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LEADING ARTICLE

Biosimilars in the USA: Will New Efforts to Spur Approvals and Access Spur Uptake and Cost Savings?

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Abstract
Unlike in Europe, US healthcare systems and payers are still awaiting significant savings related to biosimilar utilization. Costs related to biologic use continue to rise at double-digit rates, and biosimilars are seen as a major tool to control costs and increase access to biologic drugs. However, one 2018 report indicated that US$3.2 billion (only 3%) of biologic spending is subject to competition from biosimilar products. Although the European Medicines Agency did a great deal of pioneering work in biosimilar regulation, the US Food and Drug Administration is moving at approximately the same pace as the European Medicines Agency, based on the number of approvals at the same time after implementation of its regulatory pathway. Several unique factors in the USA have conspired to limit biosimilar access (e.g. delayed regulatory policies, extended patent litigation activities, federal reimbursement policies, the widespread use of rebate contracting, and limited competition). The US Federal Government is taking the initiative in an attempt to address these factors, and speed both biosimilar development and patient access. To date, the most significant cost savings in the US system associated with the introduction of biosimilars may be their ability to halt price increases of the reference product. The complexity of the healthcare delivery system, and how it is financed, will remain challenging to payers, manufacturers, health providers and patients as they seek ways to manage health expenditure growth.

Key Points

In the USA, biosimilars uptake has been stalled because of several factors unique to this marketplace.

At the federal level, action is being taken to improve access to biosimilars in the short term.

Yet some cost savings are being accrued today in the USA, despite the relatively delayed uptake of biosimilars.

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1 Introduction

The potential for cost savings associated with biosimilars around the globe is considerable. In the European Union, several reports have documented reductions in expenditures in biologic spending [1–5]. In the USA, healthcare systems and payers are still anticipating savings related to biosimilar utilization [6], but these have not yet materialized to a significant extent. Costs related to biologic use continue to rise at double-digit rates. Drug spending increased more than 15% in 2017 for US commercial payers and Medicare for the inflammatory disease category, and over 17% for US commercial payers and 12% for Medicare for the oncology drug class [7], both of which are dominated by biologic utilization. In addition, the majority of investigational new drugs in the pharmaceutical pipeline are biologic agents [8]. Together, these facts raise considerable concern for affordability and access to innovative drug therapy.

Biosimilars are seen as major tools to control costs and increase access to biologic drugs. However, one 2018 report indicated that US$3.2 billion (only 3%) of biologic spending is subject to competition from biosimilar products [9]. This figure is creeping upward, but this pace of change may not

satisfy payers and purchasers. For example, with each year that a biosimilar is not marketed for adalimumab, not only is the opportunity for savings lost, but it affords the opportunity for price increases by the reference manufacturer, resulting in greater expenditures for this biologic, year after year [10].

The European Medicines Agency (EMA) had pioneered the regulatory pathway and market development for biosimilars. Since approval of the first biosimilar (the growth hormone somatropin) in 2006, 53 biosimilars have been authorized by the EMA for 15 different reference products (as of early December 2018) [11]. As part of the Patient Protection and Affordable Care Act in 2010 [12], the US Biologics Price Competition and Innovation Act (BPCIA) mandated the creation of biosimilar approval regulations in the USA, with the first biosimilar being approved through this pathway in 2015 [13]. In contrast, since its first product review in 2014, the US Food and Drug Administration (FDA) has approved 15 biosimilars for 9 reference products (insulin glargine is not considered a biosimilar in the USA) (Table 1) [13]. The US FDA has not necessarily been approving biosimilars at a slower pace than in the EU. During the first 4 years after their respective pathways were introduced, the number of biosimilar approvals by the EMA and FDA were essentially the same. However, as of December 5, 2018, just five biosimilars (for 4 reference products) in the USA are available for prescription by physicians (Table 1).

All four manufacturers of pegfilgrastim biosimilars (approved in the USA or filed with the FDA) have received at least one "complete response letter" (i.e. rejection) from the FDA. In some cases, additional data analyses have been required (Coherus), but in others manufacturing plant issues have been cited (Pfizer, Mylan). Although the EMA authorized Hospira's application for epoetin alfa in 2007, the FDA did not approve Pfizer's version (Pfizer purchased Hospira in 2015 [14]) until May 2018—nearly 3.5 years after receiving its application [13]. Sandoz had received approval from the EMA for its rituximab biosimilar, but the FDA had rejected it. As a result of a request by the FDA for more clinical information, Sandoz has decided to no longer seek US approval for this agent [15].

