

The challenge of biosimilars

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Background: The purpose of this report was to review issues associated with the introduction of alternative versions of biosimilars used in the oncology setting.

Design: Data were obtained by searches of MEDLINE, PubMed, references from relevant English-language articles, and guidelines from the European Medicines Agency.

Results: When biosimilars are approved in EU, they will be considered 'comparable' to the reference product, but this does not ensure therapeutic equivalence. Inherent differences between biosimilars may produce dissimilarities in clinical efficacy, safety, and immunogenicity. Switching biosimilars should be considered a change in clinical management. Regulatory guidelines have been established for some biosimilar categories but, because of the limited clinical experience with biosimilars at approval, pharmacovigilance programs will be important to establish clinical databases. Guidelines also provide a mechanism for the extrapolation of clinical indications (approved indications for which the biosimilar has not been studied). This may be of concern where differences in biological activity can result in adverse outcomes or when safety is paramount (e.g. stem cell mobilization in healthy donors). These issues should be addressed in biosimilar labeling.

Conclusions: Biosimilars should provide cost savings and greater accessibility to biopharmaceuticals. A thorough knowledge surrounding biosimilars will ensure the appropriate use of biopharmaceuticals.

Key words: biosimilars, substitution, extrapolation, pharmacovigilance, labeling

introduction

Recombinant technology has provided a means of producing a variety of therapeutic proteins, allowing biopharmaceuticals to become important therapeutic options for a variety of indications [1]. The recent and pending patent expirations for a number of biopharmaceuticals (e.g. granulocyte colony-stimulating factors [G-CSFs], erythropoietin, interferons and human growth hormone) have prompted the study and development of alternative versions of biologic products, referred to as biosimilars or 'follow-on biologics.' Biosimilars are new biopharmaceutical agents that are 'similar' but not identical to a reference biopharmaceutical product. This is unlike the case with small-molecule generics, where the active substance of a generic is identical to the reference product. Characteristics of biopharmaceuticals are closely related to the manufacturing process, which cannot be duplicated. Thus, biosimilars are unique molecules and are not generic versions of the innovator biopharmaceuticals.

Biological products have revolutionized the treatment of patients with cancer, and the pending introduction of

biosimilar products in the oncology setting will have important consequences. Biosimilars should provide cost savings, which may broaden access to biopharmaceuticals and stimulate further research. However, there also are potential efficacy and safety implications, and it is important that the introduction of biosimilars in the oncology setting be conducted in an appropriate manner. Since data at approval will be limited to those from comparability exercises, post-marketing pharmacovigilance data will be critical to ensure patient safety with respect to duration of exposure, use in various patient populations, rare adverse events, immunogenicity and other treatment issues that might emerge post-approval. It is also vital that healthcare providers have access to all data regarding biosimilars, so that they can make informed clinical decisions.

There will be a number of issues facing clinicians once biosimilars come to market. Biosimilars are not generic biopharmaceuticals but rather new, non-innovative products that will be supported by limited clinical data sets at the time of approval. This article will discuss the introduction of biosimilars into clinical practice for managing cancers. The manufacturing process for biosimilars will be reviewed, as will steps for facilitating pharmacovigilance programs and approaches for the use of biosimilars for indications that are based on extrapolation of clinical data.

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characteristics of biosimilars

For small-molecule pharmaceuticals, the development and production of generic-equivalent products is relatively straightforward. All that is required is demonstration that the generic product contains the identical chemical composition of the innovator product and a bioavailability study demonstrating that the pharmacokinetic properties of the generic and reference products are similar [2].

In contrast, biosimilars are not generic equivalents of the innovator products [2]. This perspective was adopted by the European Medicines Agency (EMA) and is the basis for its biosimilar approval guidelines [3]. This is because the active ingredients in a biosimilar are not identical to the innovator product. Since biopharmaceuticals are complex proteins that require multifaceted manufacturing processes, they are far more complex than small-molecule pharmaceuticals. Unlike conventional pharmaceuticals, there is a strong relationship between the manufacturing processes of biopharmaceuticals and the characteristics of the final product [4].

Indeed, the properties of biopharmaceuticals are dependent on the manufacturing processes [4]. Differences in manufacturing processes, protein source and extraction/purification processes result in heterogeneity of the resulting biopharmaceuticals (Figure 1) [2, 4–7]. For example, the unique cellular-expression systems used in protein manufacture inherently produce a variety of isoforms [2, 8]. In addition, small changes in manufacturing methods can produce alterations in the three-dimensional structure of the protein, the quantity of acid–base variants and the glycosylation profile [2, 3].

