Biosimilars: An Emerging Category of Biologic Drugs for Emergency Medicine Practitioners

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Published online: 11 September 2013
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Abstract Biologics are the fastest growing segment of annual United States (US) drug expenditure. Biologics are complex proteins derived from living sources that are important therapy for a variety of diseases. The US is now poised to introduce biosimilars, which are copies of biologics that are not manufactured by the innovator company and are approved under an abbreviated regulatory process. Biosimilars are intended to offer comparable safety and efficacy to the reference biologic at a lower cost. Because of the complexity of producing biologics, the manufacturing process for biosimilars may differ from that of the reference biologic, which may result in subtle changes in biological characteristics and clinical activity. Questions exist regarding whether these slight differences allow the products to be interchanged with the reference product and if unique adverse events will occur with use. While the *Biologics Price Competition and Innovation Act* outlined the abbreviated approval pathway for biosimilars, guidance from the US Food and Drug Administration (FDA) is needed on specific details of the approval process. The FDA has recently provided guidance about the scientific and quality requirements for demonstrating biosimilarity, but a number of unanswered questions still remain, including concerns about immunogenicity, product naming, and the exact cost savings from biosimilars. Emergency Medicine practitioners must have a sound understanding of these issues to ensure patient safety and avoid complications in care.

Keywords Biosimilars · Biologics · Generic medications · FDA approval pathway · Immunogenicity

Introduction

Annual spending on prescription medications is forecasted to reach \$372 billion in the United States (US) and \$1.2 trillion worldwide by 2016 [1]. Biologics, medications synthesized through biotechnology, are the fastest growing segment of the pharmaceutical market. Biologics are generated by cells or living organisms through recombinant deoxyribonucleic acid (DNA) technology, controlled gene expression, or antibody production, and encompass a wide range of substances, including hormones, vaccines, growth factors, blood products, monoclonal antibodies, and advanced technology products (e.g., protein–antibody combinations, gene therapy biological products) [2]. The FDA approved the first biologic human insulin (Humulin) in 1982 [3]. Since then, the pharmaceutical industry has developed many biologics for the treatment of acute life-threatening diseases, such as cancer and cardiovascular illness, and for chronic conditions like diabetes, anemia, rheumatoid arthritis, and multiple sclerosis, and for rare genetic conditions, such as Gaucher’s disease and Fabry disease. Health providers are now trying to balance the pressures of prescribing these agents early, when the disease course may be prevented or modified, with the challenges of patient and insurer affordability. After 30 years on the market, the patents on many of these recombinant biologics will soon expire (Table 1) [4, 5] and the US pharmaceutical marketplace is now poised for the introduction of biosimilars. It is therefore important for Emergency Medicine practitioners, including physicians, physician assistants, nurses, and pharmacists to understand the issues surrounding these agents to ensure optimum patient care.

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Table 1 Biologics, therapeutic uses, global sales, and patent expiration

Product	Brand name	Category	Use(s)	Global sales	Year launched	Patent expiration
Alteplase, t-PA	Activase	Recombinant human protein	Myocardial infarction, stroke, pulmonary embolism, catheter clearance	\$440 million	1985	2005
Filgrastim	Neupogen	Recombinant human protein	Neutropenia	\$1.3 billion	1991	2013
Erythropoietin alpha	Epogen/Procrit	Recombinant human protein	Anemia	\$4.5 billion	1989	2014
Pegfilgrastim	Neulasta	Pegylated human G-CSF	Neutropenia	\$3.3 billion	2002	2015
Palivizumab	Synagis	Antibody	Respiratory syncytial virus	\$900 million	1998	2015
Dornase	Pulmozyme	Protein	Cystic fibrosis	\$513 million	1994	2015
Darbepoetin alfa	Aranesp	Recombinant variant of erythropoietin	Anemia	\$2.5 billion	2004	2019
Interferon alfa-2a	Pegasys	Pegylated recombinant human interferon	Hepatitis B, hepatitis C	\$670 million	2002	2019
Interferon beta 1a	Avonex	Recombinant human protein	Multiple sclerosis	\$2.5 billion	1996	2026
Interferon beta 1a	Rebif	Recombinant human protein	Multiple sclerosis	\$6.7 billion	2002	2026
Interferon beta-1b	Betaseron	Recombinant human protein	Multiple sclerosis	\$1.6 billion	1993	2026

JIA juvenile idiopathic arthritis, *G-CSF* granulocyte-colony stimulating factor

Definitions

Biosimilars are simply described as copies of biologics that are not manufactured by the innovator company and are approved under an abbreviated regulatory process. Because it is not possible to copy a biologic in the precise manner that small molecules can be replicated, the term “generic biologic” is inappropriate. Therefore, a variety of other terms have been used for these products, such as follow-on biologics, biogenerics, and postpatent biologics. During the last several years, and especially after the introduction of the legislation described below, the term *biosimilar* has become the standard term, but definitions are not standardized. Recently, a more detailed consensus definition was proposed: “A biosimilar is a copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise” [6].

