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Biosimilars: Primer for the Health-System Pharmacist

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Abstract

Purpose—Basic information pharmacists and other clinicians must know to successfully manage the introduction of biosimilars into health systems is summarized, including manufacturing, regulatory, and medication use policy concepts.

Summary—Under development for more than a decade, the biosimilar market in the United States is now closer to becoming a reality than ever before. Legislation granting the Food and Drug Administration (FDA) authority to approve lower cost, follow-on versions of previously approved biologics was signed into law in March 2010. Additional draft guidance further clarifying the requirements of the biosimilars approval pathway was published in February 2012, and FDA is currently conducting multiple preparatory meetings with potential biosimilar applicants. While intended to occupy a position similar to that of small molecule generics, biosimilars will present new challenges given that biologic medications are manufactured, regulated, and marketed differently from small molecules. As a result, it is critically important for pharmacists to be knowledgeable on the unique characteristics of biologics and prepare their organizations for the introduction of biosimilars, including use of the formulary system.. Biosimilars will pose questions of medication use policy around therapeutic interchange, pharmacovigilance, and in the transitions of care for health system patients.

Conclusion—As stewards of appropriate medication use, pharmacists must take the initiative to educate themselves, physicians, other clinicians and patients on these products to ensure an accurate understanding of this new category of drugs and to assure the safe and optimal use of biosimilars.

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Introduction

Over the first decade of the 21st century, the annual rate of growth for drug expenditures demonstrated a consistent and sustained moderation.[1] As an example, within the non-federal hospital setting, the most recent projections characterize a negative growth rate of −0.4%.[1] While the cost of pharmaceuticals is driven by many elements, the factor most frequently cited as helping to sustain this trend is the introduction of generic alternatives for many commonly prescribed medications.[1] At the end of 2010, 78% of all retail prescriptions dispensed were for generic drugs.[2] A recent IMS Health report suggests that between 2002 and 2011 the availability and use of generic drugs resulted in a savings of $1 trillion for the US health care system.[3] In 2012, two additional blockbusters, atorvastatin and clopidogrel reached the end of their patent protection following the recent introduction of generic formulations of products such as enoxaparin, gemcitabine, meropenem, oxaliplatin, and docetaxel.

Although generic competition has moderated expenditures for many blockbuster small molecule medications, drug expenditure growth is increasingly associated with biologics, which are drug products derived from living organisms.[1] Frequently, these biologic medications are more costly than small molecule drugs, and they have narrow indications for serious and often chronic diseases. Following patent expiration of the originator molecule, biologics have not been subject to direct competition from alternative suppliers of products were approved through an abbreviated process. Barriers to approval of follow-on versions of originator biologics, now known as ‘biosimilars’, are being removed. The purpose of this paper is to summarize basic information pharmacists and other clinicians must know to successfully manage the introduction of biosimilars into health systems, including manufacturing, regulatory, and medication use policy concepts.

The Increasing Importance of Biologics

Since the introduction of recombinant human insulin in 1982, the use of biologic medications or therapeutic proteins has continued to increase.[4] Biologic products epoetin, pegfilgrastim, infliximab, rituximab, bevacizumab and trastuzumab are all among the top 15 medications used in both the hospital and clinic settings.[1] In 2009, global sales of biologics were $93 billion and those sales are expected to grow at least twice as fast as those of small molecules.[4] By 2016, 10 of the top 20 selling drugs globally are expected to be biologics.[4] Many of these biologics no longer move through traditional distribution methods, but are supplied via specialty pharmacy distribution services. In 2011, this segment of the supply chain grew an estimated 17.1%.[5] This increasing use of existing biologics along with the presence of numerous biologics in the investigational drug pipeline illustrate the increasing importance these products will have on overall pharmaceutical expenditures.

The introduction of lower cost alternatives for branded small molecules was facilitated by the Drug Price Competition and Patent Term Restoration Act of 1984 (also informally known as the Hatch-Waxman Act), which established the abbreviated new drug application (ANDA) pathway for the approval of generic medications. The Hatch-Waxman Act balanced the needs of originator manufacturers for a meaningful period of patent protection

and marketing exclusivity to recover development costs for new pharmaceuticals with the societal expectation for eventual access to less expensive alternatives.[6] Most importantly, the legislation allowed ANDA sponsors to seek approval through a demonstration of bioequivalence, without the completion of separate clinical trials, thus enabling the marketing of generic medications at substantially discounted prices. However, the Hatch-Waxman Act only applies to small molecule medications approved under the Food Drug and Cosmetic Act (FDCA).

The need for a regulatory pathway for copies of biologics was finally addressed in 2010 when the Biologics Competition and Innovation (BPCI) Act was signed into law. The BPCI Act created an abbreviated process to approve copies of a biologic not developed by the originator. Because biologics cannot be copied in the precise way a small molecule can be duplicated, the term 'biosimilar' is used for these products. A simple definition of a biosimilar is a copy of a therapeutic protein not developed by the original manufacturer and approved through some abbreviated regulatory process.[7] Formal definitions of biosimilars are available in the BPCI Act and a consensus definition has been proposed.[8,9] At the time this paper was prepared, no biosimilar application has been approved under the BPCI Act, yet the relevant considerations for the appropriate use of these products are becoming clearer.