A previous report by the authors [6] detailed the factors that play a role in the economics of biosimilars in the USA. The reasons behind this limited access and uptake are related to several differences in the drug regulatory systems, legislated drug approval pathways, and intellectual property protection between the US and EU markets. Indeed, the way in which pharmaceuticals are purchased through third-party payers has played a highly publicized role. Alarmed at rising pharmaceutical costs, the US Federal Government has newly engaged efforts to encourage the faster approval and uptake of biosimilars [16]. This paper outlines new factors that are shaping the evolving biosimilar market in the USA.

2 Comparisons Between the American and European Markets

2.1 Experience on Clinical Use and Outcomes

With biosimilars in use since 2006, the EU has accumulated extensive experience on their clinical outcomes and safety compared with their reference counterparts [1, 4, 5,

Table 1 US Food and Drug Administration (FDA) biosimilar approvals

Biosimilar	Manufacturer	Brand name (nonproprietary name)	Reference product	Approval date
Filgrastim	Sandoz	Zarxio® (filgrastim-sndz)	Neupogen®	March 6, 2015[a]
	Pfizer	Nivestym™ (filgrastim-aafi)		July 20, 2018[a]
Infliximab	Celltrion/Pfizer	Inflectra® (infliximab-dyyb)	Remicade®	April 5, 2016[a]
	Samsung Bioepis/Merck	Renflexis® (infliximab-abda)		April 21, 2017[a]
	Pfizer	Ixifi™ (infliximab-qbtx)		December 14, 2018[b]
Etanercept	Sandoz	Erelzi™ (etanercept-szzs)	Enbrel®	August 31, 2016
Adalimumab	Amgen	Amjevita® (adalimumab-atto)	Humira®	September 23, 2016
	Boehringer Ingelheim	Cyltezo™ (adalimumab-adbm)		August 29, 2017
	Sandoz	Hyrimoz™ (adalimumab-adaz)		October 31, 2018
Bevacizumab	Allergan/Amgen	Mvasi™ (bevacizumab-awwb)	Avastin®	September 14, 2017
Trastuzumab	Biocon/Mylan	Ogivri™ (trastuzumab-dkst)	Herceptin®	December 3, 2017
Epoetin	Pfizer	Retacrit® (epoetin-epbx)	Epogen®	May 15, 2018
Pegfilgrastim	Biocon/Mylan	Fulphila™ (pegfilgrastim-jmdb)	Neulasta®	June 4, 2018[a]
	Coherus	Udenyca™ (pegfilgrastim-cbqv)		November 2, 2018
Rituximab	Celltrion/Teva	Truxima™ (rituximab-abbs)	Rituxan®	November 28, 2018

[a]Marketed and available for prescription

[b]Approved but will not be launched in the USA. Adapted from US Biosimilar approval status. Biosimilars Reviews and Reports. https://biosimilarsrr.com/us-biosimilar-filings/. Accessed December 5, 2018

17, 18]. Just three years of data on the real-world use of biosimilars in the USA has accumulated (principally with filgrastim-sndz).

In the USA, the uptake of biosimilar filgrastim, approved in 2015, is approximately 35% [19]; another filgrastim brand (tbo-filgrastim) was introduced before the BPCIA approval pathway was implemented, and this agent had already eroded some of the utilization of the reference product (Neupogen®). In comparison, biosimilar versions of infliximab, the first being approved in 2016, have seen little uptake (less than 6%) [17]. Pfizer, the marketer of infliximab-dyyb [20, 21], and two national pharmacies [22] contend that anticompetitive activities by the reference manufacturer (Janssen Pharmaceuticals) is a major reason for the insignificant biosimilar utilization.

2.2 Experience on Cost Savings

The actual cost savings associated with biosimilars in the EU varies with market penetration, which can vary substantially among member countries [23, 24]. For example, Norway has relatively high utilization of biosimilars and receives greater discounts than most other EU members. In the UK, on the other hand, adoption has been relatively slow [25]. In 2015, a report from IMS Health reported that price decreases in the filgrastim category was only 8% from the UK (Table 2) [26]. The European prices and discounts cited in Table 2 are list prices only and do not consider discounts or clawback mechanisms granted to public or private drug purchasers. In many cases, the net discounts will be far greater than shown.