Scope and Impact

Global biologics sales amounted to approximately \$93 billion in 2009 and are expected to be worth more than \$167 billion by 2015 [7]. Biologics sales are expected to continue to grow at least twice as fast as those of conventional, chemical based, small-molecule medications. By

2016, ten biologics are expected to occupy the top 20 positions in pharmaceutical industry sales. The top six biologics already consume 43 % of the drug budget for Medicare Part B [8]. As a result of this clinical and commercial success, pharmaceutical companies have invested heavily in the development of biologics. Approximately 30 % of the industry’s research and development pipeline is composed of biologics [2, 9•].

The goals for encouraging the development of generic biologics are the same as those for encouraging generic small-molecule drugs, which is to reduce costs by fostering price competition and provide patients with access to treatment at an affordable price. Generic drug use is common [10]. In 2011, approximately 80 % of the four billion drug prescriptions issued in the US were dispensed using generic medications. Estimated savings to the consumer and to the US health-care system from generic drug use reached \$193 billion in 2011. The introduction of generic biologics or *biosimilars* is projected to generate \$9 to \$12 billion in savings for the US Medicare program during the next decade [11, 12].

Small-Molecule, Biologic, and Biosimilar Manufacturing

The manufacturing process for biologics is more complex than the chemical synthesis used for conventional small-molecule

Table 2 Comparison of small-molecule medications and biologics

Characteristic	Small-molecule drugs	Biologics
Production	Chemical synthesis	Through biotechnology and host cell lines
Size	Low molecular weight	High molecular weight
Physicochemical properties	Well defined Stable	Complex Sensitive to heat, sheer stress (aggregation)
Manufacturing	Single entity, high chemical purity, standards well established Not affected by slight changes in production process and environmental conditions	Heterogeneous mixture, broad specifications which may change during development, difficult to standardize Highly susceptible to changes in production process and environmental conditions
Analytic assays	Completely characterized by analytic methods	Difficult to characterize, assays not standardized
Decontamination	Easy to purify	Lengthy and complex purification process
Quality assurance and detection	Contamination can be avoided and easily detected and removable	High possibility of contamination, detection hard, and removable impossible
Pharmacokinetic properties	Administered through different routes Rapidly enters systemic circulation through capillaries	Parenteral route of administration most common Larger molecules enter circulation through lymphatic system, subject to proteolysis and lymphatic transit
	Distributes to any organ and tissue	Distribution limited to plasma and extracellular fluid
Toxicity	Organ specific toxicity	Mostly receptor-mediated toxicity
Allergenicity	Often not antigenic	Usually antigenic

Table 3 Demonstrated differences in biologics

Medication class	Comparator	Difference	Molecular difference or cause
Coagulation factor VII	Natural factor VII	Antibody production	Pasteurization process
Interferon alfa-2a (Intron-A, Roferon-A)	Itself	Antibody production	Human serum albumin diluent and room storage
Epoetin (Eprex)	Same protein, different formulation	Antibody production causing anemia (pure red blood cell aplasia)	Change in stabilizer from human serum albumin to glycine and polysorbate 80

pharmaceuticals (Table 2) [13]. The production of biologics and their subsequent pharmacologic activity are dependent on the manufacturing processes, which, in turn, are very sensitive to changes in production [14]. Any changes occurring to the expression systems used for production, culture conditions (e.g., temperature and nutrients), equipment, purification and processing, formulation, storage, or packaging may result in subtle changes in the biological characteristics, clinical activity, and toxicity profile (Table 3) [15, 16]. In addition, while producing complex biologics, there are formulas and processes and a substantial amount of *tacit knowledge* (i.e., knowledge or functions that have not been reduced to instruction or recipe) that may affect the final product. Even when biologics are produced from the same process, technique, formulation, and packaging as the reference product, there is no guarantee that they will be identical with the reference product. To uphold their patents, innovator pharmaceutical companies have argued that there can never be a generic equivalent to a biological medication, only a similarity.