Biosimilar manufacturers will not have access to the manufacturing processes of innovator products because this is proprietary knowledge. Thus, it will be impossible for biosimilar manufacturers to precisely replicate any protein product [2]. In addition, since analytical techniques are not available for detecting or predicting all the biological and clinical properties of proteins, differences between biopharmaceutical products can easily remain undetected [2]. Regulatory guidelines must account for the differences between biosimilars and their reference products and must mandate rigorous pharmacovigilance.

The importance of the manufacturing process in the properties of biopharmaceuticals is highlighted by the variability in the composition and bioactivity of products produced outside of the United States and Europe. In a study comparing 11 epoetin products from four different countries (Korea, Argentina, China, India), the isoform distribution among these products was variable and there were substantial deviations from specifications for *in vivo* bioactivity. For example, *in vivo* bioactivity ranged from 71% to 226%, with five products failing to meet their own specifications [7]. However, it should be noted that these products are not regulated in European and US markets via the EMA and FDA.

biosimilars of drugs that are used for the treatment of cancer

There are several biopharmaceutical products used in the treatment of patients with cancer for which biosimilar products are likely to be developed. Table 1 summarizes the

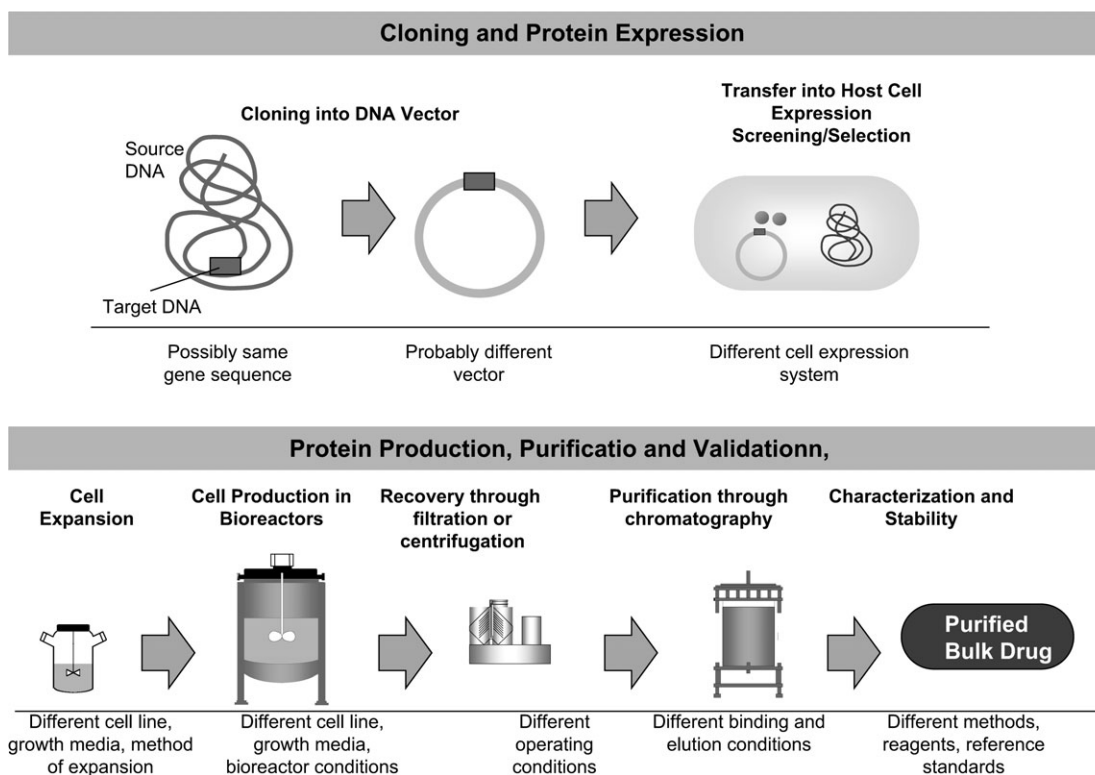


Figure 1. Recombinant protein production: sources of variation between manufacturers.