Due to their complexity, biosimilars will require a greater investment of time and clinical resources to support approval as compared to small generic molecules, which are adopted for use in health systems with little or no formulary review.[10] All clinicians must familiarize themselves with the inherent differences between generic medications and biologics and educate themselves on the clinical literature concerning biosimilars that is continuing to expand.[4, 10] If the US market is to realize the full financial and clinical benefit of biosimilars, pharmacists must take a leadership position to support an accurate understanding of these products and create a clinical environment conducive to their safe and effective use. This paper contains a summary of the key principles related to the manufacture, regulation, marketing and formulary management of biologics and biosimilars and provides an outlook regarding the anticipated market in the US based upon the experience in Europe as well as the Food and Drug Administration's (FDA) historical approach to follow-on biologic approval.

Molecular and Manufacturing Differences: Small Molecules and Biologics

In order to differentiate small molecule generics and biosimilars, pharmacists must be cognizant of key attributes of small molecule products compared to biologics. Although both categories of products are regulated and approved by the Food and Drug Administration (FDA), important differences exist in the molecular complexity and manufacturing processes with these two product types.

As their name implies, small molecule drugs are small in size and have less complex chemical structures made up of basic atomic units such as carbon, hydrogen, and oxygen.[10] The molecular weight of these molecules range from a few hundred daltons (e.g. linezolid and ondansetron) to a few thousand daltons (e.g. daptomycin and enoxaparin).[11–14] These

products are synthesized through predictable chemical processes and can be completely characterized by existing analytical methods, thus allowing for the demonstration that a generic version contains the identical active ingredient as the reference innovator product to which it is compared.[10] Given their small size, they usually are not immunogenic without binding to a carrier protein.[15]

In contrast, biologics are proteins developed via living sources such as bacteria (e.g. *Escherichia coli*), yeast, or mammalian cells (e.g. Chinese Hamster ovary cells) and are much larger, usually in the range of ten thousand daltons (e.g. filgrastim and pegfilgrastim) to several hundred thousand daltons as in the case of monoclonal antibodies such as rituximab and infliximab.[10,16–20] The basic components of biologics are glycoproteins, amino acids and sugar molecules.[10] The unique pharmacologic action of each biologic depends upon a specific sequence of amino acids.[10,21] The manufacturing steps used to create biologics are often proprietary and involve numerous complex processes including the isolation of a targeted gene sequence, the cloning of that gene sequence and the use of a DNA vector to transfer that targeted DNA into an expression system.[21] From there, effective manufacturing requires knowledge of cell expansion, filtration, centrifugation, purification, product characterization and the determination of product stability.[21] As biologics are manufactured via living organisms, the resulting purified bulk drug can vary and any modification in manufacturing steps can yield a different product.[4,10] Biologics' primary, secondary, tertiary, and quaternary structures, their tendency to aggregate and any post-translational modifications (e.g. glycosylation, oxidation, phosphorylation) can affect their activity profile as well as their capacity to behave in an immunogenic fashion.[10,15] Biologics are visible to the immune system as a result of their size and complexity and can directly induce a range of immunological responses, some of which can have substantial clinical consequences including loss of efficacy, anaphylaxis and infusion reactions .[15]

Regulatory Differences: Small Molecules and Biologics

The regulation of small molecule drugs is defined by the FDCA first enacted in 1938 and modified by the Hatch-Waxman Act in 1984 to allow for the approval of generic medications.[22] In contrast, biologics were initially regulated by the Biologics Act of 1902, which was revised and codified into section 351 of the Public Health Services (PHS) Act in 1944.[22] Just as the Hatch-Waxman Act created an ANDA companion to the previously established New Drug Application (NDA) process, the BPCI Act created a biosimilar application to accompany the Biologics License Application (BLA).[8,22] (Table 1) The section of the law that was amended is often used to identify the type of application. Therefore, products submitted as an ANDA are sometimes referred to as a 505(j) application while products submitted for approval under the biosimilars pathway are called 351(k) applications.

New molecular entities, whether they are small molecules or biologics, require full clinical evaluations of safety and efficacy, via an NDA or BLA, respectively.[23] However, the approval processes for generics, the 505(j) or ANDA pathway, and the 351(k) or biosimilar pathway vary in terms of the requirements for clinical data.[8,22,23] Given the ability to synthesize and characterize a small molecule in full, an ANDA filing for a generic

medication can be based on the demonstration of bioequivalence as a bioequivalent agent would be expected to produce the same clinical response as the reference product. An ANDA approved drug must have the same active ingredient, dosage form, route of administration, strength, conditions of use and labeling as the originator reference product.[23]

Once approved, the generic medication usually is designated as "therapeutically equivalent" through an "A" Orange Book code rating, allowing for pharmacist substitution.[7] A generic medication is approved for the same set of indications as the originator's reference product and receives the same nonproprietary name as developed by the United States Adopted Names (USAN) Council.[23,24] USAN, which is tri-sponsored by the American Medical Association, the United States Pharmacopeial Convention (USP), and the American Pharmacists Association (APhA), works to select simple, informative, and unique nonproprietary names for drugs by establishing logical nomenclature classifications based on pharmacological and/or chemical relationships.[24] Their "one substance, one name" philosophy behind generic naming is intended to help clearly identify an active substance across different brand or trade names, formulations, or in combination products.[24]

Because biologics are more complex, subject to variation in manufacturing and are difficult to characterize, it would be inappropriate to use the terms "generic" or even "biogeneric." Instead these follow-on versions of biologics are more correctly described as biosimilars, "highly similar" products approved on the basis of detailed structural and functional characterization and clinical trial information.[6,25] According to the BPCI Act, a biosimilar is a product for which "a clinical study or studies" are sufficient "to demonstrate safety, purity, and potency for one or more appropriate conditions of use for which the referenced product is licensed."[8] However, the indications for which a biosimilar is approved will not necessarily include all of the licensed uses of the innovator reference product, but could vary depending upon each biosimilar sponsor's application and the extent to which the clinical trial information supports extrapolation across multiple indications.[25] Also, the BPCI Act included a separate more rigorous designation for "interchangeability."[8] Only "interchangeable" biosimilars are substitutable by a pharmacist without the intervention of the prescriber.[8] FDA has yet to define the additional level of evidence required to achieve this higher standard, however, they have indicated that it is unlikely that "interchangeability" would be granted upon initial approval.[25] The label for biosimilars must state whether or not they have been deemed interchangeable to the reference product.[26] It is unclear how aggressively biosimilar sponsors will seek this designation.

