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Review article

Biosimilars – Science, status, and strategic perspective

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ABSTRACT

Biopharmaceuticals based on recombinant proteins have started to go off-patent, opening the way for other manufacturers to place follow-on products to the market. Meanwhile it has been recognized by all stakeholders that there are fundamental differences between conventional small-molecule based drugs and biopharmaceuticals. This has led to the adoption of distinct legal and regulatory frameworks for biosimilars (follow-on products to biopharmaceuticals) in various parts of the world. This review gives an overview on the scientific basis for the approval requirements, the regulatory and market status, open issues, and the strategic perspective.

1. Introduction

Biopharmaceuticals are well established in biomedicine and have opened new therapy options particularly in disease areas where previously no, or only insufficient, therapies were available. Some 165 biopharmaceutical products have gained approval [1]. In 2007, total recombinant protein-based drug sales were $54.5 billion, and are expected to increase to $75.8 billion in 2012 [2]. In 2006, more than 400 biotechnological medicines were in clinical trials [3].

The first recombinant protein drugs, like Eli Lilly's insulin (developed by Genentech, Inc.), were launched in the 1980's. Now, the patent and regulatory data protection periods for the first and second waves of biopharmaceuticals based on recombinant proteins have started to expire, opening the way for other manufacturers to place follow-on products to the market as this has occurred since many years for conventional medicines containing small-molecule drug substances. In the latter case regulations for generic (multi-source) products allow for abbreviated approval based on the proof of therapeutic equivalence demonstrated by analytical as well as usually by bioequivalence studies [4]. Generics manufacturers do not have to bear the cost of drug discovery, do not need to prove the safety and efficacy of their drugs through costly clinical trials, and are not subject to significant project attrition during development. Consequently, generic medicines can be offered at a significantly lower price than the innovator's drug. Competition between several generics manufacturers usually will lead to even higher price discounts [5].

Meanwhile it has been recognized by all stakeholders – politicians, regulators, innovative and generics pharmaceutical industry, payers, physicians, pharmacists, and patients – that there are fundamental differences between conventional small-molecule based drugs and biopharmaceuticals. This has led to the adoption of distinct legal and regulatory frameworks for follow-on products to biopharmaceuticals ("biosimilars") in various parts of the world. This review gives an overview on the scientific reasoning underlying the approval requirements for biosimilars, the regulatory and market status, open issues, and the strategic perspective.

2. Definition

Several terms are used in various countries for "intended copy" products to biopharmaceuticals (e.g., biosimilars, follow-on biologicals, follow-on protein products, subsequent-entry biologicals, similar biological medicinal products). In this review, biosimilars are defined as biological medicinal products which are

- similar in terms of quality, safety and efficacy to an already licensed, well-established reference medicinal product,
- marketed by an independent applicant following expiry of patent and regulatory data/market exclusivity periods of the reference product, and
- authorised for marketing through a procedure based on the proof of similarity to the reference product, using certain pre-existing scientific and regulatory knowledge.

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It should be emphasized that this definition excludes biopharmaceutical products developed and licensed as "stand-alone" products based on a full data package according to national regulations, but without comparative studies versus a reference product.

Due to the inability to characterize complex biological products sufficiently, the "biosimilar" approach is focussed on highly purified products, usually drugs containing recombinant proteins as the active pharmaceutical ingredient. It is presently not applied to blood or plasma-derived products, immunologicals, and emerging new therapies such as gene and cell therapies. However, regulators seem to be ready to accept other classes of compounds, e.g. polysaccharides such as low-molecular weight heparins [6].