Table 1. Summary of product characteristics for biopharmaceutical products that have already lost or will soon lose patent protection in Europe

Product	Description	Source	Indications
Colony-stimulating factors			
Filgrastim	Recombinant protein of 175 amino acids (extra methionine at N-terminus); nonglycosylated	<i>Escherichia coli</i>	Chemotherapy-induced neutropenia (except CML and MDS); chemotherapy for AML; receipt of BMT; mobilization of PBPC; severe congenital, cyclic, idiopathic neutropenia; HIV-related neutropenia
Lenograstim	Recombinant protein of 174 amino acids; 4% carbohydrate	CHO	Chemotherapy-induced neutropenia, receipt of BMT, mobilization of PBPC
Interferons			
IFN α 2a	Recombinant protein of 165 amino acids (lysine at position 23); nonglycosylated	<i>E. coli</i>	Minimally pretreated patients with chronic-phase Philadelphia chromosome-positive chronic myelogenous leukemia, cutaneous T-cell lymphoma, AIDS-related Kaposi's sarcoma, chronic HCV (adults), chronic HBV (adults), follicular lymphoma, advanced renal cell carcinoma
IFN α 2b	Recombinant protein of 165 amino acids (arginine at position 23); nonglycosylated	<i>E. coli</i>	Hairy cell leukemia, malignant melanoma, follicular lymphoma, condyloma acuminata, AIDS-related Kaposi's sarcoma, chronic HCV (adults), chronic HBV (≥ 1 year)
Epoetins			
Epoetin alfa	Recombinant protein of 165 amino acids; glycosylated	CHO	Anemia of CRF, chemotherapy-induced anemia, increasing yield during autologous blood transfusion, decreasing allogeneic blood transfusion during surgery
Epoetin beta	Recombinant protein of 165 amino acids; glycosylated	CHO	Anemia of CRF; symptomatic renal anemia; chemotherapy-induced anemia; anemia in patients with multiple myeloma, low-grade NHL or CLL; increasing yield for autologous blood donation

AML, acute myelogenous leukemia; BMT, bone marrow transplant; CHO, Chinese hamster ovary; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CRF, chronic renal failure; HBV, hepatitis B virus; HCV, hepatitis C virus; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; PBPC, peripheral blood progenitor cell.

characteristics of some of the innovator products used for the management of cancer that have lost patent protection in Europe or will lose it in the near future.

granulocyte colony-stimulating factors

Natural G-CSF is a single polypeptide protein with minimal glycosylation (i.e. one carbohydrate chain) that accounts for approximately 4% of overall mass and has no significant contribution to 3-dimensional structure [9]. G-CSF acts to support the proliferation, differentiation and activation of committed progenitor granulocytes. The two currently available G-CSF products in Europe (filgrastim and lenograstim) not only differ from the natural protein, but they also differ significantly from one another with respect to biological characteristics and approved indications [10–13]. Comparative studies have demonstrated differences between these products with regard to pharmacological properties and clinical outcomes [11].

Because of the differences between products, currently available G-CSFs are not considered interchangeable. For some indications (e.g. febrile neutropenia), even a slight difference in efficacy between products could result in substantial clinical risk. In particular, the risk of product-related differences is likely to be greatest in indications in which neutropenia is most prolonged and the risk of infection is greatest. Studies indicate that there are differences between filgrastim and lenograstim

with respect to stem cell mobilization. A study in healthy volunteers found that lenograstim was associated with a 28% higher concentration of stem cell production compared with filgrastim [14]. In another study, Kim and colleagues demonstrated significant differences between lenograstim and filgrastim in hematologic recovery following autologous peripheral blood progenitor cell transplant (PBPC) with high-dose chemotherapy [11]. Patients receiving filgrastim had faster neutrophil, white blood cell and platelet recovery; required fewer days of G-CSF administration and spent less time in the hospital compared with those receiving lenograstim [11].

interferons

Interferon alfa products indicated for the treatment of patients with cancer include interferon alfa-2a (Roferon-A[®]) and interferon alfa-2b (Intron A[®]) [15, 16]. Although these products are produced in similar expression systems, have similar molecular weights, and only differ by one amino acid, there are clinically meaningful differences between them, and they are not considered interchangeable. In particular, studies suggest a difference between products in the incidence of neutralizing antibodies [17–19]. Although the exact relationship between the development of neutralizing anti-interferon antibodies and treatment efficacy is unclear, a review of cancer trials observed an increased risk of relapse in patients who developed neutralizing antibodies [17].

epoetins

Currently in Europe, epoetins are indicated for treating anemia in patients with chronic kidney disease or patients with cancer receiving chemotherapy [20–23]. All epoetin products in clinical use have a similar amino acid sequence to endogenous erythropoietin, but there are differences in source (Chinese hamster ovary cells versus human cells), manufacturing processes, glycosylation patterns, erythropoietin content, potency, dosage regimens, routes of administration and indications [5, 7, 24]. While all epoetins have the same molecular mechanism of action, there are differences in pharmacologic and clinical properties that have the potential to elicit a differential clinical response. These products are not considered interchangeable.