Given the inherent variability in the active ingredient "or substance" for all biologics, it is uncertain as to whether or not FDA will conclude that biosimilars should receive the same nonproprietary name as the reference product. Current American Society of Health-Systems Pharmacists (ASHP) guidelines state that generic drugs deemed bioequivalent by the FDA do not generally require a review by institutional Pharmacy and Therapeutics (P & T) Committees.[27] As biosimilars will not be deemed bioequivalent and could vary in terms of labeled indications and even relative naming, health care institutions will need to develop policies and conduct detailed evaluations prior to formulary inclusion.[10]

Historical Lessons on Similar Biologics from Europe (and the US)

Although the formal biosimilar approval pathway is still under development in the US, biosimilars are well established in other parts of the world, most notably the European Union (EU). The EU accounts for 80% of the global spending on these molecules.[28] The EU regulatory pathway for biosimilars was established in 2005 and the first biosimilar, a version of human growth hormone (somatropin), was approved in 2006.[10,23] The EU approval pathway is governed by an overarching "Guideline on Similar Biological Medicinal Products," general guidelines on quality, safety and efficacy and product specific class requirements for insulins, somatropin, granulocyte colony stimulating factors (G-CSFs), erythropoietic stimulating agents (ESAs), interferons, low molecular weight heparins, and most recently monoclonal antibodies.[4] Currently, 12 biosimilar versions of somatropin, G-CSFs, and ESAs are approved for use.[29] While large molecules, these products are considered less complex biologics. There are currently no EU approved biosimilar versions of any monoclonal antibody, biologics of greater complexity, although two applications for infliximab have been submitted for possible approval by 2015.[30,31]

The uptake of biosimilars varies across the countries in Europe depending upon differences in local pricing and reimbursement policies, stakeholder influence, and perceptions regarding use.[28] Germany and France account for the majority of the market share in the region, 34% and 17%, respectively, although usage in Spain and the United Kingdom has started to increase.[28] Biosimilar G-CSFs appear to have achieved the highest level of uptake, 25% within their class.[28] Overall, a 30% price reduction has been observed within Europe as compared to the 70% to 80% decrease normally associated with small molecule generics.[28]

With nearly a decade of experience, clinicians and regulators in Europe have identified barriers to biosimilars adoption and possible solutions to address potential concerns. The Working Party on Similar Biological Medicinal Products (BMWP) of the European Medicines Agency (EMA) recently published an article addressing many of the perceptions that have limited biosimilar use.[32] The authors state that "a clear understanding of the scientific principles of the biosimilar concept and access to unbiased information on licensed biosimilars" is important for prescribers "to make informed and important treatment choices for their patients."[32] This article and several other recent citations are highly recommended as additional reading for health professionals preparing for the biosimilar market.[4,10,32,33]

When this paper was prepared, an officially recognized biosimilar had not been approved in the US via the 351(k) pathway, but FDA does have experience approving copies of complex molecules.[33] These products have been either follow-on versions of relatively simple recombinant agents such as somatropin, calcitonin salmon, and glucagon hydrochloride, or medications derived from naturally occurring sources, as in the case of enoxaparin, which is made from porcine intestines.[33] However, none of these agents should be considered biosimilars as the originator reference products against which they were compared were initially approved via an NDA not a BLA. Follow-on recombinant somatropin, calcitonin salmon and glucagon were all approved via a 505(b)(2) application.[33] The 505(b)(2) pathway provides a middle ground between a NDA and an ANDA filing. Like an ANDA, a 505(b)(2) product is a version of a previously approved drug.[34] In contrast to an ANDA, the

505(b)(2) pathway allows for the approval of a modification to that previously-approved drug product including a change in dosing regimen, a new active ingredient or new indication of use.[34] Although a new formulation, the 505(b)(2) product is allowed to rely on the clinical data of the originator product and is not required to repeat patient studies.[34] In the case of enoxaparin, follow-on versions of this product were approved by the ANDA pathway, not a biosimilar application. Therefore, subsequent versions of enoxaparin are true generic medications that include the same active ingredient, dosage form, route of administration and indications as the branded product and for which direct substitution as an "A" rated therapeutic equivalent is allowed.[33] Pharmacists should be cognizant of the fact that subsequent versions of biologic related medications can be approved via different pathways in the US, depending upon the application type for the originator reference product (NDA or BLA). Pharmacists must also realize that additional variation in biologic product regulation exists across different countries. For example, while regulated as small molecule products here in the US, both somatropin and enoxaparin are covered under the EMA's class specific guidance for biosimilars. Therefore, literature referencing these agents as biosimilars would be accurate for EU products, but incorrect for products currently approved in the US.

