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An Institutional Guide for Formulary Decisions of Biosimilars

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Abstract

Biologics have changed the landscape for the management of many debilitating chronic diseases but account for a significant expenditure of medications globally. Fortunately, advances in technology paved the way for the introduction of biosimilars, which are highly similar to the originator biologics. In the quest to reduce the budget impact of biologics, organizations have begun to adopt biosimilars. Institutions evaluating biosimilars for inclusion in the hospital formulary must make informed formulary decisions by conducting a thorough review of key elements for evaluation of biosimilars and address the multidimensional aspects during the selection process of different biosimilar products. Therefore, we aim to present an institutional guide of these elements to inform formulary decisions. These key elements include biosimilar evaluation for formulary addition; regulatory approval; substitution, interchangeability, and switching; extrapolation; product characteristics, manufacturing, and supply chain issues; pharmacoeconomic evaluations; traceability, nomenclature, and coding; education; and pharmacovigilance.

Keywords
biosimilars, biologics, formulary, decision-making, pharmacy and therapeutics committee, pharmacist

Introduction

The introduction of biologics changed the landscape for the management of many life-threatening and chronic, debilitating diseases. Biologics are complex, heterogeneous protein molecules produced in a living organism or derived from a biological cell through recombinant DNA or controlled gene expression methods.[1-4] Several factors play critical roles in the production process leading to the inherent variability of these biologics and even batch-to-batch variation independent of the DNA sequence.[5,6]

However, the high cost of biologics remains a limitation for their expanded therapeutic use and may deny patients' access to this therapy.[7] Fortunately, innovative technology in drug development facilitated the introduction of biosimilars at a relatively lower cost after the patency of the "originator or reference" licensed biologic product expires.[5] The World Health Organization (WHO), the European Medical Agency (EMA), and the Food and Drug Administration (FDA) define a biosimilar as a biologic agent with high similarity to a licensed reference product which has expired patency and has no clinically meaningful differences regarding safety, efficacy and quality.[5,7,8] As of August 2022, 1775 biological

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Table 1. Comparison Between Generics and Biosimilars.

	Generics	Biosimilars
By definition	Identical to a branded drug	Highly similar to a reference product
Costs to bring to the market	Low costs	High costs
Size	Small, low molecular weight (<1000 Dalton)	High molecular weight (>1000 Dalton)
Complexity	Simple and easy to characterize	Complex and difficult to characterize
Manufacturing	Chemical synthesis	Biological process (living cells or recombinant DNA)
Stability	Relatively stable	Sensitive to storage and handling
Immunogenicity	Low potential	High potential

products, including 82 biosimilar products for 38 biosimilar drugs, were licensed in the US market.[9]

Institutions face many challenges with the introduction of biosimilars regarding the selection of biosimilar products. In addition to the standard considerations of formulary management, there are specific day-to-day formulary questions to be answered such as: which biosimilar to introduce among many approved biosimilar for a reference product; whether to keep the reference product and biosimilar in the formulary; how to make decisions on interchangeability of products; what are main considerations for pharmacoeconomic, pharmacovigilance assessments; and how to educate patients, and healthcare providers.[10] Therefore, we aim to present an institutional guide to inform these formulary decisions.

Development of Institutional Guide

An expert panel, aiming to provide a systematic approach for evaluation of biosimilars in our setting and to address the previously mentioned challenges, was formulated in our institution. The panel included six pharmacists from an integrated health care system in Saudi Arabia, who are working as coordinators of the pharmacy and therapeutic committee, one pharmacist leader at our medication safety center, and one pharmacoeconomic specialist. A draft of these elements was prepared by the first author with review and refinement by other members of the panel over several iterations. We have utilized this guide in our setting and seek to share examples to illustrate different concepts that we considered critical in the evaluation process.