The differences in glycosylation patterns between epoetins are particularly important because glycosylation influences the pharmacokinetics of the product and may influence efficacy and safety, and especially, immunogenicity [24, 25]. For example, antibodies are often specific for the carbohydrate units of a particular glycosylation pattern. Depending on the structure of the antigenic site, glycosylation may also be required to allow reactivity with the antibody or may result in inactivation of the peptidic epitope [25].

The efficacy and safety of epoetins are related to the biopharmaceutical properties. Even small differences can have clinical consequences. Underscoring this is the recent observation of an increased incidence in antibody-mediated PRCA that was observed in patients with anemia of chronic kidney disease who were receiving a specific epoetin product. The increased incidence of PRCA corresponded to a change in the product formulation [26]. The removal of human serum albumin from the European formulation of Eprex®, as well as other manufacturing changes, coincided with a dramatic increase in the development of PRCA due to the development of neutralizing antibodies. The effect appears to be limited to

this formulation of Epoetin; however, the exact causes of the immunogenicity of this formulation are still under debate [27].

Another issue with epoetins is that direct dosage conversions between epoetin products are not available. Further, dosing requirements in the oncology setting are 3- to 5-fold higher than for patients with anemia of chronic kidney disease. Different dose–response characteristics between agents are important because an exaggerated pharmacodynamic response may result in the development of hypertension and thrombotic complications [24, 28–30].

regulatory recommendations

The European Union has developed a general legal pathway, and the EMEA has developed regulatory guidelines, for the approval of biosimilars (Figure 2) [3, 8, 31]. Because of the substantial differences between biopharmaceutical products, the approval process will vary according to the product. In particular, the amount of clinical data available may depend on the inherent variability of efficacy endpoints and the availability of validated surrogate markers. In general, the approval of biosimilars will be based on the demonstration of comparable efficacy and safety to an innovator reference product in a relevant patient population (i.e. ‘comparability’). EMEA guidelines will permit, with proper justification, the extrapolation of data from one therapeutic indication to another, allowing for the use of a biosimilar in indications for which it has not been formally studied. Because biopharmaceuticals are sometimes, although infrequently, associated with serious adverse events, EMEA guidelines also require immunogenicity testing and pharmacovigilance programs to monitor the efficacy and safety of biosimilar products post-approval. The importance of immunogenicity testing and pharmacovigilance is illustrated by the recent approval of the biosimilar growth hormone Omnitrope. During

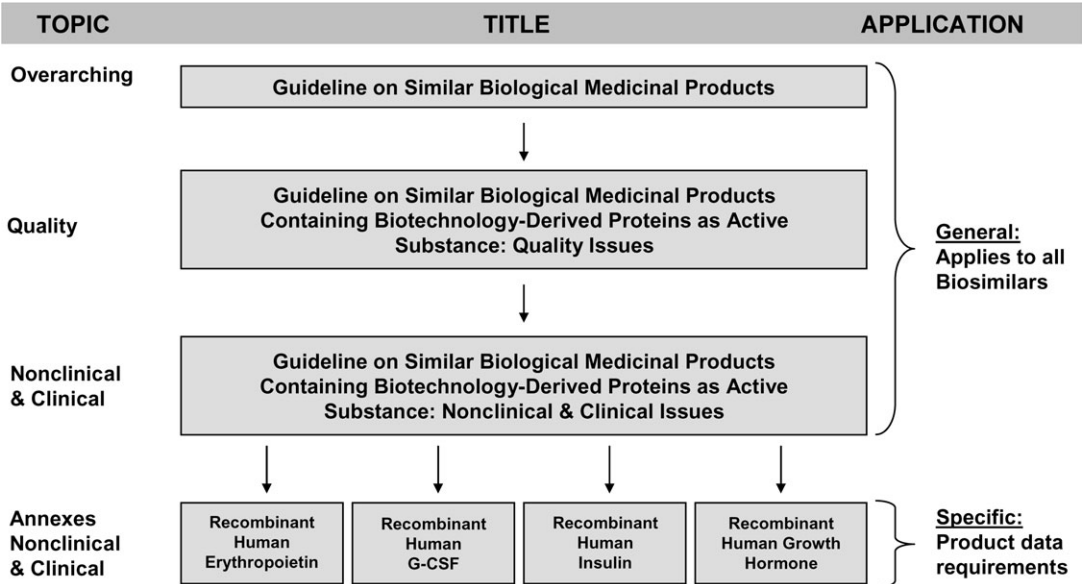


Figure 2. Overview of EMEA guidelines for biosimilars.