Understanding the BPCI Act and the FDA Guidance Documents

The BPCI Act created the 351(k) pathway allowing FDA to approve biosimilars or interchangeable biosimilars. It also defined additional parameters of biosimilar approval including the timing of application submission and the duration of marketing exclusivity for originator reference products. According to the BPCI Act, FDA cannot accept an application for a biosimilar until 4 years after the licensure of the originator reference product and cannot approve a biosimilar until 12 years after the reference product was approved.[8] The BPCI Act also defines the circumstances by which marketing exclusivity can be extended for the originator reference product based upon the completion of pediatric or orphan drug studies.[8] In addition, the first interchangeable biosimilar approved receives a 12 month exclusivity period during which no other related biosimilar can be designated as interchangeable.[8] Perhaps of greatest importance regarding the ultimate use of the biosimilar pathway, the BPCI Act defines a formal resolution process for the negotiation of patents.[6,8]

According to the BPCI Act, within 20 days of FDA accepting a biosimilar application for approval, the biosimilar applicant must also share its application with the originator reference product sponsor so work can begin to identify, negotiate and if necessary litigate patent infringement disputes.[8] There have been some suggestions that such disclosure of confidential information may limit the number of suppliers willing to pursue this route to approval and instead prompt biosimilar applicants to seek approval via a full BLA application.[35] The actual extent of use remains to be determined as the industry and FDA gain greater experience with the 351(k) pathway.

The FDA published additional guidance concerning the biosimilar pathway on February 9, 2012 in the form of three draft documents, two of which address individually the scientific and quality considerations for demonstrating biosimilarity to an originator's reference product and one which provides answers to key questions biosimilar applicants have posed

regarding implementation of the BPCI Act.[25,26,36] The guidance revealed key principles FDA is using to implement the approval pathway.

Throughout the guidance, FDA emphasized it will use a "totality of the evidence" approach in reviewing all of the information submitted in support of biosimilar approval, including detailed analytical testing, clinical immunogenicity evaluation, animal studies and human clinical trials.[26] In addition, FDA encourages sponsors to use a "step-wise" process for biosimilar development.[26] At each step of the development process, sponsors should identify the extent of remaining uncertainty regarding the demonstration of biosimilarity and use subsequent development steps to address those residual concerns.[26] Advances in analytics and manufacturing technology should enable applicants to characterize a proposed biosimilar more accurately.[26] The foundation for the biosimilar development program will be the availability and quality of comparative analytical data.[26] Biosimilar sponsor applicants must be able to demonstrate the comparability between their proposed product and the reference product in terms of primary structure (i.e. amino acid sequence), higher order structures, enzymatic post-translational modifications such as glycosylation and phosphorylation, other potential variants such as protein deamidation and oxidation, and intentional chemical modifications.[36] Biosimilar applicants must demonstrate that the mechanism of action for the proposed product is the same as that of the reference protein product. FDA will require applicants to use endpoints and study populations that will be clinically relevant and sensitive in detecting meaningful differences in safety and efficacy.[26]

According to the guidance, FDA will allow the biosimilar sponsor to pursue all or only a subset of indications, routes of administration, or presentations associated with the originator's reference product.[25] Also, FDA will allow the sponsor to use comparator data involving a non-US-licensed product in support of the overall biosimilar application.[25] However, this allowance does not eliminate the need for clinical data comparing the proposed biosimilar with the originator's US-licensed product.[25] FDA is currently finalizing these guidance documents. The February 2012 guidance did not address biosimilar naming or requirements to achieve an interchangeability approval. In addition to these remaining regulatory issues, other decisions by FDA will continue to shape the biosimilar pathway including such items as its response to the Citizen's Petition filed by AbbVie concerning the scope of the biosimilar pathway for biologics approved prior to enactment of the BPCI Act.[37] Pharmacists must be aware of these developing regulatory decisions.

Before Biosimilarity, There was Comparability

Biosimilarity may appear to be a new concept to pharmacists and other practitioners. In fact, it is an extension of a well-defined process established by regulatory organizations such as FDA and EMA and accepted within the pharmaceutical industry.[4,33] Given the fact that biologics come from living organisms, the resulting end products can vary from batch to batch. In addition, over the life cycle of a biologic, originator companies implement manufacturing changes to scale up production and may even relocate production from one location to another .[4,10] Any such process modification can result in variation in the resulting biologic. Therefore, originator manufacturers must evaluate their products pre- and post-manufacturing change to ensure there are no differences in clinical efficacy or safety.

To support this evaluation, FDA developed the concept of "comparability" in a 1996 guidance document "Demonstration of Comparability of Human Biological Products, including Therapeutic Biotechnology-derived Products."[4] This concept has since been incorporated into the International Conference on Harmonisation (ICH) guidance Q5E "Comparability of Biotechnology/Biological Products Subject to Changes in Their Manufacturing Process", for use in Europe, Japan, and the United States.[33] The ICH is a global initiative involving the regulatory authorities of Europe, Japan and the US and experts from the pharmaceutical industry in these regions.[38] The intent of the ICH is to discuss the scientific and technical aspects of pharmaceutical product registration to eliminate the duplication of testing involved in the development of new medications.[38] ICH Q5E guidance was the basis for the development of the EU biosimilars pathway.[33]

According to ICH Q5E, the demonstration of comparability does not necessarily require the quality attributes of the pre- and post-manufacturing change products to be identical.[39] Instead, comparability means that the products are highly similar and sufficient knowledge is provided to ensure that any differences in quality attributes which do exist do not result in an adverse impact on the safety or efficacy of the drug.[39] Comparability can be based on analytical testing, biological assays and possibly, nonclinical and clinical data.[39] However, rarely does a comparability determination require a manufacturer to conduct clinical trials.[4] Manufacturers have never been required to conduct "switching" studies where study subjects are alternated between therapy with the pre- and post-manufacturing change products in order to assess their relative safety and efficacy.[4]