We suggest that the evaluation of a biosimilar for formulary addition follows a systematic process addressing efficacy, safety, and pharmacoeconomic aspects. Members of institutions evaluating biosimilars should be able to understand the differences between generic drugs and biosimilars.[3,10-12] Table 1 presents a comparison between generics and biosimilars.[13,14]

Key Elements to Consider in Evaluating Biosimilars

A thorough review is necessary to address the multidimensional aspects associated with biosimilars to make informed formulary decisions which includes: 1) biosimilar evaluation for formulary addition, 2) regulatory approval, 3) substitution, interchangeability, and switching, 4) extrapolation, 5) product characteristics, 6) manufacturing and supply chain issues, 7) pharmacoeconomic evaluations, 8) traceability, nomenclature, and coding, 9) education, and 10) pharmacovigilance.

The Biosimilar Evaluation for Formulary Addition

Committees evaluating the introduction of a biosimilar to their institution need a structured method to select a biosimilar product since multiple biosimilar products may be available in the market with favorable features for one product over the other (e.g. quality of clinical trials conducted on the product, cost, approval status, labeled indications, supply chain, country of origin, and others).[15] Key steps include an initial review, formulary decision, organizational plan for the transition phase to the biosimilar when both originator and biosimilar are available at the same time, and, finally, actions to take once only the biosimilar is available. A scientific evaluation is necessary to assess clinical trials and real-world evidence to make sound comparison between products and guide evidence-based informed decisions. Table 2 presents a summary of the critical considerations during the evaluation of biosimilars which will be further discussed in the below sections. We believe these considerations are required as a part of a comprehensive evaluation of biosimilars, preferably by a specialized committee such as the pharmacy and therapeutics committee (P&T).

Regulatory Approval

Institutions should be aware of the different regulatory requirements for approval of biosimilars in the market. The approval process depends on comparative analytical data and, to a lesser extent, clinical trials with the reference products.[16] The EMA paved the way globally by implementing a framework for the approval of biosimilars in 2003 with the first biosimilar (Omnitrope®) that was approved in 2006.[17] The EMA requires identical types of product life-cycle studies for the approval of biosimilars and reference biologics with fewer clinical studies for biosimilars.[18,19] A biosimilar approval is based on totality of evidence and knowledge gained from the licensed reference product and, therefore, similar efficacy and safety of all clinically approved indications are extrapolated to the biosimilar without the need to replicate the studies in each of these indications.[18,19]

Table 2. Summary of Critical Considerations During the Evaluation of Biosimilars Based on Subsequent Steps of Formulary Evaluation.

Key considerations	Specific details
Initial review	What are the considerations for systematic approach for the evaluation of a biosimilar?
Available biosimilar products	• What are the current available biosimilars on the market? • Is the product classified as biosimilar, non-innovator, or biobetter? • Which regulatory body approved the product?
Substitution, interchangeability, switching	• Will the reference product stay on the formulary? • Will there be a complete switch to the biosimilar? • Are there any potential risks in switching to the biosimilar?
Extrapolation of indications to various population	• What are the approved indications? • Are there any indications not labeled for the biosimilar but labeled for the originator? • What are the indications studied in RCTs? • What indications were approved based on extrapolation only? • Which population(s) will be using biosimilar?
Product characteristics	Are there notable differences in packaging, labeling or storage in comparison to the reference product?
Pharmacoeconomic evaluation	• What is the budget impact of the formulary addition? • Is a cost-minimization analysis necessary? • Do we need a cost-effectiveness analysis for comparing biosimilars of first-generation biologics vs. second generation reference products? • Can we expand access to care through the addition of the biosimilar on a budget-neutral basis? • Are there any unintended direct or in-direct costs that may impact presumed cost savings?
Manufacturing and supply chain	• Will there be a sustainable supply chain and quantities to meet institutional demands? • Does the biosimilar manufacturer have a good track reputation of safety, quality, and meeting demand?
The formulary decision	What are possible critical decisions for regulating use of biosimilars and other formulary biologicals?
A thorough review	• Will the biosimilar fully replace the originator, or will both be available at the institution? • Is the approval of the biosimilar a blanket approval for all approved biosimilars available in the market, or specific to one product? • Will the approved biosimilar be used across all indications to which the reference product was used for? • If there is an off-label use, will the biosimilar be used in that indication too? • Is there a need to restrict the biosimilar? Or will current formulary restrictions may change due to lower acquisition cost? • Is there any specific population in whom the biosimilar may not be suitable for use? • Will the addition of the biosimilar require updates on drug-use policies or institutional guidelines?
The transition phase	What do we have to consider during formulary transition phase from a reference product to a biosimilar?
Adoption	• How will the institution handle the transition phase? • Will specific patients be able to continue treatment with the remaining stocks of the reference product, while new patients start on the biosimilar?
Logistics considerations/ information technology support	• What are the current supplies of the reference product and when will the procurement of biosimilar be available? • How will traceability, nomenclature, and coding of biosimilars in electronic medical records (EMR) be arranged? • Is there a need for mitigation strategies to avoid any inadvertent mix-ups if both biosimilar and reference product are available in hospital?
Biosimilar available	What is next after the biosimilar is available in the formulary?
Education	• How Patient education will be arranged? • What are the plans to educate prescribers/other healthcare professionals to enhance the uptake of biosimilars?
Pharmacovigilance	• What processes will there be in place to monitor for the incidence of allergic reactions? • How will loss of efficacy be monitored? • Will Medication Use Evaluations be necessary? • Will there be specific Therapeutic Drug Monitoring tools? • How to handle immunogenicity: will the institution arrange a pathway to provide the reference product on non-formulary basis for patients in case of a significant allergic or immunogenic reaction?