With recent biotechnology advances, manufacturers are able to create accurate protein copies by using microbial rather than mammalian cell lines. Proteins created through microbial fermentation in *Escherichia coli*, without post-translational modifications, can be produced cheaply, easily, with high purity, and with reliability. Most of the early biologics (e.g., insulin, growth hormone, filgrastim, and interferons) can be produced in this fashion. Future advances in microbial cell lines may remove the need for mammalian cell cultures altogether [17].

Characterization

For conventional, chemical based, small-molecule medications, generic approval hinges on pharmaceutical equivalence (i.e., identical active substances) and bioequivalence (i.e., comparable pharmacokinetics) to the innovator agent. Chemical identity can be confirmed by exact analytical techniques, for example high-performance liquid chromatography (HPLC), mass spectrometry (MS),

nuclear magnetic resonance (NMR), and X-ray diffraction. Bioequivalence and rate and extent of absorption is usually established in a single study involving 24–36 healthy volunteers [17].

The larger molecular size and structural complexity poses a challenge for the characterization of biosimilar medications. Although techniques such as HPLC, MS, NMR are still used, newer techniques such as capillary electrophoresis and peptide mapping have been introduced to identify protein structure and function. Collectively these advances have improved molecular understanding, yet it is unclear whether they are capable of detecting all structural differences or whether these differences affect clinical efficacy and safety [18]. Consequently, analytical tests for characterizing structure and physicochemical properties may provide an incomplete picture. For example, the helical, pleated, folded, and interactive conformational states of a protein can be difficult to detect and the assays limited to a particular fingerprint region of the product. Furthermore bioassays, measuring receptor binding and cell response, have not been standardized, which prevents the comparison of results between different laboratories. These limitations increase the obstacles to establishing equivalence between a biosimilar and a reference product [15•].

Legislative History, Approval Process, and New Approval Pathways for Biosimilars

The FDA approves and licenses conventional small-molecule medications under the *Federal Food, Drug, and Cosmetic Act* (FD&C), enacted in 1938. In contrast, permission to introduce a biologic requires a Biologic License Application (BLA). A BLA for vaccines, toxins, antitoxins, blood, blood components or derivatives, allergens, or analogous products is approved through the 1944 *Public Health Services Act* (PHS). Large, complex biologics are required to follow the BLA process for approval and licensure [19]. A large number of chemically or biologically active compounds show early promise as medications in preclinical trials. However, few emerge through the FDA approval process and become established as safe and effective therapy.

The *Drug Price Competition and Patent Term Restoration Act* (also commonly known as the *Hatch–Waxman Act*) amended the FD&C Act in 1984, establishing the current system of generic drug approval. The revision provided two abbreviated pathways for the approval of generic small-molecule drugs, a small number of natural-source products, and simple recombinant proteins. More importantly, the pathways eliminated preclinical and human studies in the New Drug Application (NDA) of a generic drug. For a new small-molecule entity to be

approved, it must follow the 505(b)1 pathway, complete clinical trials (Phase I, II, III), and safety and efficacy in the treatment of the targeted disease state must be demonstrated. The 505(j) pathway sets forth the process by which the manufacturer of a generic drug, one that is bioequivalent to a previously approved product, can file an Abbreviated New Drug Application (ANDA) to seek FDA approval. An ANDA allows the applicant to rely on the FDA's previous finding of safety and efficacy for the already approved drug and bypass clinical trials. The 505(b)(2) pathway also allows an existing medication to be approved by using study data from a prior application and either limits clinical studies (3–6 months in duration) or avoids them completely. However, because of the size and complexity of the biologic molecules, manufacturers have not been able to demonstrate that their biologic is identical to an already existing, approved product. Therefore, the abbreviated 505(j) approval pathway has not been routinely available for biosimilar protein products. Similarly, the FDA has limited the 505(b)(2) pathway, which allows direct comparison of the generic drug with a product already approved, to a small number of natural source products and recombinant proteins (e.g., human and bovine hyaluronidase, salmon calcitonin, human glucagon, and human growth hormone). In these instances, while data about each biologic were provided, the structural characterization, comparative pharmacokinetics, pharmacodynamics, and immunogenicity were well known. The approval was based on the knowledge about the safety and effectiveness of a similar, already approved product [20•]. In at least one case where a non-innovator human growth hormone was approved under this pathway, the FDA made it clear this was not a pathway for future approvals [21].