Two recent publications have demonstrated this process in the current marketplace.[4,40] One example illustrates the product variations seen secondary to manufacturing changes for darbepoetin sourced in the European Union.[40] In this analysis of product sourced over a two and a half year period, capillary zone electrophoresis revealed differences in sialic acid content, the presence of which is responsible for the extended half-life of darbepoetin. From November 2008 to April 2011, the relative content of darbepoetin isoforms containing different amounts of sialic acid appeared to change noticeably, likely following a modification in the manufacturing process. Similar examples of this type of variation have been reported for etanercept and infliximab.[40] While manufacturers periodically implement such changes, the product label is not altered to reflect these modifications.[33,40] The post-manufacturing formulation retains the same name as the original version and both the pre- and post-manufacturing product are allowed to remain on the market at the same time.[33,40]

In its guidance documents, the FDA acknowledged that some of the scientific principles described in ICH Q5E may also apply to the demonstration of biosimilarity.[36] However, they also state that as biosimilar sponsors will be using different cell lines, raw materials, equipment, processes, and process controls, the amount of data and information required to establish biosimilarity will be greater than what is required to determine comparability following an originator's manufacturing change.[26] Still, the concept of establishing the similarity of biologics manufactured via modified processes is not new to the pharmaceutical industry or FDA.

Putting Biosimilar Safety into Context

A primary concern regarding biosimilars is the potential for small manufacturing or formulation differences from the originator to affect the clinical profile of the product, especially the safety of these biologics.[41] Concerns exist that biosimilars may exhibit unique adverse events compared to the originator. A frequently cited set of events that occurred in the European Union over a decade ago with a manufacturing change and the associated outbreak of a rare anemia syndrome, pure red cell aplasia (PRCA) illustrate the potential clinical consequences of small changes in manufacturing and formulation of all biologics. PRCA is characterized by a low reticulocyte count, the absence of erythroblasts in the bone marrow, resistance to recombinant human erythropoietin and neutralizing antibodies to erythropoietin.[42]

In 1998, Johnson & Johnson reformulated its European version of epoetin (Eprex®) due to concerns that the product's stabilizing agent, human serum albumin, could transmit a variant of Creutzfeldt-Jakob disease.[43] The human serum albumin component was replaced with polysorbate 80. In the ten years prior to this change, 1988 to 1998, PRCA had been reported in only 3 patients receiving recombinant human erythropoietin.[43] From January 1998 to April 2004, 175 cases of PRCA, were reported in patients receiving Eprex.[43] Multiple factors have been proposed regarding why this increase in PRCA events occurred including increased subcutaneous administration of epoetin (a more immunogenic route than intravenous administration), failure to maintain the product under appropriate storage conditions, or potential interactions between the new stabilizer, polysorbate 80, and the uncoated, rubber stoppers used in Eprex syringes.[43] To address this increased incidence of PRCA, health authorities recommended adherence to storage and handling requirements and mandated the intravenous administration of Eprex for patients with chronic kidney disease.[44] Johnson & Johnson replaced the uncoated rubber stoppers with Teflon-coated plungers.[44] The incidence of PRCA events has since declined although the specific cause of this surge in PRCA cases continues to be debated.[42] However, this example is consistently referenced in the clinical literature as a warning about the potential safety considerations of biosimilars, even though Eprex was and remains a fully licensed, originator biologic.[21,41,45]

This perception is further clouded by the availability of alternative biologics marketed incorrectly as biosimilars in the developing world where regulatory standards are less robust than what is present in Europe and what is being developed in the US.[46,47] Additional incidences of PRCA along with substantial variability in active ingredient content for ESAs have been reported with these non-biosimilar, alternative biologics.[46,47] Due to the potential for confusion, the BMWP of the EMA has proposed a more precise terminology to differentiate biologic products.[9] (Table 2) Under this proposed classification, only products with demonstrated similarity in physicochemical characteristics, efficacy and safety would be labeled as biosimilar.[9]

The incidence of adverse events associated with the use of biosimilars has not increased in highly regulated markets such as the EU.[33] A recently published review evaluated the EMA dossiers and journal publications for the follow-on epoetins licensed in Europe, including two products approved as biosimilars and one product that although going through a full

development program, is usually classified as a biosimilar.[48] The review revealed a similar safety profile compared to what is known about epoetin alfa and ESAs.[48] A review of the biosimilar G-CSFs licensed in Europe similarly concluded that what is known about originator filgrastim in general can be extended to the biosimilar versions of this product.[49] Another review of the medical literature for EU human growth hormone, ESAs, and G-CSF revealed no safety issues switching between products, including switching between innovator products within the same product class and switching to and from biosimilars.[50] Analyses of the active ingredient content for multiple ESAs marketed in the EU reflect consistency for biosimilars equal to if not greater than that seen for innovator products.[33,51]

Appropriate monitoring for adverse events, including immunogenic related reactions, is important for all biologics, innovator products and biosimilars. Although an abbreviated process, the regulatory requirements for biosimilar approval in the EU and US are stringent and require thorough evaluation of safety and efficacy. As with all biologics, appropriate post-marketing pharmacovigilance will be critical to the appropriate use of biosimilars.[26]