development, production of this product was transferred from one facility to another. While qualitative testing demonstrated no notable differences between the end products of these facilities, a difference was observed with respect to immunogenicity, which was subsequently resolved by the manufacturer prior to approval [32]. There is currently no legal pathway in the United States for the approval of biosimilars and, accordingly, the US Food and Drug Administration has not yet developed guidelines regarding these types of products.

It is important that healthcare professionals be aware of the differences between the concepts of therapeutic equivalence (i.e. substitutability) and 'comparability'. Therapeutic equivalence is a term used with reference to generic equivalents, in which the generic and reference products have identical chemical composition and are bioequivalent (have similar pharmacokinetic profiles). In the context of biosimilars, comparability is used to convey the concept that the biosimilar and reference products are not identical but have comparable efficacy and safety. Studies establishing therapeutic comparability do not guarantee therapeutic equivalence.

product-specific regulatory guidelines

Although no biosimilar G-CSFs have yet been approved, current EMEA guidelines state that the clinical model for the demonstration of comparability of biosimilars to the reference product in this case is the prophylaxis of severe cytotoxic chemotherapy-induced neutropenia (Table 2) [10]. A two-arm comparability study is recommended for chemotherapy regimens with known frequency and duration of severe neutropenia, and a three-arm study (including placebo arm) is required for other chemotherapy regimens. The guidelines also allow for extrapolation of the results to the other indications of the reference product if the mechanism of action is the same, although no specific criteria are recommended [10]. Alternative

models, such as pharmacodynamic studies in healthy volunteers, may also be allowed in the demonstration of comparability if justified.

The EMEA recognizes that erythropoietin is one of the most difficult products for the development of biosimilar agents (Table 2). The EMEA guidelines for erythropoietin state that comparability studies should be performed in patients with anemia due to chronic renal disease and that at least two randomized clinical trials are required [24]. In addition, clinical comparability should be shown for both intravenous and subcutaneous routes of administration. Current EMEA guidelines also allow for the extrapolation of safety and efficacy data from patients with renal anemia to other indications if the extrapolation can be appropriately justified [24].

issues to be considered with clinical use of biosimilars

pharmacovigilance

Because there is a limited clinical database at approval of a biosimilar, it is important to collect post-approval safety data for these drugs. This is because differences between biosimilars, with respect to efficacy and/or safety, may not become apparent in the pre-approval period, during which only limited numbers of patients receive the product over a specified time-span [3]. An important component of post-approval data collection is the ability to distinguish readily between different biosimilar products and the reference products, so that it is clear which specific product a patient has received.

The importance of post-marketing pharmacovigilance is highlighted by experience with epoetins, where the development of antibody-mediated pure red cell aplasia (PRCA) in patients with chronic kidney disease was associated with a formulation change for one product [26]. As noted

Table 2. Summary of EMEA requirements for approval of biosimilar G-CSFs and epoetins

	G-CSF	Epoetin
Preclinical studies	<ul style="list-style-type: none"> Comparative non-clinical studies 28-day toxicology 	<ul style="list-style-type: none"> Comparative non-clinical studies 28-day toxicology
Human PK & PD studies	<ul style="list-style-type: none"> Single-dose s.c. and i.v. in healthy volunteers 	<ul style="list-style-type: none"> Single-dose s.c. and i.v. in healthy volunteers
Efficacy studies	<ul style="list-style-type: none"> ANC and CD34⁺ in healthy volunteers Two-arm (vs reference product) OR Three-arm (vs reference product + placebo) equivalence trial in CIN OR PD study in healthy volunteers (if justified) 	<ul style="list-style-type: none"> Include PD evaluation (reticulocytes) in PK studies Two randomized, double-blind studies in nephrology Both routes of administration (s.c. and i.v.)
Extrapolation	Yes—equivalence in CIN will allow extrapolation to other indications if mechanism of action is the same	<ul style="list-style-type: none"> Dose and Hb levels to be collected Yes—equivalence in renal anaemia may allow extension to other indications if justified by applicant
Safety	<ul style="list-style-type: none"> Evaluate AE's and immunogenicity in CIN study Six-month follow-up 	<ul style="list-style-type: none"> Safety from efficacy studies is adequate for approval Twelve-month, comparative immunogenicity data
Post-approval commitments	Specific monitoring for lack of efficacy in extrapolated indications	PRCA to be addressed Safety in cohort of patients from all indications (i.e. including extrapolated indications)