In March 2010, the *Biologics Price Competition and Innovation Act* (BPCI) became law as a section of the *Patient Protection and Affordable Care Act* (PPAC). BPCI amended the PHS Act by adding subsection (k), which finally established an abbreviated approval pathway for copies of biologic medications [20•]. The legislation permits a biological product to be evaluated against only a single reference biological product and outlines the requirements for achieving biosimilarity (Table 4). Based on data derived from analytical, animal, and clinical studies, the biologic product must be “highly similar to the reference product” and have “no clinically meaningful differences in safety, purity, and potency.” The FDA is given flexibility in the approval process and can determine that one or more of these data requirements are not needed. The Health and Human Services (HHS) secretary will then decide whether the biologic is licensed as *biosimilar to* or *interchangeable with* the reference product. (Although the law as written is such that the HSS secretary will make this decision, these decisions are expected to be delegated to

Table 4 US Food and Drug Administration (FDA) abbreviated approval requirements for biosimilar medications

Domain	Characteristic of biosimilar
Pharmacology	Utilizes the same mechanism or mechanisms of action for the condition(s) of use prescribed, but only to the extent the mechanism or mechanisms of action are known for the reference product
Delivery	Utilizes the same route of administration
Formulation	Same dosage form, same purity
Pharmacokinetics	“Highly” similar
Potency	Same potency
Indications for use	The condition or conditions must be previously approved for the reference product
Data supporting safety and efficacy	Analytical studies that demonstrate that the biological product is highly similar to the reference product Animal studies (including assessment of toxicity) Clinical study or studies (including assessment of immunogenicity and pharmacokinetics or pharmacodynamics) to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed
Excipients	Minor differences in clinically inactive components are allowable
Manufacturing facilities	Must follow “good manufacturing practices”
Substitution	Product may be biosimilar or deemed interchangeable
Patent protection	Innovator is granted 12 years of exclusive use to manufacture the reference product Six month extension is granted for pediatric studies Biosimilar is granted exclusive use for one year if licensed as the first interchangeable biosimilar
Guidance	FDA may issue general or specific guidance on the science and experience required for the product or product class The issuance or nonissuance of such guidance does not preclude approval of a biosimilar FDA establishes a process through which the public can provide FDA with input regarding priorities for issuing guidance
Risk Evaluation Mitigation Strategy Programs (REMS)	Same REMS programs required of the innovator agent are applied to the biosimilar

the FDA). Therefore, it is important to note that BPCI establishes a framework where two types of biosimilars may reach the US market—those that are considered biosimilar and those products that are considered both biosimilar and interchangeable.

The BPCI Act includes provisions for *exclusivity* for economic protection. The FDA may not approve a BLA for a biosimilar until 12 years after the reference product was first licensed. The exclusivity period can be extended by six months if studies involving pediatric patients are completed. In addition, the BPCI Act encourages biosimilar development by granting one year of exclusive marketing rights to the first biosimilar that is approved as being *interchangeable* with a reference product [19].

In July 2012 President Obama signed the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, which reauthorized the *Prescription Drug User Fee*

Act (PDUFA). PDUFA allows the FDA to collect user fees for new drug applications. FDASIA contained provisions for biosimilars, which is referred to as the *Biosimilar User Fee Act of 2012* (BsUFA). This new legislation authorizes the FDA to assess and collect fees from biopharmaceutical manufacturers seeking approval for biosimilars. These resources will be used to hire staff that can provide feedback to companies seeking to develop biosimilars, expedite the application review process, and ultimately speed up the arrival of biosimilars to the marketplace [22].

FDA Guidance Documents

Guidance from the FDA on biosimilars is critical, because the BPCI Act provides the FDA with flexibility to define specific details of the biosimilar approval process. In February 2012 the FDA released three-part draft guidance

Fig. 1 Food and Drug Administration guidance for industry

to the industry regarding the development and approval processes for biosimilars [23•, 24, 25]. The FDA emphasizes that they will consider the totality of evidence to support a demonstration of biosimilarity. Each part outlines the complexity and challenges of developing and securing FDA-approval for a biosimilar medication. The FDA recommends a stepwise approach to demonstrating biosimilarity that includes scientific, animal, and human studies, where the evidence supports safety and effectiveness comparable with that of the reference product (Fig. 1).

In addition, the FDA describes the quality requirements for biosimilarity. Manufacturers must ensure their expression system codes the same protein sequence as the reference product. The manufacturer must understand all manufacturing steps with physicochemical assessments identifying structures (primary, secondary, tertiary, and quaternary) and post-translational modifications. Functional bioassays should complement all analytic activities and when receptor binding is critical, comparison studies must be completed versus the reference product. Manufacturers are required to characterize, identify, and quantify impurities in both the reference product and their biosimilar. Finally, a complete characterization of the finished product, including stability testing under accelerated stress study conditions (i.e., high temperature, light exposure, agitation, etc.) is required to ensure product degradation and clinical performance are comparable with those of the reference product. Manufacturers are expected to generate reference standards or databases of scientific knowledge that can be relied upon for both the biosimilar and the reference product [24, 25].