The Anticipated Biosimilars Market in the United States

In addition to the differences described above, the market for biosimilars will vary substantially from that of traditional generics. While the biosimilar approval process is abbreviated, sponsors must still make a substantial investment in complex manufacturing processes, clinical trial expenses as well as the anticipated costs of patent litigation. Some estimates suggest that the development cost for a biosimilar could range from $100 million to $250 million.[28] In comparison, the cost of developing a small molecule generic is estimated to range from $1 million to $4 million.[28] Therefore, discounts associated with biosimilars are expected to be only 20% to 30%, much less than the price decreases frequently seen with generic small molecules.[28] However, given the overall expense associated with biologics and their traditional resistance to cost management strategies such as therapeutic interchange, prior authorization and discounted contract pricing, even these more modest savings will still be of substantial value and interest to hospitals and clinics, payers, and group purchasing organizations (GPOs).

Unlike the current landscape where suppliers primarily focus solely on branded or generic products, the biosimilars environment will include a blended array of manufacturers. Suppliers traditionally identified as “generic companies” such as Teva, Hospira and Sandoz are expected to compete directly with originator companies such as Genentech.[28] Branded companies such as Merck and Pfizer may make competing version of other originator companies’ molecules. Amgen recently announced that while it is working to defend its epoetin and filgrastim franchises, it too will pursue development of biosimilar versions of product such as bevacizumab, infliximab, and adalimumab with hopes of launching some of these agents by 2017.[52] Multiple collaborations between generic and branded manufacturers specifically for the purpose of participating in the biosimilars market have already been announced. Each of these organizations and collaborative groups appear to be targeting many of the same molecules for initial biosimilars development as patents continue to expire.[28,53] It is expected that the initial products marketed will be versions of less complex

molecules such as filgrastim and epoetin with more complex biologics like the monoclonal antibodies only becoming available towards the latter part of this decade.[53] (Table 3)

Also in contrast to the traditional small molecule market, the uptake of biosimilars will be much more influenced by the availability of clinical information both for and against the use of these products. Originator companies will create marketing messages challenging the extent to which a different manufacturing process can truly yield a comparable or highly similar product and if a biosimilar can be considered to provide an equivalent level of safety, purity and potency. Such messages can already be seen in the clinical literature directed specifically at nephrologists, dermatologists, diabetologists, hematology and oncology physicians, as well as health care providers in general.[54–58] Given recent assessments of clinician understanding regarding biosimilars, these messages have the potential to influence perceptions substantially.

In a survey of 277 clinicians conducted by the National Comprehensive Cancer Network (NCCN) in 2011, over half of respondents including physicians, nurses, and pharmacists stated they were either not at all familiar (36%) or only slightly familiar (19%) with recent developments for biosimilars.[10] However, a recent internet survey of 376 physicians yielded slightly different results.[59] The survey, reported in August 2012, was conducted for the Alliance for Safe Biologic Medicines (ASBM), an organization whose membership includes Amgen, Genentech and the Biotechnology Industry Organization and who advocates for the use of unique nonproprietary names for biosimilars and has expressed concerns regarding biosimilar interchangeability. In its survey, 24% of respondents stated they were very familiar or had a complete understanding of biosimilars while 54% voiced a familiar or basic understanding.[59] The survey also characterized the survey respondents' feelings towards biosimilar naming, interchangeability and the ability to maintain 'dispense as written' authority for biosimilars.[59]

Based upon these results, it appears that there are varying levels of perceived understanding of the biosimilar market. Both the manufacturers of the originator reference products and their biosimilar counterparts will be working to fill in the educational gaps that currently exist, an area where the branded supplier would appear to have the resource advantage. As drug information experts, pharmacists will have a critical role in leveling the playing field to support an accurate perspective of biosimilars within their institutions. Pharmacists will also need to look towards various professional and business related organizations such as NCCN, ASHP, and GPOs who will also be expected to provide additional educational materials and information about biosimilars. One excellent resource for pharmacists is the ASHP Advantage 'biosimcentral.org' web site which offers on-demand educational activities, a continuing education discussion guide and quarterly newsletters on the latest legislative and regulatory trends related to biosimilar development.[60]

It is expected that FDA will release additional guidance information concerning the outstanding issues of biosimilar naming and interchangeability. In addition to federal guidance, several states have begun to entertain legislation directing the prescribing and dispensing of biosimilars. The primary focus of the legislation appears to be on ensuring pharmacists do not automatically substitute "non-interchangeable" biosimilars, that

appropriate notification is given to prescribers when “interchangeable” biosimilars are substituted, and in some cases that pharmacists obtain patient consent for biosimilar substitution.[61] At the time of preparation of this document, North Dakota, Virginia and Utah had adopted such legislation.[62] Conversely, biosimilar legislation in states such as Colorado, Indiana, Maryland, Mississippi, Nevada, Texas and Washington failed to be approved.[62] The impact of such regulations on inpatient practice is uncertain. Still, health system pharmacists whose practice settings include outpatient environments should be aware of their state’s requirements for pharmacy concerning biosimilars.