Table 3. FDA Approval Pathways for Chemical Drugs, Generics, Biologics, and Biosimilars.

	Chemical drugs	Generics	Biologics	Biosimilars
Application	New drug application (NDA)	Abbreviated NDA (ANDA)	Biologics License Application (BLA)	Abbreviated application
Pathway	505 (b)	505 (j)	351 (a)	351 (k)
Law	Federal Food, Drug, and Cosmetic Act	Hatch-Waxman Amendment 1984	Public Health Service Act	BCPI Act
Evidence	Full safety and effectiveness data*	Bioequivalence and Pharmacokinetic (PK) studies	Full safety and effectiveness* and purity	Full safety and effectiveness*, analytical data, comparative studies to demonstrate safety, efficacy, and purity
Designation	Reference Standard (RS) "Patent" Exclusive marketing	Therapeutic Equivalent to RLS. Many generics can be produced for an original product	Original or Reference listed drug which is "Patent" for 10–15 years with exclusive marketing	Interchangeability to be determined. Many biosimilars can be produced for a reference product
Indexed	FDA approval list	Orange book†	Purple book‡	Purple book

*Full safety and effectiveness data include preclinical, pharmacokinetics /pharmacodynamics, and human clinical studies.
†Orange book includes approved drug products with therapeutic equivalence evaluations by FDA.
‡Purple book includes lists of licensed biological products with reference product exclusivity and bio-similarity or interchangeability evaluations.

Almost a decade later, the FDA followed the EMA's approval process, and the Biosimilar Price Competition and Innovation Act (BPCI) Act was passed in 2010 with the first biosimilar approved in the USA in 2015.[18,20] Table 3 outlines the differences between the approval pathways for chemical drugs, generics, biologics, and biosimilars as per the FDA.

Additionally, the FDA approves some biosimilars to reference products known as "follow-on biologics". In this case, there is an expedited approval process through the 505 (b)(2) pathway based on the safety and effectiveness data of the reference product and not through 351(k) pathway.[20] For example, the manufacturers of both Admelog® and Basaglar® completed phase III, non-inferiority RCTs in patients with type I and type II diabetes against the reference products.[21-25] Their findings have been reported in a systematic review and meta-analysis, demonstrated no differences in any of the endpoints between long-acting or short-acting insulin biosimilars versus the reference products and gained regulatory approvals.[26]

Non-innovator or copy-version products are another category of biologics, known as "non-comparable biotherapeutic products" by the International Federation of Pharmaceutical Manufacturers & Associations, that have been confused with biosimilars.[27] These biologics have been approved and marketed in some countries without clear standards for the production and comparability to the reference products and have questionable efficacy, safety, and purity.[7] In 2019, India had approved 83 non-innovator biologic products whereas the US had approved 26 biosimilars and the EU had approved 66 biosimilars.[28] In Mexico, approval of these drugs followed the same criteria as that of the generic drugs until recently.[29] While use of non-innovator biologics has allowed less affluent countries to have access to biologics, some products (e.g., Kikuzubam®) were withdrawn due to adverse events (AEs) and lack of regulation.[27]