Immunogenicity

Immunogenicity is the major safety concern for biosimilars and can be described as either classic immune reactions to foreign proteins or as a breakdown of immune tolerance (Table 5). Classic immune reactions are associated with

products of human, animal, microbial, or plant origin and occur immediately, usually after a single injection. The clinical consequence, in most cases, is loss of medication efficacy and the reaction itself may force the patient to stop their treatment [26]. The second mechanism leads to the development of neutralizing antibodies against the biosimilar. While the mechanisms by which the breakdown of immune tolerance is induced are not completely understood, it appears that aggregation in protein drugs and impurities are the most important factors in precipitating the generation of neutralizing antibodies [27].

Factors affecting the immunogenicity of a biologic include structural properties (e.g., sequence variation and glycosylation), the patient's genetic background, the route of administration (evidence suggests that intravenous administration is less likely to elicit an immune response than subcutaneous or intramuscular administration), and the product formulation [26]. Appropriate formulation, handling, and storage of a biologic is important, particularly with regard to stabilization. With inadequate stabilization, the protein may aggregate or denature, increasing its immunogenic potential. In a study of interferons, the most immunogenic formulation was a freeze-dried, human serum albumin (HSA)-containing formulation, which was kept at room temperature. The interferon reacted with HSA to form aggregates, which in turn induced immune responses. Changing to an HSA-free formulation and storing it in a refrigerator reduced the product's immunogenicity [26].

Antibodies can affect biologic pharmacokinetics and efficacy. Both increases and decreases in half-life have been reported, resulting in enhancement or attenuation of activity. In a study of hepatitis C virus (HCV) treatment, patients with the highest antibody titers had the lowest response rates to interferon treatment. Furthermore, neutralizing antibodies will inhibit the efficacy of all products in the same class, which can result in serious consequences for patients if there is no alternative treatment. Finally, antibody neutralization of naturally occurring proteins can have more serious consequences for the patient. Pure red cell aplasia was associated with the production of erythropoietin-neutralizing antibodies that resulted from exogenous epoetin (Eprex-Ortho Biotech LLC, Manati, Puerto Rico) administered to patients with anemia from chronic kidney disease (CKD). The immune reaction appeared to be related to changes in product formulation. The Eprex formulation in Europe was changed when the HSA stabilizer was replaced by polysorbate 80 and glycine. Protein aggregates generated from the vial rubber stoppers were blamed for eliciting the immune reactions [28].

The ability to predict immunogenicity in patients is limited. Sensitivity and specificity of assays for testing immunogenic responses are inadequate to predict rare cases of

Table 5 Immune reactions to biologics

	Classic reaction	Breakdown of immune tolerance
Antigen properties	Human (growth hormone, blood clotting factor VII) Animal (bovine and porcine insulins, heparins) Bacteria (streptokinase, staphylokinase) Plant (asparaginase)	Human recombinant proteins (epoetin, interferons, colony stimulating factors, interleukin-2)
Onset	Immediate	Slow
Incidence	High	Low
Antibody formation	Neutralizing antibodies	Neutralizing antibodies
Duration	Long	Disappear after treatment stops or after prolonged treatment
Cause	Foreign, nonself-antigens	Impurities and presence of aggregates
Consequences	Loss of efficacy, discontinuation of treatment	Larger doses

immunogenicity. The lack of standardization and validation of assay methods makes it virtually impossible to differentiate antibodies across laboratories. Conventional animal models may be useful for studying the relative immunogenicity of different biologic formulations and may be useful for screening different formulations or structural differences between products during product development and during the assessment of storage and handling [29].

Naming of Biosimilar Products

Concerns exist that adverse events unique to biosimilars may appear, therefore adequate mechanisms for tracing and determining if a patient received the reference biologic or the biosimilar are needed. Several approaches exist to track the use of biosimilars for pharmacovigilance, and one approach that has been suggested is assigning unique nonproprietary names to biosimilars. The United States Adopted Names Council (USANC) approves nonproprietary (generic) names for all pharmaceuticals in the US. The World Health Organization (WHO) coordinates the International Nonproprietary Name (INN) program that standardizes drug nomenclature for new agents, worldwide. Small-molecule manufacturers do not have to go through the USANC process because their generic products are identical to and have the same nonproprietary name as the innovator drug. Although the WHO INN program is planning to develop, establish, and promote international standards for “biological, pharmaceutical, and similar products,” the FDA has not decided whether biosimilars and innovator biologics will share nonproprietary names [20•]. The WHO INN Program advises that biosimilars should have a unique brand name and use lot numbers to ensure traceability, but they oppose unique generic names to identify nonglycosylated biosimilars. Furthermore, they recommend that glycosylation differences should be indicated by unique Greek letters (e.g., epoetin α , epoetin β)

when naming epoetins and other glycoproteins, both reference products and biosimilars.