Also, the central underlying premise of biosimilars is that a highly similar product of comparable safety and efficacy can be manufactured at a lower cost. Therefore, the payer community is expected to be a source of information and support concerning biosimilar adoption. A recent on-line survey of 102 health plans revealed that 49% of respondents currently plan to place biosimilars at a lower cost share tier than branded specialty drugs while 64% envision implementing step edits for use of biosimliars prior to branded products.[63]

Formulary Management Strategies for Biosimilars

Even in the event that FDA or a state does not permit automatic substitution of products, health systems may still consider using the formulary tool of therapeutic interchange. Defined as the authorized exchange of therapeutic alternatives in accordance with previously established and approved written guidelines or protocols within a formulary system, therapeutic interchange is a powerful tool in the management of the formulary within health systems.[64] With a therapeutic interchange program, mechanisms are established with approval of the medical staff within an organized health system to substitute one product for another once the organization has determined that they are therapeutically equivalent. Often this is done to streamline the available products on the formulary and to create a financial savings.

Criteria for an effective therapeutic interchange program include the presence of products that can be considered therapeutically equivalent in their efficacy and safety, the potential for savings through the use of one product over another, the development of a clear process for interchange and understanding by prescribers within the system, the ability to “opt out” in specific circumstances if clinically warranted, and ideally the ability to assess the outcomes of therapy with the agents.[64] In many health systems today, therapeutic interchange programs are already in place for a variety of biologic agents. In these situations, health systems have employed therapeutic interchange programs such that there is a primary agent established within the therapeutic category and the automatic conversion to this agent is approved by the medical staff except under very specific criteria. For example, with erythropoietic stimulating proteins there are often automatic interchange programs that convert orders to a single ESA in order to simplify the formulary and consolidate market share of one product in order to improve contracting and to lower overall costs.[65,66] Similar types of programs have been employed with other biologic agents such as human insulin and intravenous immune globulin.[67] It is likely that health systems will employ a similar approach to consolidate the use of biosimilar agents within their formularies.

Pharmacists will be expected to provide leadership and guidance in balancing the financial and clinical issues associated with formulary decisions and the selection and use of these products. It is clear that there will be significant financial pressures and opportunities to utilize biosimilar products to affect savings, but this must be done in a way that protects the quality and safety of medication use outcomes. This is a role that pharmacists have fulfilled historically through the P & T committee and formulary process.

Use of sound principles of formulary management will be critical in providing an objective and rational analysis to assure the appropriate utilization of biosimilar medicines. Included in this analysis will be consideration of factors including data on efficacy and safety, the range of indications for use, the potential for immunogenicity, safe use through appropriate naming and labeling of the products within the medication use system, an effective pharmacovigilance plan, economic considerations (from both the health system and the patient perspectives), appropriate and effective interchange processes (particularly at the transitions of care), and provider and patient education needs. ASHP has published a policy statement supporting this approach.[68]

It is unlikely that the FDA will declare any of the early biosimilar products to be automatically interchangeable by pharmacies, although that designation does exist in the BCPI Act. State pharmacy practice acts have oversight for pharmacy level substitution practices and some states have provided different approaches to substitution. Pharmacists will need to be aware of both FDA and state regulations when determining what levels of interchange or substitution may be permitted. However, regardless of these regulations around automatic substitution, health systems will likely be allowed to set up therapeutic equivalence programs within the framework of their formulary systems as approved by their medical staff.

One area that will be particularly challenging for pharmacists and health system pharmacy and therapeutics committee will likely be around the transitions of care. As mentioned previously, payers undoubtedly will provide significant incentives to use biosimilar medicines to reduce or control costs.[63] These could include prior authorizations or substantial co-payment or co-insurance premiums for use of the originator product when a biosimilar medicine is available. Pharmaceutical industry contracting with health systems could involve significant discounts to encourage the health systems to continue to use the originator product even when biosimilar products are available. This will create a dilemma regarding whether to forgo these discounts in order to minimize the switching between similar products at the transitions of care, or to assure that the financial impact on the patient is minimized when they are discharged out of the hospital.

In addition to these formulary management aspects, many operational and educational needs will need to be addressed prior to the introduction of biosimilars.[27,67] (Table 4) Given the possibility of having different non-proprietary names than the originator, health systems must ensure that processes exist to distinguish biosimilars throughout all components of the medication management continuum including the electronic medical record, the medication administration profile, the order entry interface, predefined order sets, care paths, and protocols through final product labeling and even bedside barcoding.[69] Inventory

management systems including automated dispensing devices and their associated software as well as purchasing systems must reflect biosimilars in a way that allows for their accurate identification by technicians, pharmacy buyers and all those that manage the pharmacy supply chain.

In order to support appropriate pharmacovigilance, health systems must ensure mechanisms are in place to track the potential for unique adverse events associated with biosimilars not observed with the originator.[69] This preparation includes an accurate understanding of the baseline adverse event rate for each organization for the use of the originator product.

Most patient populations have a reasonable understanding of the concept of generic medications. However, substantial education will be required to assist patients in understanding the differences between generics and biosimilars.[10] Pharmacists, physicians, and nurses will need access to drug information on biosimilars, including content appropriate for patient audiences to address the numerous questions that will arise as these products initially come to market.

Putting Knowledge into Practice with the First Non Innovator Biologic

On August 29, 2012, FDA approved Teva's tbo-filgrastim, its version of filgrastim previously only marketed as Neupogen (Amgen).[70] Although approved as a biosimilar in Europe, Teva filed a complete BLA application in November 2009 prior to enactment of the BPCI Act. Teva will not market its product before November 2013 due to the settlement terms of a patent infringement suit with Amgen.[71] Although not a biosimilar by US standards since the product was approved using a full BLA, this approval does reflect a significant milestone in the advancement towards marketed biosimilars in the US. It also provides a representative example of how pharmacists will need to evaluate and manage similar, follow-on biologics.