On the other hand, biobetters require the same process of evaluation for approval by a regulatory agency as the reference product and are designed to improve upon some aspect (i.e., mechanism of action, bioavailability, safety, immunogenicity) of a biologic.[30] In July 2021, Sorrento Therapeutics received marketing approval for its infliximab biobetter (CMAB008) in China.[31] Due to its production in Chinese hamster ovary cell rather than murine cell lines, it is expected to be safer with less immunogenicity compared to marketed Tumor necrosis factor-α antibody.[31]

Finally, institutions must understand the necessity of regulation of these products due to significant variability in the production process, which is attributed to microheterogeneity or manufacturing process changes.[32,33] The inherent variability in the manufacturing of the biological products generally lead to the batch-to-batch variation independent of the same DNA sequence, which may impact on the efficacy, safety, and purity of these products.[32,33] For these reasons, assessment of the biosimilar's regulatory status must be made during the evaluation.[5,6]

Substitution, Interchangeability, and Switching

Institutions face challenges regarding substitution, interchangeability, and switching between reference products and biosimilars or biosimilar-to-biosimilar.[14] There are different views by EMA and FDA regarding interchangeability. The EMA does not designate biosimilars as interchangeable but left it for the Member States to outline legal prescribing authorities and responsibilities.[19] Physicians are able to substitute an approved biosimilar for the reference product.[34] On the other hand, the FDA allows biosimilar manufacturers to seek an "interchangeable" designation where there are specific conditions for these products compared to standard biosimilars.[35] These conditions include: 1) clinical efficacy

where the biosimilar is expected to produce the same clinical effect compared to the reference product; 2) the risks (i.e., increased AEs, decreased efficacy) of repeated use of the biosimilar are not higher than what would be expected with repeated use of the reference product alone without alternating between biosimilar and reference product; and 3) the biosimilar can be auto substituted for the reference product by pharmacists without the need for a new prescription of the physician who prescribed the reference product.[35] The FDA provides an updated monthly list with details on approved and licensed biologicals (including biosimilars and interchangeable products) in the Purple Book.[9]

To date, the FDA approved only three interchangeable biosimilars (seven products), insulin glargine-yfgn, (Semglee)®, adalimumab (Cyltezo®), and ranibizumab-eqrn (Cimerli ®), which allows pharmacists to auto-substitute (switch) the reference product without prior authorization of the prescriber.[9,36,37] The auto-substitute privilege is only for those interchangeable products unlike other biosimilars, which require the pharmacist to obtain an approval from the prescriber before substituting the reference product with the biosimilar in most states in the US. Patients also must authorize the change, and some states require an informed consent before dispensing the biosimilar product.[38]

There have been some concerns with legal responsibilities for switching patients from a reference product to a biosimilar compared to prescribing biosimilars to biological naïve patients; hence, many organizations adopted shared decision-making and informed consent before switching.[39]

In general, institutions seek to keep the least expensive options on their formularies. On some occasions, this may lead to brand products costing less than biosimilars due to price competition where biosimilar companies have to offer further discounts to be competitive with their originator as it happened in our organization; however, the most common scenario is where a biosimilar is added to the formulary to generate cost-savings opportunities. In turn, the institution must address and develop policies related to automatic substitution, therapeutic equivalency between the biosimilar and the reference product, exclusion criteria, and issues related to transitions of care.[4,13,30]

For example, a recent review including RCTs and real-world evidence observational studies demonstrated the safe and effective switch between biosimilars and reference products for the treatment of rheumatoid arthritis (mostly driven by studies for CT-P13 and SB4; the first biosimilars approved by EMA for infliximab and etanercept and respectively).[40] However, the study pointed to the need for extensive educational programs for the prescribers and patients to lessen the nocebo effects against biosimilars.[40]

