Optimizing Use and Addressing Challenges to Uptake of Biosimilars

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ABSTRACT

With the passing and implementation of the Biologics Price Competition and Innovation Act in 2010, biosimilars became a new classification of FDA-approved drugs. The biosimilar classification, created with a streamlined drug approval process, was intended to spur competition and reduce the cost of biological product therapies. Since the first FDA-approved biosimilar in 2015, the impact of biosimilars on the US biological product market remains to be seen. As more biosimilar products are approved and marketed, cost-savings are expected with predictions ranging from $54 billion to $250 billion by the mid-2020s. However, a multitude of factors may diminish the cost-saving potential of biosimilars. For biosimilars to gain market share, patients, physicians, and other healthcare professionals will need to accept biosimilars as safe and effective alternatives to reference-biologic products. A key factor in gaining this acceptance is educating the public, physicians, and healthcare professionals on the rigorous approval standards required of biosimilars by the FDA. Other factors that will affect market share of biosimilars include litigation actions by biopharmaceutical manufacturers; positions stated by physician organizations; and the influences of insurers and managed care. The clinical and basic science required for biosimilar approvals will be major underlying elements driving biosimilar acceptance and increased market presence.

Impact of Biosimilars on Market and Costs

The availability of biologic medications has significantly improved patient outcomes for many different disease states. Biologics continue to be an essential component of new drug development and there continues to be expansion into new areas of treatment. The most recent estimated cost for developing a novel medication is $2.6 million. Biologic drugs are typically associated with a significantly higher research and development expense due to the...
cost associated with acquiring the expertise and establishing the technology to support the manufacturing. Because biologics often have very specific indications, there is a smaller target patient population, which often results in high medication costs. The burden that high drug costs are putting on the healthcare system are often excessive and will be unsustainable.

As described in part 1 of this supplement, the Biologics Price Competition and Innovation Act (BPCIA) included a provision to create a streamlined approval process for biosimilars, which are biological products that are similar to a reference product (the originally approved biological product). Under the 351(k) pathway, the biosimilar drug needs to demonstrate that the proposed biosimilar product is biosimilar to the reference product. This includes comparative data with the reference product, as well as publicly available information regarding the FDA’s previous determination that the reference product is safe, pure, and potent. The biosimilar product application also requires 1 clinical trial.9,10 Two goals of the 351(k) application pathway were to increase competition in the biologic product marketplace and to reduce the costs of biological products. With just 3 years of biosimilar experience in the United States, there are limited direct data on cost reductions. In an analysis of costs borne by patients, Yazdany and colleagues determined that Medicare Part D beneficiaries could end up with higher annual out-of-pocket costs for a biosimilar of infliximab, compared with the reference product (estimated increase of $1686).11 A major reason for the additional projected patient costs was the manufacturer discount that Medicare Part D beneficiaries receive for brand-name drugs and biologics.6 Regarding Medicare Part B pricing, CMS instituted a change in its biosimilar reimbursement policy by issuing unique Healthcare Common Procedure Coding System (HCPCS) codes to each biosimilar product, which became effective in January 2018.12 This change in coding policy is a reversal of the prior CMS policy, whereby all biosimilar products of a reference product were assigned the same HCPCS code; the change may help to create a more competitive biosimilars market.13 Medicare B reimbursement rates for biosimilars are based on the average sales price (ASP) of the originator minus 22.5%; the exception is for biosimilars that qualify for pass-through status, and these are reimbursed at the biosimilar ASP plus 6% of the originator ASP.14 Although reimbursements are higher for pass-through biosimilars, a patient’s co-insurance is not based on the higher reimbursement rate. A summary analysis, however, highlighted substantial ambiguity with respect to the impact of biosimilars on drug spending due in part to the uncertainties of biosimilar market uptake and biosimilar cost savings.15 The example of granulocyte-colony stimulating factor biosimilars in the United Kingdom may provide an encouraging sign regarding market uptake, as the daily dosed biosimilar eventually surpassed the originator in terms of market share.

Predictions on the impact of biosimilars on costs can range widely based on modeling parameters, assumptions, and perspectives. In a forecast on spending, a major pharmacy benefit management company predicted that the United States would save $250 billion over a decade-long period between 2014 and 2024.16 On the lower end of cost-savings predictions, Mulcahy et al estimate savings of $54 billion by the year 2026 (range, $24 billion-$150 billion).17 Other analysts predict substantial variability in the impact of biosimilars on prescription drug spending as each biosimilar would have unique circumstances affecting its market penetration.18 Furthermore, in early 2018, FDA Commissioner Scott Gottlieb, MD, gave a speech at America’s Health Insurance Plans’ National Health Policy Conference in which he described “the weakening of market incentives” that could affect the biosimilar pipeline. Gottlieb also described the negative impact of rebate and contracting practices on competition.19 Competition for market share, however, does not rest solely between reference-biological products and biosimilars. As reference-biological products near the end of their patent life, biopharmaceutical companies may develop updated biologics through newer manufacturing processes, formulations, indications, and/or delivery technologies to maintain and expand market presence. Examples of these approaches include an on-body injector delivery system kit for pegfilgrastim19 and a new formulation of rituximab for subcutaneous injection.20