3. Scientific considerations

3.1. The complexity of the protein molecules

Proteins are much more complex molecules than conventional drug substances, i.e. chemically synthesized small molecules. Differences comprise –

- *Size* – The molecular weight of drug-like chemical compounds usually is in the range of a few hundred Daltons [7]. In contrast, proteins have molecular weights from about 10,000 up to more than 200,000 Daltons, so typically they are 100- to 1000-fold larger molecules.
- *Structure* – To possess biological activity, proteins have to adopt the correct three-dimensionally folded secondary, tertiary, and quaternary structures.
- *Structure–function* relationship – Whereas in small molecules, it is often known that every atom of the molecule will play a role in defining the clinical profile of the compound, the structure–function relationship is usually unknown, or at best partially known, for proteins. Thus, the impact of differences in the molecular structure in most cases cannot be predicted.
- *Stability* – Proteins are inherently unstable molecules, and may structurally be damaged by heat, prolonged storage, denaturants, organic solvents, oxygen, pH changes, and by other factors, leading to reduction or complete loss of biological activity.
- *Microheterogeneity* – No protein product will leave the producing cell and the manufacturing process as predicted theoretically based on the encoding DNA sequence alone. Proteins are rather modified both biologically by the producing cell – e.g., by glycosylation, acylation, sulfatation, phosphorylation, and proteolysis – as well as by the process conditions, e.g. by oxidation, deamidation, reaction with auxiliary substances, partial denaturation, and aggregation [8]. Further heterogeneity may arise if the protein is intentionally modified, for example by multi-site pegylation [9]. Thus, even highly purified proteins never consist of one single molecular entity but are mixtures of many closely related molecular species. This microheterogeneity can be substantial: even for "simple", unglycosylated proteins expressed in bacteria, considerable heterogeneity has been observed, e.g. amino acid substitutions may occur at a significant level of 2% in human growth hormone [10]. In complex, glycosylated proteins, heterogeneity is much greater. It has been estimated that in an immunoglobulin G molecule, there might theoretically be up to 10^8 different species [11] considering only a limited number of all possible glycosylation variants.

3.2. The importance of the manufacturing process – "The process is the product"

Proteins are made by living cells – such as bacteria, yeast, plant, or mammalian cells – acting as the "manufacturing facility". The development and manufacturing of recombinant protein products include

- cloning the coding DNA sequence into a suitable DNA vector;
- transfecting this vector into a host cell;
- screening for the cell which forms the product in the desired quality and required quantity;
- subcloning and developing this cell further concerning expression yield, growth properties, etc. into a master and working cell bank respectively from which all subsequent production runs are performed;
- growing the recombinant cell in large bioreactor vessels (up to, and even exceeding, 10,000-L scale) depending on the supply needs;
- purifying the target protein using a multi-step downstreaming process; and finally
- bringing it into a formulation and device suitable for transport, storage, and application to the patients.

The whole process has to be run under strictly controlled, validated conditions in closed systems to assure consistency and avoid any contamination, and in accordance with GMP requirements.

A second manufacturer aiming to replicate a protein product independently has to run through an analogous procedure as above, but will not be able to reproduce it in an identical way unless he has access to the originator's materials (such as cell banks) and information (standard operating procedures). Particularly, transfection of the host cell represents a unique event which cannot be identically replicated – if done twice, the result would be a manufacturing cell line with different properties. The conditions used for cell fermentation will depend on the properties of the master cell bank and therefore cannot be identical for a second manufacturing process. In addition, the details of upstream and downstream manufacturing and the methods and criteria chosen for in-process analytics are not in the public domain and are therefore not known to a second, independent manufacturer.

The pattern and variability of protein microheterogeneity will depend on the way how the protein is manufactured. Not all of these variations will have an impact on the clinical safety and efficacy profile, but since only a limited number of attributes can be assessed analytically, one cannot assume *a priori* that proteins which are produced using different processes have identical properties. It should be emphasized that batch-to-batch variations are unavoidable even with well-controlled, consistent protein manufacturing procedures and are acceptable within the limits defined by the specifications, but usually they are much smaller than differences between products made by totally different manufacturing processes.

3.3. Similarity vs. comparability after manufacturing changes

Manufacturers sometimes change their manufacturing processes for good reasons – e.g., for upscaling due to increased demand; for replacement of raw materials which are no longer available; to run the process in a new facility; or to improve process robustness, yield, product quality, or stability. It has been asserted that these changes may lead to differences just as they occur in independently manufactured biosimilar products. However, these scenarios are very different: on process changes, a comparability exercise [12,13] is required to evaluate the relevant quality attributes of the pre- and post-change product in order to demonstrate that no modifications occurred that would adversely impact drug safety and efficacy. This will be supported by the extensive knowledge on the product resulting from development, in-process, release and stability data available only to the manufacturer, and includes a combination of analytical testing, biological assays,