Another practical challenge for institutions is the limited evidence on how often a hospital formulary can change from one biosimilar to another or if an organization can retain more than one biosimilar in the formulary for a reference product.[16] Therefore, it is reasonable to assume that each institution defines a period (e.g., 2 years) before one biosimilar can be exchanged to another biosimilar. Furthermore, any new biosimilar should also be carefully evaluated as pointed earlier. From a pharmacovigilance perspective, the frequent switching between a biosimilar and a reference product or biosimilar-to-biosimilar of different manufacturing companies may lead to different efficacy or safety outcomes, making it difficult to infer causality.[30]

Finally, the situation is further complicated by different preference of insurance plans for biosimilar coverage and indication-specific plans. For example, some plans have "preference coverage" to access reference product only after using biosimilar.[41]

In other instances, plans have "non-preference coverage" where patients are required to use reference product first before gaining access to biosimilar or sometimes coverage plans do not prioritize either product.[41]

Extrapolation

Institutions should assess the following for extrapolation of indications: 1) mechanism of action (including targeted receptor and downstream signaling); 2) studied population; 3) different clinical settings; 4) safety data; and 5) immunogenicity.[19] For example, Admelog® and Basaglar® were studied in adults patients (>18 years of age); however, they were approved for use in children >3 and 6 years based on the extrapolation from their reference products of insulin lispro (Humalog®) and insulin glargine (Lantus®), respectively.[42] Data from particular indications may not be extrapolated in terms of efficacy and safety to other indications with a different mechanism of action and pharmacokinetic parameters (e.g., rheumatoid arthritis and malignancy).[19] Safety and comparability studies can be extrapolated once it is established for one indication; however, immunogenicity may vary by indication as it is dependent on several other factors such as immune status of the patient, comorbidities, concomitant therapy, frequency, and length of exposure to the drug.[19]

Furthermore, several biologics are accepted for use to treat many off-label indications in clinical practice. For example, decision-makers can extrapolate evidence for two FDA approved biosimilars filgrastim-sndz and infliximab-dyyb based on their reference products for the treatment of symptomatic anemia in myelodysplasia syndrome in combination with epoetin (off-label indication) and immune-mediated colitis (labeled indication), respectively utilizing the framework of extrapolation of indications for biosimilars by the FDA.[43]

Institutions should specify the following points in the formulary decision: the approved indications; extrapolation of the indication to various populations (pediatrics, adults); interchangeability; and off-label indications that will or will not be covered by the biosimilar (e.g., bevacizumab has an off-label intravitreal use for the treatment of age-related macular degeneration).[44]

Furthermore, institutions may update their prescribing privileges, drug-use policies, or guidelines for the management of various diseases by prioritizing biosimilars over other formulary biologics to generate cost-minimization opportunities.

Product Characteristics

The evaluation should consider specific variations in storage conditions, shelf-life, and dosage forms (e.g., pre-filled-syringe vs vials for injections, calibrated vs non-calibrated dosage forms). Additionally, there may be other product characteristics that should be considered if the drug is administered through a device or injector such as the precision of the dose and the ease of administration. The use of familiar devices can facilitate patient's acceptance to the switch and adherence to the new biosimilar product.[14]

Manufacturing and Supply Chain

Patients may suffer poor outcomes due to unavailability or continuous switching between different biologics. Therefore, institutions should ascertain history of recalls or shortages of the manufacturers and if they can maintain the supply chain to meet the demands.[13,28] Furthermore, it is crucial to consider the availability of various production sites, backup, and a clear process for handling of drug shortage or recalls.[13,28] Institutions should evaluate all these factors and consider if the manufacturer has a security protection mechanism against counterfeit or illegal drug diversion.[13,30] In general, institutions can utilize several resources to obtain data on drug shortages and set up mitigation plans accordingly.[45,46] The FDA launched drug shortages databases and a mobile application which provide details on drug shortages including issues with supply, quality of products, discontinuations, and communication information with manufacturing companies to minimize the impact of drug shortages.[45] Furthermore, the American Society of Health System Pharmacists (ASHP) provides detailed web page for drug shortage resources including real-time reports on shortages, statistics, guidelines, tools, and publications to improve the quality and resilience of United States healthcare supply chain.[46]

Pharmacoeconomic Evaluation

Biosimilars are added to formularies to substantially reduce expenditures within a healthcare system, and a pharmacoeconomic evaluation (PE) is necessary to aid decision makers by analyzing all costs and clinical outcomes comparing biosimilar(s) to reference product.[47] Ideally, the analysis should be conducted by a pharmacoeconomist or experts of pharmacoeconomic analyses.