ANC, absolute neutrophil count; CIN, chemotherapy-induced neutropenia; Hb, hemoglobin; i.v., intravenous; PD, pharmacodynamics; PK, pharmacokinetics; PRCA, pure red cell aplasia; s.c., subcutaneous

previously, differential immunogenic responses have also been observed between similar biopharmaceutical products (e.g. IFNs, epoetins).

Because of the potential risks associated with biopharmaceuticals, particularly immunogenicity, and the potential for clinically meaningful differences between products, there is a need for rigorous pharmacovigilance programs to monitor all biopharmaceuticals (including innovator products and biosimilars) for safety and efficacy issues during the post-approval period. Such post-marketing programs will need to be tailored to each biopharmaceutical category to address product-specific issues.

The EMEA in Europe and the Food and Drug Administration (FDA) in the United States have well-established pharmacovigilance programs for the monitoring of adverse events to medicinal products [33, 34]. EudraVigilance is the EMEA network for reporting and evaluating suspected adverse reactions during development and following marketing authorization. One component of pharmacovigilance is spontaneous reports by healthcare professionals. Ideally, these reports should contain as much information as possible, including the type of adverse event and information on the drug (e.g. proprietary name, INN, dosage given and lot number). However, adverse events are frequently not reported or the reports are incomplete. In addition, the rules for reporting vary from country to country [35, 36].

Pharmacovigilance plans developed and implemented by manufacturers are frequently part of the post-approval commitments to regulatory agencies to provide follow-up safety assessments [33, 34]. These programs provide a means of quantifying the frequency of adverse events and a way of expediting the reporting of serious or previously unknown adverse events. These programs may include patient registries and retrospective or prospective observational and pharmacoepidemiologic studies.

Pharmacovigilance programs for biosimilars are required by the EMEA to provide a continuous method for the monitoring and evaluation of safety issues so that responses are rapid and accurate [31]. Pharmacovigilance programs may be useful for the early detection of emerging safety issues. Pharmacovigilance programs are also important for assessing the safety of products in specific patient populations. This is particularly important for the safe use of biosimilars in therapeutic indications for which the product may not have been formally evaluated (i.e. for an extrapolated indication).

substitution

Automatic substitution allows for the dispensing of generic drugs in place of prescribed innovator products by pharmacists without the knowledge or consent of the treating physician. For the majority of small-molecule generics, automatic substitution is appropriate and can produce cost savings. However, there are situations where automatic substitution is not advisable and may compromise safety and pharmacovigilance programs. Automatic substitution may be inappropriate for drugs with a narrow therapeutic index, such as modified-release theophylline and calcium channel blockers [37]. For these drugs, the differences between drug concentrations required to

produce therapeutic effect and concentrations associated with toxicity are too small to assume that the generic will have the same risk/benefit profile as the innovator.

In some European countries and US states the automatic substitution of such drugs is prevented by placing them on 'do not substitute' lists [38], while other European countries rely on the training and expertise of physicians and pharmacists to prevent inappropriate substitution. Regardless, inappropriate substitution with such drugs can occur when physicians and/or pharmacists do not understand the potential risks involved and the distribution systems allow or encourage automatic substitution. As a risk prevention measure, French legislators in early February 2007 approved a law that clearly distinguishes biosimilars from generics and prohibits automatic substitution with biosimilars [39].

For a variety of reasons, automatic substitution is not appropriate for biopharmaceutical products. As noted, biosimilars are not generic versions of innovator products, and there will be limited clinical experience with biosimilars at approval. Small differences between biosimilars and innovator products may affect clinical outcomes. Further, if automatic substitution is allowed, patients could receive multiple biopharmaceutical products over the course of therapy. Such practices would confound the collection of pharmacovigilance data. If an adverse event were to emerge after switching from one biopharmaceutical to another without documentation of the product change, the event would not be able to be linked to a specific product during the pharmacovigilance assessment, or it could be ascribed to the wrong product. For reasons of safety monitoring, it is essential that clinicians be aware of the exact biopharmaceutical product their patients are receiving.

naming and labeling biosimilars

For accurate pharmacovigilance, it is essential that physicians, pharmacists and patients are able to distinguish easily between biopharmaceutical products. It may not be possible to properly link adverse events to a specific product, if multiple products share one International Nonproprietary Name (INN) and pharmacovigilance reports do not contain additional identifying data for the specific product. The importance of this concept is supported by the EMEA. The position statement from the EMEA emphasizes that 'In order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified' [3].