and in some cases non-clinical and even clinical data. The extent of the studies necessary to demonstrate comparability will depend on the production step where the changes are introduced, the potential impact of the changes on the purity as well as on the physicochemical and biological properties of the product, the availability of suitable analytical techniques to detect potential product modifications, and the relationship between quality attributes and safety and efficacy, based on overall non-clinical and clinical experience. Additional evidence from non-clinical or even clinical studies is required when quality data are insufficient to establish comparability. Their extent and nature will be determined on a case-by-case basis in consideration of various factors including the quality findings, the nature and level of knowledge of the product, existing non-clinical and clinical data relevant to the product, aspects of product use and product class [12].

In the case of biosimilars, the demonstration of similarity to the reference product is limited to comparison of the final drug product or drug substance reprocessed from the formulated drug product (which may be a challenge [14]), and thus will be restricted to a much smaller set of data.

3.4. Will analytical characterization help to avoid differences?

Today, highly sensitive, orthogonal physicochemical methods are used for the analytical characterization of proteins, and these methods continue to be improved further. Nevertheless, it is not possible to resolve and quantify all variants of a protein preparation with a single method, or even with a combination of very sophisticated analytical methodologies. Therefore, differences in protein product characteristics may not be detectable by analytical characterization.

A comparison of products from different manufacturing processes based on the product specifications (as e.g. available in pharmacopoeial monographs) is insufficient because specifications, by definition [15], are always linked to a particular manufacturing process, analytical procedures, and pre-clinical and clinical data. They confirm an expected process output, i.e. the quality of the product to be suitable for the intended use, to make sure that batch-to-batch variability is within acceptable and pre-defined limits, rather than establish full product characterization.

The greater the resolution of analytical methods will be, the more the heterogeneity will become apparent: variability is due to the biological system producing the protein as well as to process differences, so it will not disappear on more sensitive analytical characterization. Analytical comparison can never show "identity" but, at best, the presence or absence of detectable differences in the particular studied parameters.

It is sometimes speculated that using a "quality by design" concept, it might be possible to define a design space – i.e., the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality [16] – of the reference product which then might be applied by a second manufacturer for development of his own process. However, the design space always relates to an established process design and requires an understanding of the relevance and impact of variability of product attributes to clinical safety and efficacy which, for the reference product, is not available to a biosimilars manufacturer. So a follow-on manufacturer may well establish the design space for his own product but cannot use this concept to ensure similarity with the reference product.

3.5. The impact of differences

The impact of even small structural differences on clinically relevant properties of proteins may be significant. Differences in the primary structure would not be compatible with "biosimilarity" according to the European Medicines Agency (EMEA) guidelines. For glycosylated proteins, differences in the glycopattern may significantly influence receptor binding, protein–protein interaction, and pharmacokinetics of protein substances [17–19]. For immunoglobulins, small differences in core fucosylation can lead to big changes in Fcγ receptor binding and consequently impact immune effector functions [20,21] such as antibody-dependent cellular cytotoxicity which is believed to be a major mechanism of action contributing to the potency of many monoclonal antibodies, particularly in oncological indications.

A key safety parameter in protein medicines is immunogenicity, i.e. the ability of a substance to trigger an immune response in the patient. Nearly all biopharmaceuticals induce antibodies [22,23], due to either the presence of foreign sequences or epitopes, or the breaking of immune tolerance to self-antigens [24,25]. The latter mechanism which is not completely understood apparently does not only depend on patient characteristics, route of administration, and disease-related factors but also on the quality of the protein product: the presence or absence of glycosylation, impurities such as aggregates, as well as product handling issues have been associated with the induction of antibodies [26,27]. Therefore, products from different sources cannot be assumed to be equivalent concerning their immunogenic potential. Whereas in most cases, the presence of antibodies has no major clinical consequences and can be managed, e.g. by adaptation of the therapy, there can be dramatic effects if a natural human protein with an essential activity is neutralized. Such cases had been described some years ago for an erythropoietin product where a post-approval formulation change led to an increased number of cases of pure red cell aplasia (PRCA) [28], as well as for megakaryocyte-derived growth factor where severe thrombocytopenia was induced in volunteers and cancer patients, and led to the termination of product development [29]. Unfortunately, immunogenicity in humans is not predictable based on *in-vitro* or animal tests so that always data generated by clinical testing are required for assessment of immunogenicity.