PEs must include all potential direct medical and non-medical costs associated with the adoption of a biosimilar such as the acquisition cost, additional costs of outpatient visits to initiate the biosimilar, administrative costs if there are changes in administration device, laboratory tests and patient/provider education, transportation costs, and pharmacovigilance studies.[13,30] It is also important to consider the cost of increasing biosimilar doses or shifting to more expensive treatment options due to treatment failure, patient or physician resistance, or biosimilar supply shortages. Additionally, a budget impact analysis is used to evaluate the budget impact of substituting a biologic with a biosimilar. There are four types of economic evaluations commonly used: cost-benefit, cost-effectiveness, cost-minimization, and cost-utility.[48]

Clinical outcomes from the trials required for regulatory approval and real-world effectiveness data should be considered during the evaluation process.[47] As we assume similar effectiveness profile, some consider a cost-minimization analysis is the most appropriate economic assessment to evaluate biosimilars compared to reference biologic as they are associated with cost reduction, however there is debate on whether this is sufficient.[47] Cost-effectiveness analyses are appropriate when comparing biosimilars of first-generation biologics with second generation biologic reference products. For example, subcutaneous formulas of rituximab and trastuzumab are second generation biologics that offer convenient administration which save infusion time compared with biosimilars of intravenous formulas of rituximab and trastuzumab.[49,50]

Some have argued the traditional PE have limitations including the concern that cost-effectiveness is not always budget neutral relative to a given outcome and the variation in treatment regimens.[51] Researchers evaluated potential benefits of adding a biosimilar on a budget-neutral basis, allowing expanded access to other treatments.[52-55]

PEs should be conducted initially and regularly throughout the life cycle of the biosimilar given the uncertainty of long-term safety data and the market competition by the reference product or other biosimilars.[47] For example, the introduction of a biosimilar filgrastim in the US market provided a PE framework model to highlight factors impacting the cost-saving of a biosimilar, including the patient, and provider's perceptions. The PE demonstrated a 5-year cost savings of $256 million, of which 18% represented the patient's costs, 34% for commercial payers, and 48% for Medicare.[56] These cost savings will in turn pose additional stress on the manufacturing companies which invest large funds in the production of biosimilars to launch biosimilars at competitive prices to meet the market's expectations.[57]

There are key differences between Europe and the US in the government's role in the pharmaceutical marketplace.[58] In Europe, many countries regulate prices by using various strategies: maximum prices, mandatory discounts, reference pricing, or the set price for reimbursement of a specified group.[58] Additionally, physicians may receive incentives to prescribe or set up quotas.[58] The US government, however, does not have control over the pharmaceutical marketplace whereas NHS England proposed a 30-50% price reduction of

biosimilar compared to reference product.[58,59] While in the US, a price reduction of 15-30% for the biosimilar compared to the reference product was predicted to have a significant impact on the cost of management of many diseases requiring biologics.[13,30,47,60] These savings are expected to rise as the projected growth of the market share for biosimilars increases with time.[13,30,47]

Therefore, it is crucial that institutions proactively assess biosimilars, once approved and pricing data are available, as delaying their adoption has been linked to significant economic loss. For example, delayed introduction of adalimumab biosimilar in the US resulted in a $2.19 billion loss in savings to Medicare over 4 years.[61]

Traceability, Nomenclature, and Coding of Biosimilars in Electronic Healthcare Records (EHRs)