Although the dosing and frequency of administration for filgrastim and tbo-filgrastim are the same, the Teva product was not approved with all the indications for which the Amgen product is approved.[16,72] Tbo-filgrastim is licensed for use in cancer patients receiving myelosuppressive chemotherapy, but not for other indications such as the use in cancer patients receiving bone marrow transplants or patients undergoing peripheral blood progenitor cell collection and therapy.[72] As a result once this product comes to market, pharmacists and their respective P & T committees will have to make decisions regarding whether or not the mechanism of action and the associated clinical evidence supports use of the product outside of the labeled indications. While quite similar, the name of the Amgen and Teva products also vary. Therefore, should a health care organization choose to use the Teva product, steps must be taken to ensure that all order entry processes including protocols, care paths,electronic medication administration records (eMARs), as well as the representation of the product on the displays of automated dispensing devices reflect the correct agent. As the biosimilars market continues to develop, so will the diversity in the processes manufacturers choose to seek approval for their products. Some suppliers may file for approval via a full BLA pathway, as in the case of tbo-filgrastim, whereas others will choose the biosimilar review process. Others will seek to characterize their products as

"biobetters", biologics engineered to achieve an improved or different clinical performance.[9] In addition, naturally sourced biologic molecules approved through the 505(b)(2) pathway also exist and must not be confused with biosimilars. Pharmacists will need to understand the differences in all of the approval pathways to educate physicians and other clinicians on the labeling associated with each medication and the manner in which they should be used.

Conclusion

Over the remainder of this decade, biosimilars will represent one of the most tangible opportunities for health care organizations to manage the growth of pharmaceutical expenditures. However, due to their inherent complexity and variation, the level of analysis required to evaluate biosimilar products for formulary inclusion will be much more intense and will require substantial preparatory work in advance of these agents coming to market.

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Table 1

Approval Processes for Drug and Biologics[8,22,23]

Product Designation	Application Type	Application Pathway	Clinical Studies Required
Drug Food, Drug, and Cosmetic Act	New Drug Application (NDA)	505(b)1	Yes, full evaluation of safety and efficacy
		505(b)2	Yes, however, studies do not have to be done by the application sponsor
	Abbreviated New Drug Application (ANDA)	505(j)	No, but must demonstrate bioequivalence
Biologic Public Health Services Act	Biologics License Application	351(a)	Yes, full evaluation of purity, safety and potency
	Biosimilar Application	351(k)	Yes, but abbreviated process

Table 2

Proposal for Precise Biosimilar Terminology[9]

Term(s)	Definition	Implications
Biosimilar	Copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise.	Only very small differences between biosimilar and reference with reassurance that these are of no clinical relevance. Extrapolation of clinical indications acceptable if scientifically justified.
Me-too biological/biologic Noninnovator biological/biologic	Biological medicinal product developed on its own and not directly compared and analyzed against a licensed reference biological. May or may not have been compared clinically.	Unknown whether and which physicochemical differences exist compared to other biological of the same product class. Clinical comparison alone usually not sensitive enough to pick up differences of potential relevance. Therefore, extrapolation of clinical indications problematic.
Second-generation (next-generation) biological/biologic Biobetter	Biological that has been structurally and/or functionally altered to achieve an improved or different clinical performance.	Usually stand-alone developments with a full development program. Clear (and intended) differences in the structure of the active substance, and most probably different clinical behavior due to, for example, different potency or immunogenicity. From a regulatory perspective, a claim for “better” would have to be substantiated by data showing a clinically relevant advantage over a first- or previous-generation product.

Table 3

Projected US Patent Expirations for Major Biologicals[53]

Product	Brand Name	Potential Biosimilar Entry
Filgrastim	Neupogen	2013
Epoetin alfa	Epogen/Procrit	2014
Pegfilgrastim	Neulasta	2015
Palivizumab	Synagis	2015
Rituximab	Rituxan	2016
Cetuximab	Erbitux	2016
Adalimumab	Humira	2016
Infliximab	Remicade	2018
Trastuzumab	Herceptin	2019
Bevacizumab	Avastin	2019
Darbepoetin	Aranesp	2024
Etanercept	Enbrel	2028

This table represents the best available projections. Patent expirations are subject to rapid change, including various legal and regulatory actions. Patent expiration does not guarantee biosimilar availability. .

Table 4

Educational and Operational Issues Related to Biosimilar Adoption[27,67]

Medication Management Process Areas	Key Preparatory Steps for Biosimilars
Formulary analysis	Understand the approval history of the biosimilar, labeled and off-label indications, branded and non-proprietary names, clinical safety and efficacy information, dosage forms, use in special patient populations, and economic aspects. Determine if multiple biologics be on formulary; if multiple products are formulary determine any criteria for use of each product (e.g. indication, patient age, etc). Determine if therapeutic interchange programs will be implemented; if used, obtain P&T approval. Devise a plan for transitions of care, including implications of patient's insurance coverage.
Order management/Information systems	Differentiate biosimilar and originator product in computerized order entry systems, electronic medication records, medication administration profiles, order sets, and protocols.
Inventory management	Ensure pharmacy buyer has adequate information (e.g. NDC number, wholesaler order number) to purchase biosimilar. If the pharmacy will maintain both biosimilar and originator product, establish par levels for each product.
Financial analysis	Identify the base price, contract price, and reimbursement for biosimilar when compared to originator product Determine financial impact from both health system as well as patient perspective Consider the availability of patient assistance programs.
Education	Provide drug information and other education resources to the pharmacy, physician and nursing audiences for biosimilars Develop appropriate patient educational materials