**Barriers to Acceptance of Biosimilar Products**

**Physician–Provider Acceptance**

A key component to acceptance of biosimilars is the confidence of physicians. Providers are struggling with the lack of indication-specific clinical data and are hesitant to accept extrapolation of data to support multiple indications.21,22 Physicians can influence the acceptance of biosimilars through the many roles they serve in the healthcare system. With direct patient contact as prescribers and clinicians, physicians serve as a key entry point and an information resource for patients using biologics and, potentially, biosimilars. Through their many other functions (eg, key opinion leaders, members of a pharmacy and therapeutics [P&T] committee, or managed care formulary), physicians can play active roles in the use of biosimilars. To make progress in biosimilars, it is necessary to look back at experiences with generic medications. The driving force for adoption of generics, similar to biosimilars, is cost. Widespread adoption of generics was successful through various formulary management strategies and incentives, such as tiering and co-payment programs. Europe offers lessons, where additional approaches to increase prescribing of biosimilars included implementing quotas for physicians.23 Based on their numerous and prominent influence points, physicians may be considered the key demographic for biosimilar acceptance.

Various physician societies have presented perspectives on biosimilars through position papers and policy statements. These publications provide insight into the collective perspectives of different physician groups, and, although they may reflect the
majority opinion in the respective organization, they would not represent a unanimous opinion. Many of the position papers and policy statements also address the issue of interchangeability, a special designation of biosimilars whereby, per the BPCIA, an interchangeable product can be substituted for a biological product by a pharmacist. To date, no application for the interchangeable designation has been received by the FDA. Of interest are the opinions of physician organizations that represent specialty practices with substantial use of biologics. Naturally, physicians with such specialties will have heightened interest in the issues surrounding biologics and biosimilars. Rheumatology and oncology are 2 of the specialty practice areas. The American College of Rheumatology (ACR) issued a position statement on biosimilars and health policy statements that discuss biosimilars. Those statements emphasize the need for a strong scientific basis regarding the use of biosimilars and the need for prescriber approval of substitution. In addition, the ACR published a perspective in early 2018 that a future change in the associations’ cautious positions on biosimilars is forthcoming based on the biosimilar experience in Europe. Many current and pending biologics have indications in oncology. The American Society of Clinical Oncology (ASCO) published its position statement on biosimilars in February 2018 focusing on 5 areas: (1) naming, labeling, and other regulatory considerations; (2) safety and efficacy of biosimilars; (3) interchangeability, switching, and substitution; (4) value of biosimilars; and (5) prescriber and patient education. As with the ACR statements, ASCO emphasized a strong reliance on sound science to guide regulations and government policies. On the topic of substitution and interchangeability, instead of citing a need for prescriber approval of substitution as did ACR, ASCO stated that “physicians and patients should be aware of potential product substitutions” in the interest of informed treatment decision making.

Other groups have formed specifically to address physicians’ perspectives on biosimilars. The National Physicians Biologics Working Group (NPBWG), formed in 2011 as part of the Alliance for Patient Access (AfPA), is such a group that provides a forum for physicians who have interests in biologics, particularly with respect to issues of patient access. The NPBWG and AfPA have written several white papers and policy briefs that address public policy issues on biologics and biosimilars. The FDA has recognized the importance of educating physicians about biosimilars and has created resources for physicians and other clinicians that describe numerous aspects about biosimilars and the approval process.

Barriers to Market Access

Litigation

Legal wrangling, which is generally focused on patent infringement among biopharmaceutical companies, can delay the development and marketing of biosimilars. One aspect of the legal maneuvering is the “patent dance,” which colloquially describes a provision in the BPCIA that requires the manufacturer of reference-biological products to share patent-related information with biosimilar manufacturers. Reluctance to fully comply with this provision may contribute to slow biosimilar development. Some biopharmaceutical manufacturers, or their subsidiaries, produce both reference-biological products, as well as biosimilars for competitive practices to prevent insurers from covering biosimilars of infliximab. If there continues to be significant financial barriers to access biosimilars, patients will not be able to begin therapy or will be forced to discontinue chronic therapy, ultimately resulting in higher healthcare costs due to adverse outcomes.

Manufacturing and Interchangeability

Although an interchangeable biological product has yet to be approved by the FDA, the lack of clarity surrounding the requirements for interchangeability may also be stifling development of interchangeable products and, possibly, biosimilars. Positions expressed by various physician organizations, such as the ACR, highlight the concerns that prescribers have, particularly surrounding the specific wording in the BPCIA. The FDA’s drafted guidance on interchangeability stimulated discussion but may have also created confusion. Because regulations regarding substitution lie with each state, the United States could have a myriad of different rules and regulations governing biologic substitution, similar to individual state professional licensing regulations.