4. Legal and regulatory status

It has been long recognized by the regulatory authorities that differences in the manufacturing process of biopharmaceuticals necessarily will lead to differences in the product attributes which cannot be fully assessed by analytical characterization. Therefore, not only physicochemical–biological testing, but also the manufacturing process was made part of the determination of product quality ("process equals product" paradigm) [30,31], emphasizing the importance of process control, process validation, and product testing [11]. As a consequence, therapeutic proteins derived from independent manufacturing processes can never be identical, but at best be "similar", i.e. possessing the same clinical safety and efficacy profile in spite of not being "the same" molecule.

A legal and regulatory process allowing for an abbreviated approval of biosimilar products has to ensure an appropriate balance between the aim to facilitate market entry and competition for off-patent medicines, the endeavour to foster scientific and medical innovation [32] and reward it appropriately, and particularly the need to avoid any unnecessary risks for patient safety. Whereas it is desirable to avoid unnecessary or even unethical animal or human trials, it has to be kept in mind that biosimilars, although offering economical benefits, by definition do not bring about any medical progress since the reference products are available and have proven safety and efficacy over many years. Thus, the biosimilars approval process should make sure that the same high standards and stringent requirements for quality, safety, and efficacy are ensured as for innovative medicines. While it is generally

accepted that the "generic pathway" as existing for conventional small-molecule medicines is not appropriate for biopharmaceuticals, specific regulatory pathways for licensing biosimilar medicinal products have been adopted in some parts of the world already.

4.1. European Union

The difference between conventional generics and biosimilar products has been acknowledged in Article 10(4) of EU Directive 2001/83/EC as amended by Directive 2004/27/EC [33]. It is stated there that "*where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided*". Based on this legislation, the European Union became the first region globally to introduce a particular regulatory framework for biosimilars developed by EMEA's Committee for Medicinal Products for Human Use (CHMP). It consists of an overarching guideline [34], a guideline on quality issues [35], a guideline on non-clinical and clinical issues [36], as well as class-specific guideline annexes describing the non-clinical and clinical requirements for specific classes of new products. At the time of writing of this article, annexes were adopted for human soluble insulin [37], somatropin [38], G-CSF [39], and epoetins [40], and guidance for interferon alfa [41] and low-molecular weight heparins [6] was under review. Based on the experience gained with scientific advice procedures and marketing application assessments, the epoetin guideline is presently being revisited [42].

Generally, the European biosimilar guidelines require the demonstration of the similar nature in terms of quality, safety, and efficacy of the new product and a chosen reference medicinal product which has to be authorised in the European Community based on a full dossier. Comparison to publicly available standard materials is not appropriate because these may not have known and defined safety and efficacy profiles. The applicant has to deliver

- a full *quality dossier* plus, as an additional element, comparison to the reference product (including both physicochemical and functional characterization data),
- *non-clinical and clinical data* obtained in comparative studies vs. the reference product, as described in the product class-specific annexes.

The results of the comparative studies done at the quality level may allow a reduction in the non-clinical and clinical data requirements compared to a full dossier. It should be emphasized that subtle differences to the reference product in the quality attributes are not excluded, but even expected, and have to be justified concerning their potential implications with regard to the safety and efficacy of the product. The clinical studies should be designed to demonstrate equivalence rather than non-inferiority, i.e., a "better" outcome is not an option because it indicates lack of similarity. Efficacy and safety have to be justified or demonstrated separately for each of the claimed indications, however it may be possible in certain cases to extrapolate therapeutic similarity shown in one indication to other indications of the reference product [36].