The EMEA does not oversee the allocation of INNs; this activity is conducted by a committee of the World Health Organization on the advice of an international expert advisory panel. It would appear prudent for this committee to assign unique INNs to biopharmaceuticals. This would help to facilitate accurate prescribing and dispensing of biopharmaceuticals. The EMEA should consider requiring comprehensive labeling of biosimilars so that physicians and pharmacists can make informed decisions. Because biosimilars are not equivalent to reference products and because unique efficacy and safety data will be available, labeling should include these data. Furthermore, labeling should note those indications that are based on extrapolation of data.

extrapolation of clinical data

Extrapolation involves the approval of a drug for indications for which it has not been evaluated in clinical trials. Extrapolation has played a role in drug development and has a rational basis, but it is only applicable in limited circumstances, such as line extensions, new formulations, or new indications in closely related diseases [40]. The EMEA has generally endorsed the concept of data extrapolation for biosimilars with the appropriate justification. The rationale is that if the biosimilar shows adequate comparability to the innovator product for one indication, it may be reasonable to extend the approval of the biosimilar to all the indications of the innovator product. The biosimilar manufacturer would have to provide an adequate scientific explanation, although 'adequate' is not always well defined. If the mechanism of action differs between indications, the biosimilar manufacturer may have to provide additional clinical data.

The recent approval of two biosimilar growth hormones included extrapolation of clinical data for some indications. The approval process for Omnitrope included a number of comparability studies to the reference product, Genotropin, including quality studies, pharmacokinetic and pharmacodynamic studies, clinical efficacy and safety studies, and immunogenicity studies [32]. While the efficacy and safety comparability studies between Omnitrope and the reference product (Genotropin) were conducted only in children with growth disturbances, the product labeling for Omnitrope is virtually identical to that of the reference product, including the indication for use in adults. Reasons for the extrapolation of data between the innovator and biosimilar growth hormone products appear to include: (1) the long clinical history of safe use of growth hormone; (2) the wide therapeutic window of the drug; (3) the rarity of reports of neutralizing antibodies; (4) the ability to characterize the structure and biological activity of growth hormones by physicochemical and biological methods; and (5) the variety of assays available to characterize the active and product-related substances [41, 42].

While these criteria may be appropriate for the use of well-characterized proteins, such as growth hormones, in average-risk populations, they may not be applicable to more complex biopharmaceutical products or those used in critically ill patients. A potential concern with the concept of data extrapolation is that the risks for using a biopharmaceutical may differ in various patient populations (e.g. between patients with cancer and those with other diseases). This concern has a precedent in cytotoxic chemotherapy, in which the differences in biology between adult and pediatric tumors and in physiology between adults and children usually preclude extrapolation of clinical activity data from adults to children [43]. There may also be differences in immune responses between patients who are receiving recombinant G-CSF for chronic neutropenia versus chemotherapy-induced neutropenia. Since patients with chronic neutropenia are not immune suppressed, they may be more likely to develop antibodies to biopharmaceutical agents, although no antibody-related treatment issue has emerged to date with current G-CSF products.

Although data extrapolation has a rational basis as long as appropriate criteria are met, the process by which indications

for a product were approved should be clear to healthcare professionals and patients. Physicians, pharmacists and patients should be aware of the clinical data directly supporting an indication and of the instances in which indications are based on extrapolation of data. Because the Summary of Product Characteristics (SmPC) of the biosimilar Omnitrope is virtually identical to that of the innovator product Genotropin, physicians and pharmacists reading the SmPC of Omnitrope will be unaware that the drug was approved based on clinical data that differ from those in the label, and that its indication in adult patients with growth hormone deficiency was based on data extrapolation [32, 44]. A more comprehensive and accurate approach would be for the SmPC to specify which data are based on extrapolation. With any biopharmaceutical, clinicians need to know the basis of approval for an indication so that they can make informed decisions.