The complexities of biological products and their manufacturing processes can result in slight changes to the reference product between different batches. Some scholars have highlighted these variations to promote the acceptance of biosimilars by asserting that the differences would classify a different batch as a biosimilar. A real-world example occurred when Genzyme expanded production of its alglucosidase alfa product in a new plant. The FDA ruled that the revamped process created a new biologic sufficiently different from the reference product. Genzyme applied for approval as a new biologic—reference product and gained additional exclusivity time. Schneider highlighted the number of process changes of rheumatology biologics in Europe, which ranged from 2 process changes for golimumab to 36 process changes for infliximab. Alternate views on this concept may contribute to confusion surrounding biosimilars. Hassett et al presented a case study on etanercept, finding that manufacturing changes do not result in de facto biosimilars for the reference-biological product. On the other hand, as Ramanan...
and Grampp pointed out, known and unknown alterations in the manufacturing process can create downstream changes in the reference-biological product. When coupled with analogous changes in biosimilars, the “drift” and “evolution” of the reference product and biosimilar could theoretically result in nonsimilar products.47

**Optimizing Biosimilar Uptake**

**Education, the Key Driver of Biosimilar Acceptance**

Although physicians are a major factor in the uptake and acceptance of biosimilars, surveys have highlighted the need for physician education, even among specialty physicians. Cohen et al reported results from a survey conducted by the Biosimilars Forum with participants from specialties that prescribe biologics. One of the more striking results from the survey is that 20.5% of the responders incorrectly indicated that a pharmacist could substitute a biosimilar for a reference-biological product without prescriber permission.22

Additionally, the survey results suggest that sizable percentages of the physician responders were not up-to-date on the biosimilar approval process, as 43.8% were not aware that biosimilars must be comparable in safety and efficacy to the originator biologic; 35.9% expressed a belief that biosimilars will be less safe than the originator biologic; and 38.9% expressed interest in learning more about the FDA approval process for biosimilars.22 The survey results, along with the perspective of European clinicians and regulators46 who have more extensive experience with biosimilars, emphasize the need for additional physician education on the specifics of biosimilar approvals. Patient understanding of biosimilars is lacking, as described in a survey of patients in the European Union and the United States. Just 6% of the general patient population surveyed were aware of biosimilars, and just 20% to 30% of patients in advocacy groups had similar awareness.49 It will be necessary to address the knowledge gaps with physicians from all practice areas to facilitate biosimilar acceptance and uptake, as well as patient education. As the use of biosimilars increases, the familiarity with biosimilar agents will help mitigate preexisting concerns.

**Managed Care Aspects**

Healthcare professionals in managed care may need to use a variety of tools to aid in the acceptance and uptake of biosimilars. Reducing costs will clearly play a role; however, physicians, other healthcare providers, and patients will need confidence in the safety and efficacy of biosimilars.50 51 Confidence will grow through education. Managed care professionals will also likely use formulary tools and fee schedules to affect biosimilar uptake where reduced costs are expected.52 As highlighted previously, lower patient costs are not assured based on the use of biosimilars.11 Although costs will be a major driver, healthcare professionals on P&T committees have other factors to evaluate when reviewing biosimilars for formulary inclusion, such as clinical, product, and institutional considerations.53

Managed care professionals will also have to navigate government policy changes that impact biologics and biosimilars. There is the potential to shift site of care under the Trump administration’s blueprint regarding Part A and Part B drug benefits. The blueprint examines the impact of certain drug classes if they were shifted from Part B benefits to Part D. These changes to reimbursement models and shifts in site of care directly impact the way that hospitals and health systems provide care to patients.53 54 Payers have begun to implement policies that require proof of medical necessity before providing infusion medication therapy in the outpatient or physician-based settings. Inpatient administration and reimbursement are based on the diagnosis-related group (DRG) and oftentimes the inpatient administration of these agents exceeds the DRG payment. Therapy is now required to be given at alternative sites, such as physician offices or ambulatory infusion centers.55 The complexity of the healthcare and biopharmaceutical landscapes provide both challenges and opportunities for biosimilars.

**Conclusions**

With the era of biologics and biosimilars maturing, biopharmaceutical companies are honing their business, research, and legal strategies to gain and maintain market share for their products. To have a chance to provide cost benefits to patients, providers, and payers, biosimilars will need to be commonly accepted by physicians, patients, and other healthcare professionals. Gaining acceptance will require confidence in the regulatory approval process to ensure safety and efficacy; adequate education of physicians, nurses, pharmacists, and patients; and real cost-savings to warrant the use of biosimilars. Solid basic and clinical science will serve as the backbone of biosimilar acceptance. On the other hand, an inability to gain biosimilar acceptance will result in pharmaceutical companies leaving the space, as well as lack of competition and potential cost-savings to overall healthcare.

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