The EMEA guidelines state that it is not expected that the quality attributes of the biosimilar and reference products will be identical, so that usually differences will be observed [35]. To be acceptable these have to be justified by the applicant with regard to safety and efficacy of the drug, and may have consequences as to the amount of non-clinical and clinical data to be provided. For those product classes for which guideline annexes are available at present, relatively simple, easy-to-measure clinical endpoints or accepted surrogate endpoints are available which facilitate comparative trials. In future, with products requiring more complex clinical endpoints (e.g., monoclonal antibody products), the design of the comparative equivalence trials may become much more challenging. Furthermore, since differences may not be fully apparent at the time of approval, the guidelines request [36] that for biosimilars (as for all biological medicinal products) pharmacovigilance monitoring has to be performed. For this purpose, the specific product given to the patient should be clearly identified.

Using this regulatory framework, a number of biosimilar products already have been licensed in the European Union (Table 1), and are being marketed in several, but not yet in all, European countries. Details on the various biosimilar products and the data which led CHMP to recommend their approval can be found in the European Public Assessment Reports accessible via the EMEA webpage [43]. At launch, these products were offered with about 15–35% price discount vs. the list prices of the innovator products (depending on the product, country, and package size). On the other hand, one interferon alfa product has been rejected by CHMP [44], and the applications for three insulin products have been withdrawn [45] demonstrating that the European regulations, in order to ensure a high standard of quality, safety, and efficacy, represent significant hurdles as appropriate to prevent the market entry of sub-standard products.

4.2. United States

The U.S. Federal Drug Administration (FDA) recognized the need to implement new regulations for the abbreviated approval for biosimilars early. Meetings on the scientific considerations for this

Table 1
EU Biosimilars Approvals, Status February 25, 2009.

Biosimilar Product	Company	INN	Reference Product	Date of Approval
Omnitrope	Sandoz	Somatropin	Genotropin	April 12, 2006
Valtropin	Biopartners	Somatropin	Humatrope	April 24, 2006
Binocrit	Sandoz	Epoetin alfa	Erypo/Eprex	August 28, 2007
Epoetin alfa Hexal	Hexal	Epoetin alfa	Erypo/Eprex	August 28, 2007
Abseamed	Medice	Epoetin alfa	Erypo/Eprex	August 28, 2007
Silapo	Stada	Epoetin zeta	Erypo/Eprex	December 18, 2007
Retacrit	Hospira	Epoetin zeta	Erypo/Eprex	December 18, 2007
Ratiograstim	Ratiopharm	Filgrastim	Neupogen	September 15, 2008
Tevagrastim	Teva	Filgrastim	Neupogen	September 15, 2008
Biograstim	CT Arzneimittel	Filgrastim	Neupogen	September 15, 2008
Filgrastim ratiopharm	Ratiopharm	Filgrastim	Neupogen	September 15, 2008
Zarzio	Sandoz	Filgrastim	Neupogen	February 6, 2009
Filgrastim Hexal	Hexal	Filgrastim	Neupogen	February 6, 2009

new class of products were held in 2004 and 2005, as well as a workshop at NY Academy of Sciences in 2005 [46]. FDA officials have stated [47–49] that FDA has considerable experience with reviewing protein products and intends to prepare guidance documents broadly applicable to follow-on protein products which will be based on a scientifically based, case-by-case approach. However, for mainly historical reasons, protein products in the U.S. are licensed under two different legal frameworks [50,51] –

- *Federal Food, Drug, and Cosmetics (FD&C) Act* – small-molecule drugs, but also some proteins ("biological drugs") such as hormones like insulin or somatropin, menotropins, and hyaluronidase, are licensed under the FD&C Act,
- *Public Health Service (PHS) Act* – biologics, including most protein products generally are regulated under the PHS Act section 351.

Whereas the FD&C Act contains provisions both for "generic" products (section 505(j)) and for abbreviated applications relying, to some extent, on the agency's conclusions regarding safety and effectiveness of an approved product (section 505(b)(2)), no such provisions are available in the PHS Act. Sandoz' somatropin product Omnitrope was approved by FDA based on section 505(b)(2) [52], but this regulatory pathway cannot be used for most potential future biosimilar products such as epoetins or interferons. So in the U.S., at present there is no legal framework yet which would allow for an abbreviated approval of (most) biological products. Several draft bills have been published addressing this issue, and it is generally expected that legislation will be introduced in 2009 or 2010, at the latest.