Several options in the US have been proposed for the surveillance of biologic and biosimilar medications; these include:

- 1 assigning different nonproprietary names to biosimilar and innovator compounds;
- 2 developing different physician-administered billing codes (Healthcare Common Procedure Coding System (HCPCS) codes);
- 3 utilizing National Drug Codes (NDC); and
- 4 establishing prospective electronic health data registries [20•].

Unique biosimilar names could prevent the substitution of one product for another. Clinicians and patients may interpret different names to mean that the products do not have similar efficacy and safety, even if regulatory agencies have determined that they meet biosimilarity requirements. Unique names could also cause confusion among prescribers, which may lead to prescribing errors and adverse events. Confusion of drug names has been frequently cited as a cause of medication errors [18]. HCPCS, NDC, and lot numbers are not captured uniformly in electronic health records in health-care institutions and office practices. However, NDCs can be used for tracking small-molecule generics dispensed through outpatient pharmacies, they are included as a reporting element in the FDA’s MedWatch Safety Information and Adverse Drug Event Reporting Program, and are often available on the packaging of patient medications. Patients and clinicians may require additional education on the possible use of NDCs for reporting events [20•].

European Experience

Neupogen was used as the reference product for the approval of filgrastim biosimilars. Filgrastim is indicated in

adults and children to shorten the duration of neutropenia and to reduce the incidence of febrile neutropenia following receipt of cytotoxic chemotherapy. It is also used to aid in the delivery of chemotherapy to maintain dose intensity and to support dose-dense chemotherapy. Filgrastim is also indicated to mobilize peripheral blood progenitor cells (PBPC) in both cancer patients and healthy donors and to support engraftment and neutrophil recovery after stem cell transplantation. Outside the oncology setting, filgrastim is indicated for the treatment of severe chronic neutropenia and to maintain neutrophil counts or for the reversal of neutropenia in patients infected with human immunodeficiency virus (HIV).

The biosimilars were compared to Neupogen through physicochemical, pharmacokinetic, pharmacodynamic, and clinical studies. Comparability was assessed in a single indication for which Neupogen is approved, the reduction of chemotherapy-induced neutropenia (CIN) in accordance with European Medicine Agency (EMA) guidelines. Safety and efficacy was assessed in a comparative study involving breast cancer patients at high risk of CIN, with supportive studies providing safety data for patients with other malignancies (e.g., lung cancer, non-Hodgkin's lymphoma). Duration of neutropenia, time to white blood cell recovery, incidence of febrile neutropenia, and adverse events were similar and led the EMA to extrapolate the data and approve these biosimilars across all indications of the reference product [30].

The EMA has not approved all biosimilar applications. Biosimilar interferon was recently rejected because of quality concerns (i.e., inadequate stability data and process validation for the finished process), insufficient immunogenicity testing, and clinical differences from the reference product [15•]. Biosimilars have been introduced in countries without structured regulatory approval processes. Quality concerns may exist with these products, and, therefore, it is important to differentiate non-innovator biologics approved in countries with limited or no regulations from products approved in countries with well-developed regulatory structures. In a comparative study of 11 different epoetin products sold in East Asia and South America, none of them had the same molecular patterns as the reference product [17].

Economic Impact

It is estimated that generic medication use has saved the US health-care system an estimated \$824 billion over the past decade [20•]. The introduction of generic medications for conventional small-molecule drugs offered price reductions of up to 80 % compared with their branded counterparts. However, the economics surrounding biosimilars are different and the number of successful companies are

expected to be limited. Because of higher development, facility, and manufacturing costs, biosimilar profits are expected to be more modest. It is estimated that the costs of developing a biosimilar product in the US may range from \$75 to \$250 million. Government regulations and potential requirements for comparative studies that prove biosimilarity to the reference biologic enhance the risk and uncertainty of this investment and years may be required for a company to recoup its initial investment [31].