We suggest that institutions design a simple and accurate method for nomenclature and coding of the biosimilar in EHRs. Our P&T committee has recommended to include brand names of the biosimilars in the computerized prescribing order entry in addition to its international non-proprietary name (INN) or generic names for efficient pharmacovigilance monitoring. Biosimilar product is identified as a "biosimilar" in the order entry screen by adding the term "biosimilar such as RiTUXimab (Truxima®—biosimilar). The EMA specifies the use of international non-proprietary names (INNs) of the drug along with the trade name of the biosimilar.[19] However, the FDA recommends the addition of a suffix with no meaning to INNs of the drugs such as Amjevita® (Adalimumab-atto) and Erelzi® (etanercept-szzs).[4,16] It is crucial to distinguish a biosimilar agent from a reference product within a formulary to allow for an efficient tracking system for AEs. [62,63] Differences in product packaging, labeling, and stability between the biosimilar and the reference product should be reflected in the EHRs to optimize product tracking and minimize potential errors. Additionally, effective use of technology such as barcode scanning for products can link the product information to the EHRs of the patient.[13,64]

Education

Patient education. Plans should be made for patient education, providing resources and educational materials using the native language while being sensitive to the cultural context.[65] Standard tools for patient education can be utilized along with biosimilar infographics, consumer updates, and videos.[66] These tools are crucial to empower patients with information on the approval process of biosimilars in simple language, identifying the differences between the reference product and the biosimilar product in administration, storage, and dosing to avoid administration errors; parameters to monitor for efficacy; and appropriate channels to report any side effects.[65]

It is also essential to assess the impact of the nocebo effect, defined as the negative symptoms or outcomes that a patient may encounter after receiving a sham or an active treatment as opposed to the well-known placebo (positive) effect, on patients' acceptance of biosimilars.[67] This may be due to psychological (negative expectations as per own conception or driven by the prescribers) or neurobiological factors (endogenous opioids and dopamine).[67] Studies have recommended informed consent and positive framing of the risks as effective strategies to diminish nocebo effects.[67,68] Therefore, it is imperative to open dialogue with patients and invest time to engage them in the decision process.[65] Adding a patient-advocate as a member to the decision-making committee contributes to the goal of patient-centered care and is one way to integrate the patient's perspective in the decision process.[69]

Physician/other healthcare professionals. One of the significant barriers to the uptake of biosimilars is the lack of knowledge and understanding of prescribers regarding the science and regulatory approval process of biosimilars and their impact on the healthcare system.[13,14,70] It is prudent that institutions fill in these knowledge gaps by educating various healthcare professionals to reduce nocebo effects.[4,40,71] The negative impressions of the prescribers, evident in verbal or nonverbal communication, may trigger nocebo effects in patients.[67] Furthermore, physicians are encouraged to monitor their patients, report loss of efficacy, safety, or immunogenicity concerns upon starting or switching to a biosimilar.[4,13,72] Many institutions engage stakeholders in evaluation, selection of biosimilars for formulary addition, and designing educational tools for other healthcare professionals, which will enhance their confidence in prescribing biosimilars and contribute positively to patient care. We suggest that institutions should design precise mechanism to notify all healthcare providers once the biosimilar is available in the institution and provide the necessary prescribing details (dosing, monitoring, storage, and administration, etc.).

Pharmacovigilance

We suggest that institutions design clear mechanisms to monitor and report aspects related to the pharmacovigilance of biosimilars.[73,74] AEs may have acute or delayed onset associated with a wide array of mild to life-threatening conditions.[75] Symptoms of acute onset side effects include hypotension, bronchospasm, laryngeal, or pharyngeal edema, urticaria while myalgia, arthralgia, and skin rash are more common with delayed onset.[73,75] Loss of efficacy is one of the most significant unwanted possible immune responses to biologics in general and biosimilars due to the development of anti-drug antibodies (ADA) and cross-reactivity with other endogenous proteins.[73,75] The presence of impurities, specific vehicles, stabilizing agents, different host cell lines, and glycosylation are manufacturing processes that can affect

immunogenicity. In addition, treatment-related factors (e.g., dose of the drug and route of administration) and product related-factors (e.g., storage conditions and handling) can contribute to immunogenicity.[73,75] For example, intramuscular and subcutaneous are the most immunogenic routes of administration compared to intravenous route, while topical use is the least immunogenic.[60]

We suggest that institutions to be vigilant in monitoring for post-market surveillance studies and take necessary actions when there are safety signals identified by local or international regulatory agencies.