4.3. Other countries

Activities are ongoing in several other countries to introduce regulations for the approval of biosimilar products. In Australia, the EMEA guidelines have been directly adopted [53]. Regulations based on the same principles have been introduced in Switzerland [54] as well as in Malaysia [55], Turkey, and Japan. Draft regulations are under review in, e.g. Canada and other countries.

Numerous "intended copy" biopharmaceuticals which not in all cases would correspond to the standards of quality, safety, and efficacy as defined in the EMEA guidelines have been licensed following national regulations on the basis of a reduced data package in some countries (e.g., India, China, Latin America, and CIS countries). Since the scientific justification for the various approval pathways is not really clear in all cases, the World Health Organization (WHO) has recognized a need for defining regulatory expectations for these products at the global level. Therefore, a WHO working group was established with the aim to develop a guideline to promote global consensus on the regulation of biosimilars, assist in their registration based on an abbreviated regulatory process based on the claim of similarity to a reference product, and thus enhance the availability of safe and effective biosimilar products worldwide [56].

4.4. Open issues

Although regulatory frameworks for biosimilars have been adopted, or are upcoming, in many parts of the world, there are some open issues left which are presently under intense discussion.

- *Reference product* – According to the EMEA guidelines, the reference product has to be authorised in the EU based on a full dossier, and the same reference product has to be used throughout the comparative studies for quality, safety and efficacy. Data generated from studies with medicinal products authorised outside the Community may only provide supportive information [40]. This request is made to ensure that the regulatory authority has full access to the relevant data and regulatory history of the reference product in order to assess similarity. However, innovator products authorised in different countries may differ concerning, e.g. production site, formulation, and strength, so if the same demand would be made for all countries, a biosimilars manufacturer may be faced with the need to do comparative studies separately for each country versus the locally authorised reference product (provided a suitable nationally licensed reference product is available). Therefore, the option of national regulatory authorities to accept a reference product not licensed within their jurisdiction is under discussion but would call for information sharing between the regulatory authorities, and/or additional data to be provided by the biosimilars manufacturers.
- *Labelling* – The summary of product characteristics (SmPC) as well as the package insert (collectively called "the labelling") should provide transparent information to healthcare professionals and patients on issues relevant to the safe and effective use of a medical product [57]. For conventional generic small-molecule drugs, labelling is to all intents and purposes identical to that of the reference product. This approach, however, is not appropriate for biosimilars because they are not identical, but only similar to their reference products and are licensed on the basis of their own development, including clinical data. Therefore, the labelling should differentiate clinical safety and efficacy data which have been obtained with the biosimilar product itself from those which just have been taken over from the reference product, particularly in extrapolated indications where no studies have been done with the biosimilar at all [58]. This distinction is presently not evident from the labelling of some EU biosimilars.
- *Pharmacovigilance* – for all new medicines, marketing authorisation holders of biosimilars should make sure that they have an appropriate system of pharmacovigilance in place to assure responsibility for their products on the market and to ensure that appropriate action can be taken if necessary [59]. For biosimilars, this requirement is even more important because the pre-authorisation safety database will be relatively small due to the abridged clinical development program. Pharmacovigilance is of special importance in case of rare serious adverse events (such as the PRCA cases on epoetin treatment) which might not be evident at approval due to the limited data package available at this time. Pharmacovigilance systems based on spontaneous reporting will be limited by under-reporting as well as by data quality, which is often insufficient to allow a meaningful assessment [60]. Therefore, a more proactive approach may be required.
- *Naming* – In order to support post-approval monitoring, the specific medicinal product given to the patient must be clearly identified [34]. International non-proprietary names (INNs) are assigned to drug substances by the WHO INN Programme. WHO does not intend to introduce a specific process for naming biosimilars [61], and the INN as a cataloging system for drug substances can neither be relied upon as an appropriate means to ensure identification and traceability of biological, including biosimilar products nor as the sole indicator of product interchangeability. Therefore, it will be necessary that biosimilar products are marketed using brand names.