The US Congressional Budget Office has estimated biosimilars will provide a discount of up to 40 % off the price of the reference product. In Europe, epoetin biosimilars have provided a 25–30 % cost savings compared with their innovator products [20•]. While the savings from biosimilars have been modest compared with the savings from small-molecule generics, they are still meaningful because they are expensive therapy. Filgrastim biosimilars have captured about 50 % of the total market share [31]. The use of filgrastim has increased dramatically, which is thought to be a consequence of improved access and the increase in use among patients who had been untreated previously. Innovator companies have remained competitive with price, focusing on brand loyalty and marketing the uncertainties of biosimilars in the areas of safety and efficacy. The automatic substitution of a reference product with a biosimilar in the US, a practice which has not been employed in Europe, would facilitate the rapid penetration and market share uptake of biosimilars [32].

The Role of Emergency Department Practitioners

A recent survey of oncology clinicians suggests that practitioners who care for cancer patients are unfamiliar with issues surrounding biosimilar medications [20•]. Because patents are expiring on many biologics, it is crucial that Emergency Medicine practitioners become familiar with recent advances surrounding biosimilars and, where appropriate, lead their introduction. Clinicians may be forced to evaluate biosimilars and the data that supported their FDA approval for their own prescribing and for formularies at hospitals and health-care insurance plans. Clinicians must be prepared to identify unique safety and efficacy concerns, should they occur with biosimilars. This is especially important if treatment is changed with existing products or if biosimilar products are switched. Clinicians must assist with educating the medical community, and patients, about recognizing that biosimilars are not exact copies of their reference products, and explain both the benefits and potential pitfalls involved. Because the FDA has yet to define detailed standards for interchangeability or whether unique names will be used for specific biologics, clinicians should be vigilant to identify complications that occur from this confusion. Finally, clinicians must be

aware of the manufacturer's handling and storage requirements surrounding biologics, be comfortable in providing patients with instruction, and intervening when a medication may be questioned or a product's integrity compromised.

Conclusion

In summary, the arrival of biosimilar products in the US may make these agents more accessible for patients as alternative, less expensive therapy. Emergency Medicine clinicians should understand issues that surround biosimilars and play an active role in advising other clinicians and patients.

Compliance with Ethics Guidelines Conflict of Interest J. Fani-kos: consultant for/received honorarium from GTC Biotherapeutics, Inc. M. Rocchio, K. Sylvester, and N. Beik have nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of importance, published recently, have been highlighted as:

- Of importance
- Of major importance

1. IMS Health. IMS Institute for Healthcare Informatics, IMS study forecasts rebound in global spending on medicines, reaching nearly \$1.2 trillion by 2016. IMS web site (12 July 2012). <http://www.imshealth.com/portal/site/ims/menuitem.d248e29c86589c9c30e81c033208c22a/?vgnextoid=4d47d1822e678310VgnVCM10000076192ca2RCRD&vgnextchannel=437879d7f269e210VgnVCM10000071812ca2RCRD&vgnextfmt=default>. Accessed 1 July 2012.
2. Leader B, Baca QJ, Golan DE. Protein therapeutics: a summary and pharmacological classification. *Nat Rev Drug Discov*. 2008; 7(1):21–39.
3. Genentech Inc. Corporate chronology: 1982. Genentech web site. <http://www.gene.com/gene/about/corporate/history/timeline.html>. Accessed 1 July 2012.
4. EvaluatePharma LTD. Surveying tomorrow's biopharma landscape. <https://www.evaluatepharma.com/secure/FileResourceDownload.aspx?id=847d45d7-07a9-4171-9085-d1a2584b0b29>. Accessed 1 July 2012.
5. Drug patent watch. Drug patent expirations and intelligence. <http://www.drugpatentwatch.com/subs/>. Accessed 1 July 2012.
6. Weise M, Bielsky MC, De Smet K, et al. Biosimilars—why terminology matters. *Nat Biotechnol*. 2011;29:690–3.
7. International Market Analysis Research and Consulting (IMARC) Global Biopharmaceutical Market Report (2010–2015). 29 Oct 2010.
8. McCamish M, Woollett G. The state of the art in the development of biosimilars. *Clin Pharmacol Ther*. 2012;91(3):405–17.
9. • Sekhon BS, Saluja V. Biosimilars: an overview. *Biosimilars*. 2011;1:1–11. *This article provides a detailed overview of bio-similar medications. It specifically addresses the regulatory pathway, method for developing biologic drugs, and processes implemented to ensure quality, safety and efficacy. The article also discusses the role of biosimilars in clinical practice and the responsibility of each provider in the healthcare system.*
10. Generic Pharmaceutical Association (GPhA). The generic pharmaceutical industry—improving lives for less. www.gphaonline.org/about-gpha/about-generics/case/generics-providing-savings-americans. Accessed 9 Aug 2012.
11. Medicare Payment Advisory Commission (MedPAC). Report to the Congress: improving incentives in the Medicare Program (MedPAC, Washington, DC, June 15, 2009). http://www.medpac.gov/documents/jun09_entirereport.pdf. Accessed 1 July 2012.
12. Hennessy S, Leonard CE, Platt R. Assessing the safety and comparative effectiveness of follow-on biologics (biosimilars) in the United States. *Clin Pharmacol Ther*. 2010;87(2):157–9.
13. Lacan E, Amur S, Mummannoni P, et al. The emerging role of pharmacogenomics in biologics. *Clin Pharmacol Ther*. 2007;82: 466–71.
14. Mellstedt H, Niederwieser D, Ludwig H. The challenge of bio-similars. *Ann Oncol*. 2008;19(3):411–9.
15. • Schellekens H. Biosimilar therapeutics—what do we need to consider? *NDT Plus*. 2009;2(suppl 1):i27–i36. *This review article provides a summary of issues surrounding biosimilars including manufacturing, variability, the regulatory process and post-marketing surveillance. Of particular interest, the authors evaluate the impact on patient safety and discuss current biosimilars on the market.*
16. Roger SD. Biosimilars: how similar or dissimilar are they? *Nephrology (Carlton)*. 2006;11(4):341–6.
17. Genazzani AA, Biggio G, Caputi AP, et al. Biosimilar drugs: concerns and opportunities. *BioDrugs*. 2007;21(6):351–6.
18. Chirino AJ, Mire-Sluis A. Characterizing biological products and assessing comparability following manufacturing changes. *Nat Biotechnol*. 2004;22:1383–91.
19. Kay J. Biosimilars: a regulatory perspective from America. *Arthritis Res Ther*. 2011;13(3):112.
20. • Zelentz AD, Ahmed I, Braud EL, et al. NCCN biosimilars white paper: regulatory, scientific, and patient safety perspectives. *J Natl Compr Cancer Netw*. 2011;9 (suppl 4): s1–s22. *Although focused on oncology care, this white addresses topics relevant to the use of biosimilars in emergency medicine such as health care provider knowledge, substitution practices, pharmacovigilance, naming and product tracking, coverage and reimbursement, use in off-label settings, and data requirements for approval.*
21. Hoffman JM, Shah ND, Vermeulen LC, et al. Projecting future drug expenditures-2007. *Am J Health-Syst Pharm*. 2007;64: 298–314.
22. US Food and Drug Administration (FDA). Biosimilar User Fee Act (BsUFA). FDA web site. <http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm>. Accessed 9 Aug 2012.
23. •• US Food and Drug Administration (FDA). 2012 Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. FDA web site. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>. Accessed 9 Aug 2012. *This document gives an overview of the FDA's approach to determining biosimilarity between a proposed therapeutic protein product and a reference product. Understanding this approach is paramount for clinicians to evaluate biosimilars and integrate them into their*

- own practice. This is one of three FDA guidance documents addressing biosimilars.*
24. US Food and Drug Administration (FDA). Guidance for industry: quality considerations in demonstrating biosimilarity to a reference protein product: 2012. FDA web site. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf>. Accessed 9 Aug 2012.
 25. US Food and Drug Administration (FDA): 2012 Guidance for industry: biosimilars: questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009. FDA Web site. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf>. Accessed 9 Aug 2012.
 26. Schellekens H. Factors influencing the immunogenicity of therapeutic proteins. *Nephrol Dial Transplant*. 2005;20(suppl 6):vi3–9.
 27. Schellekens H. The first biosimilar epoetin: but how similar is it? *Clin J Am Soc Nephrol*. 2008;3(1):174–8.
 28. Schellekens H. Follow-on biologics: challenges of the “next generation”. *Nephrol Dial Transplant*. 2005;20(suppl 4):iv31–6.
 29. Locatelli F, Roger S. Comparative testing and pharmacovigilance of biosimilars. *Nephrol Dial Transplant*. 2006;21(suppl 5):v13–6.
 30. Niederwieser D, Schmitz S. Biosimilar agents in oncology/haematology: from approval to practice. *Eur J Haematol*. 2011;86(4):277–88.
 31. Dranitsaris G, Amir E, Dorward K. Biosimilars of biological drug therapies: regulatory, clinical and commercial considerations. *Drugs*. 2011;71(12):1527–36.
 32. Crommelin D, Bermejo T, Bissig M, et al. Pharmaceutical evaluation of biosimilars: important differences from generic low-molecular-weight pharmaceuticals. *Eur J Hosp Pharm Sci*. 2005;11(1):11–7.