Epoetin biosimilar provides an example for the importance of pharmacovigilance studies after the detection of safety signal of approved biosimilars. The use of epoetin biosimilars in Europe over a decade demonstrated comparable efficacy and safety to the reference products and advocated for expanded use biosimilars due to cost-saving opportunities.[76,77] Later, post-market surveillance studies identified signals of pure red cell aplasia (PRCA) associated with the subcutaneous use of Eprex®/Erypo®, and it was contraindicated for use in Europe from 2002 to 2006 until the company replaced the uncoated rubber stoppers with coated ones and implemented strict cold chain supply.[77] In another instance, two patients developed PRCA with subcutaneous HX575 due to an immunogenic reaction as a result of increased exposure to tungsten and protein aggregation in the prefilled syringes.[77,78,79] The manufacturer worked on producing low tungsten syringes, and the drug was successfully studied in pre-dialysis and dialysis patients with no patient developing neutralizing antibodies.[80]

Furthermore, relatively long-term studies detect safety signals such as immunogenicity between the biosimilars and reference product. For example, there was no difference in 12- and 6-months incidence of immunogenicity between biosimilar insulin lispro and the reference in patients with type I and type II diabetes, respectively.[81]

All health care professionals are encouraged to proactively monitor and report AEs, lack of efficacy, immunogenicity concerns, and medication errors associated with the use of biosimilars.[73] Furthermore, each institution should have an effective monitoring and reporting system for AEs and utilizes technology to establish causal associations and all these reports should be shared with regulatory authorities.[73]

Medication Use Evaluations (MUEs). MUEs are quality improvement monitoring tools that can be adapted to provide real-world evidence of utilization of biosimilars.[82,83] MUEs help to identify cycles of improvement in pattern of prescribing, fill in practice-gaps about uncertainty of patients' response, and answer questions about effectiveness and safety outcomes associated with switching to biosimilars for stable patients.[82,83] A quasi-experimental study using a pre-post design is a useful approach to compare outcomes for the same patients before and after the introduction of a biosimilar.[84] Since there is frequent under reporting of adverse drug reactions, MUEs may provide valuable information on hypersensitivity, infusion reactions, immunogenicity, cross-immunogenicity, or loss of efficacy by gathering long-term efficacy and safety data using EHRs.

Evidence of achieving target therapeutic outcomes will increase confidence and uptake of biosimilars.[85] Furthermore, monitoring trends of utilization of other biologics used for the treatment of the same indications as the biosimilar may identify potential shifts in the prescribing patterns among physicians who question the effectiveness of biosimilars, which may increase expenditures and off-set the cost savings gained by biosimilars. We have two real world evidence studies under progress in cancer patients at our organization.

Therapeutic Drug Monitoring (TDM). TDM can facilitate individualization of therapy, provide objective tools to optimize therapeutic outcomes, and explain causes for loss of efficacy (low serum concentration of the drug or the presence of ADA) whenever there is an available bioanalytical assay for the product.[38,86] TDM for anti-tumor necrotizing factor has been utilized to optimize therapeutic outcomes in patients with inflammatory bowel diseases in general, and in the era of biosimilars.[87] For example, it presented opportunities to use a patient-centered approach to assess efficacy, intensify dosing, and change to another class based on the clinical response or low serum drug levels, or by detecting titers of ADA when patients with Crohn's diseases were newly started or switched to biosimilars.[86,88]

Conclusions

As the biosimilar market grows, healthcare organizations are facing challenges in the selection among various biosimilars and should carefully design a thorough, systematic evaluation to address the multi-dimensional aspects associated with selection of biosimilars for formulary addition. The evaluation should address the transition phase and design tools to empower patients, physicians, and other healthcare professionals to enhance uptake of biosimilars and design plans to monitor the efficacy and safety of biosimilars.

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