economic and societal consequences

Biopharmaceuticals are more expensive than small-molecule drugs, and their use is increasing. An important benefit of biosimilars is that they are likely to be associated with cost savings. However, it is unclear how cost pressures from biosimilars will affect the prices of innovative products, as manufacturers may alter pricing strategies prior to patent expiration to help them recoup investment costs. Furthermore, the cost savings for biosimilars will likely not be as significant as those seen with small-molecule generics because of the substantial manufacturing costs for biosimilars and the costs of bringing the products to market. It also must be noted that drugs represent only a small fraction of the total cost of treatment for cancer patients [45]. Nevertheless, cost savings with biosimilars will likely increase access to therapeutic proteins and stimulate innovative research.

stem cell mobilization in healthy donors

The increasing use of CSFs for stem cell mobilization and collection from healthy donors for use in allografting [46–49] presents an ethical dilemma for biosimilar use. A 2003 survey by the European Group for Blood and Marrow Transplantation (EBMT) found that 65% of the 7091 allogeneic first transplants in Europe were performed using peripheral blood stem cells from related and unrelated healthy donors [50]. While the procedure appears to be relatively safe for donors, adverse events are common and include transient bone pain, headache, nausea and fever [51–53]. Serious and long-term adverse events appear to be rare, but the high incidence of CSF-induced splenomegaly has raised concern about the risk of splenic rupture [54]. Since healthy donors receive no therapeutic benefit from the receipt of CSFs for stem cell mobilization, ethical concerns dictate that drug safety be of paramount concern for these individuals. Considering the detrimental effect that unexpected toxicity might have in normal individuals donating their peripheral stem cells, sufficient experience with the biosimilar product and adequate follow up should be required. Needed safety data can only be obtained by performing an adequate number of stem cell mobilization procedures (successful mobilization procedures in 500 individuals might be sufficient) and conducting long-term

follow up (3 years' follow-up) in patients undergoing autologous stem cell transplantation. Such experience has to be collected within a clinical study and analyzed by experts in the field and by regulatory authorities before healthy donors are routinely treated with growth factors. In general, a good history of clinical safety (low incidences of adverse events and immunogenicity) may be a more appropriate consideration for choosing a G-CSF product in these patients than any cost savings achieved with the use of a biosimilar.

conclusions

Since a number of biosimilar products are either already approved (somatropins, glucagons, hyaluronidase, calcitonin) or are under development (e.g. epoetins, G-CSFs), these agents will undoubtedly play an increasing role in disease management. While biosimilars provide a number of opportunities, it is important that they be introduced in an appropriate manner.

There are potential concerns regarding the use of biosimilars in patients with cancer that warrant consideration when making a biopharmaceutical product choice. Clinicians require a thorough understanding of the issues associated with biosimilars so that they can make informed decisions. Of primary importance, clinicians need to be aware that biosimilars are not generic versions of innovator products. Biosimilars will be approved as safe and efficacious agents by the EMEA, but they will be inherently different from innovator products. Therefore, switching or substitution between innovator products and biosimilars should be viewed as a change in clinical management. Because of the limited clinical experience with biosimilars at the time of their approval, these potential clinical differences may not become apparent until after approval. Thus, rigorous pharmacovigilance programs are needed to capture this data and to build a database establishing the clinical use of each product. To ensure that such pharmacovigilance programs establish an accurate database, automatic substitution should be prohibited, because physicians need to effectively monitor patients receiving a biopharmaceutical and such authorizations would confound accurate pharmacovigilance. This is particularly relevant in the community setting but also in the clinical trial setting when biopharmaceuticals are used as non-study drugs.

Extrapolation of clinical data from one therapeutic indication to another for biosimilars also warrants concern. Ultimately, data extrapolation entails a risk/benefit assessment. The assumption that a biosimilar will be effective for indications beyond those for which it has been formally tested is balanced against the implications for the patient if the efficacy or safety profile differs from that of the innovator product. Because the inherent differences between biopharmaceutical products may involve a greater risk-to-benefit ratio for certain patient populations (e.g. stem cell donors) than for others, extrapolation should be implemented on a case-by-case basis. If extrapolation of data is allowed, the package labeling should explicitly state this along with the clinical data used to support extrapolation.

In summary, information is the key to mitigating the potential concerns regarding the use of biosimilars. In

particular, physicians and pharmacists must be fully aware of the differences between biosimilars and innovator biopharmaceuticals. For complex biopharmaceutical agents, any change from one product to another (innovator to biosimilar or vice versa) should be considered a change in clinical management.

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