheumatoid arthritis* *Ulcerative colitis*	September 10, 2013
	Remsima	*Ankylosing spondylitis* *Crohn's disease* *Psoriatic arthritis* *Psoriasis* *Rheumatoid arthritis* *Ulcerative colitis*	September 10, 2013
Insulin glargine	Abasaglar (previously Abasria)	*Diabetes*	September 9, 2014
Somatropin	Omnitrope	*Pituitary dwarfism* *Prader–Willi syndrome* *Turner syndrome*	April 12, 2006
	Valtropin	*Pituitary dwarfism* *Turner syndrome*	April 24, 2006 Withdrawn on May 10, 2012

* Adapted from European Medicines Agency (EMA); updated on May 20, 2016.

biological drug, constituted by large and complex molecules similar but not identical to the originator and also subject to different post-translational processes.

- The goal of biosimilar studies is not to demonstrate safety and efficacy per se but rather to prove that safety and efficacy are comparable to the originator's. Hence, the clinical trials needed in the frame of a

Table 5
Biosimilars under review by European Medicines Agency.*

Active substrances	Therapeutic area	Number of applications	Originator products
Adalimumab	*Immunosuppressant*	2	*Humira*
Enoxaparin sodium	*Anticoagulant*	2	*Lovenox*
Etanercept	*Immunosuppressant*	1	*Enbrel*
Insulin glargine	*Diabetes*	1	*Lantus*
Pegfilgrastim	*Immunostimulant*	3	*Neulasta*
Rituximab	*Antineoplastic medicine (anticancer)*	1	*MabThera/Rituxan*
Total		**10**	

* Adapted from European Medicines Agency (EMA); updated on May 20, 2016.

biosimilar development may differ substantially from those for an innovative product.

- The post-marketing evaluation of the safety profile of biosimilars is a regulatory requirement of EMA as stringent as for any new biological product and requires a comprehensive risk management plan, including a plan for post-authorization safety surveillance.
- Internists should be confident that the development process of biosimilars ensures a comparable risk-to-benefit balance with the originators. On the basis of the available evidence and pharmacovigilance network, there are no grounds to believe that the use of a biosimilar carries more risks for the patient than the use of an originator.

Conflict of interest

All the authors declare that they do not have any conflict of interests in the submitted manuscript.

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