According to the WHO naming policy for glycosylated proteins [62], differences in glycosylation should be reflected by adding a Greek letter to the INN, as for example in epoetin alfa, beta, and omega. However, the INN system cannot demand that a manufacturer applies for an INN [63], and although all epoetin biosimilars licensed hitherto use the same reference product (Erypo/Eprex),

one group of suppliers has chosen to use the same INN (epoetin alfa) as the reference product whereas another group uses a distinct INN (epoetin zeta). This situation may be considered confusing and certainly does not really support the objective of the INN system to facilitate "clear identification, safe prescription and dispensing of medicines" [64].

- *Interchangeability and Substitution* – An interchangeable pharmaceutical product is one which is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice [4]. In many countries, interchangeability is linked, by national administrative processes, to the permit, recommendation, or even requirement for pharmacists to switch patients from the prescribed medicine to another known to have the same quality, safety, and efficacy, a practice known as "automated substitution". Whereas conventional generic medicines are usually considered or classified as interchangeable, this is not necessarily the case for biosimilars: here interchangeability should be demonstrated by scientific data proving that two products can be safely substituted for one another and do not create adverse health outcomes, e.g. generating a pathologic immune response after repeated switching. In the absence of such data patients and physicians should be aware that protein products with similar molecular composition may indeed not be interchangeable [34,35]. Since biosimilar and biological reference medicines are not identical, EMEA recommends that the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional [65]. Automated substitution of biopharmaceuticals (including biosimilars) on the pharmacy level has been excluded by legal or administrative regulations in several European countries.

5. The strategic perspective

The rising pressure of cost-containment in all major markets is driving the uptake of generics and also creates a demand for biosimilars. However, the cost and duration of development for biosimilars are much greater than for small-molecule generics, and presents a significant barrier to entry and a resistor of biosimilars market growth [66].

The possible savings achievable through biosimilar products have been estimated very differently in various studies – e.g., estimations of U.S. savings achievable from follow-on biologics vary between $378 billion over the 20-year period 2010–2029 [67] and $2.0–2.8 billion over 10 years [68] or $3.6 billion in 2008–2017 [69]. A recent estimation by the Congressional Budget Office [70] estimates that enactment of biosimilars legislation would reduce total U.S. expenditures on biologicals by $25 billion (thereof federal savings $5.9 billion plus increased revenues of $0.8 billion) over the 2009–2018 period, with competition beginning for most products not before the second half of this period. This would equal about 0.5% of national spending on all prescribed medicines. The study assumes a 35% sales-weighted average market share for biosimilars by the fourth year after launch.

The "philosophy" of the European biosimilars guidelines is based on the request that the applicant has to provide comparative data convincingly showing similarity vs. the reference product concerning quality, safety, and efficacy. This will be more challenging in the case of more complex or multifunctional molecules, and particularly for medicines where no "simple" (or accepted surrogate) clinical endpoints exist. So for example, in the case of cancer medicines based on monoclonal antibodies – which are glycosylated, multifunctional proteins with complex mechanisms of action often involving immune effector functions, and may require long and costly trials with survival endpoints to demonstrate clinical similarity – it may even be more straightforward for a second manufacturer to perform a stand-alone development than to demonstrate analytical, non-clinical, and clinical similarity in comparative equivalence trials [71].

Biosimilars are a reality and, as conventional generics, are part of the "rules of the game" in pharma industry. Besides flexible pricing strategies, an appropriate defense strategy by the innovator companies will focus on differentiated next-generation products which bring about convincing medical progress and make the first-generation, off-patent products obsolete, such as pegylated interferons which have largely taken over the market from interferon alfa products (e.g., Roche's Pegasys, Schering-Plough's Pegintron), or long-acting epoetins (e.g., Amgen's Aranesp, Roche's Mircera) which may replace the first-generation unmodified erythropoietin products. In this context, it has even been considered [72] that competition in future indeed might not primarily be between innovators and price-cutting copiers, but rather with second-generation biopharmaceuticals based on improved formulation or delivery systems, or derivatized biologics with improved performance. Thus the ultimate benefit of the emergence of biosimilars, in the end, may be in stimulating innovative research resulting in new options to treat serious diseases. It will be essential that the regulations introduced in various parts of the world do not hinder, but promote pharmaceutical innovation to the benefit of patients, healthcare systems, and industry.

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