The discounts each country sees are largely related to its tendering or bidding system for pharmaceutical purchasing [27]. Healthcare financing of several countries is based on a single-payer model, which assists in maximizing the leverage it can use in the purchasing process.

The UK's guidance [28] states a potential to realize savings of at least £200 million per year by 2020/21 if the National Health Service (NHS) embraces the use of best value biological medicines in a proactive, systematic, and safe way. The UK goal is for at least 90% of new patients to be prescribed the best value biological medicine within 3 months of launch of a biosimilar medicine, and at least 80% of existing patients within 12 months.

In the USA, manufacturers must negotiate with numerous government and commercial payers for reimbursement of their products. This yields myriad contracts, commonly resulting in different final costs for each health plan, medical facility, or pharmacy benefit manager. Typically, these contracts utilize one of two reference prices, the wholesale acquisition cost (WAC), which represents the list price, or the average sales price (ASP), which considers discounts and rebates. These agreements are proprietary and rarely publicized.

Table 2 Price changes following biosimilar introduction in European countries Adapted from: IMS Health. The Impact of Biosimilar Competition 2017 [25]

Country	Epoetin (%)	Filgrastim (%)
Germany	−55	−27
France	−39	−14
Italy	−13	−4
Spain	−24	+1
United Kingdom	−18	−8

2.3 Interchangeability

One major difference between the EMA and FDA biosimilar approval regulations involve the potential in the USA for a biosimilar drug to be deemed "interchangeable" [29] with the reference agent. None of the approved US biosimilar drugs have earned this designation, which is considered essential to optimizing biosimilar use.

When the FDA designates a biosimilar to be interchangeable, it is expected to yield essentially no differences in clinical outcomes compared with the reference product in any given patient. This designation can only be achieved when the manufacturer has submitted adequate "switching" studies, demonstrating that there is no safety risk or reduced efficacy when patients receive the reference drug, the biosimilar, and then back again. Interchangeability would allow pharmacists to automatically substitute a biosimilar for a reference product at the point of service, often without notifying the prescribing physician.

Ninety percent of US states have passed legislation that will allow at least some form of substitution by the pharmacy of an interchangeable biosimilar once one is available [30]. In comparison, the concept of interchangeability does not exist within the approval framework of the EMA as it does in the 351(k) pathway. It leaves the decision as to whether to allow "non-medical switching" (i.e. for economic reasons) in the hands of its members and local providers [31]. As such, prescribing practices and advice to prescribers in the EU fall under the responsibility of member states.

3 Federal Efforts to Address Market Factors Interfering with Biosimilar Uptake

Recognizing the potential role biosimilars can play by injecting competition into several specialty drug categories, the US Federal Government has begun to take a more aggressive stance. In May 2018, FDA

Commissioner Scott Gottlieb and Secretary of Health and Human Services Alex Azar announced plans to address several barriers to biosimilar market entry. In July 2018, Dr. Gottlieb unveiled the FDA's "Biosimilar Action Plan" [16], which outlined 11 steps to improve the efficiency of the clinical review process; add clarity to the regulations and scientific expectations surrounding the biosimilar development process; assist educational efforts aimed at patients, providers, and payers; and reduce the ability of reference drug manufacturers to delay biosimilar development, and thus marketing, access, and competition.

In addition, Secretary Azar released a proposed rule titled "Removal of Safe Harbor Protection for Rebates to Plans or [Pharmacy Benefit Managers] PBMs Involving Prescription Pharmaceuticals and Creation of New Safe Harbor Protection" [32]. This follows statements by Gottlieb and Azar on the need to address the heart of the matter: redefining pharmaceutical rebating practices as anti-competitive. Previously, Gottlieb had stated that payers will need to wean themselves from their reliance on drug rebate revenue if they wished the biosimilar drug industry to be viable over the long term [33].

A recent Centers for Medicare and Medicaid Services (CMS) policy change addresses the way in which biosimilars are reimbursed, specifically in the government program that provides health benefits for the elderly (Medicare). Biosimilars had been disadvantaged once a Medicare beneficiary entered the "coverage gap", in which they are responsible for a greater share of the costs. Under the Affordable Care Act, biosimilars were treated in the same manner as generics (instead of biologics) in terms of cost sharing [12]. Policy changes made in 2018 (effective in 2019) resulted in a reclassification, allowing biosimilars to be treated as biologics within the Medicare coverage gap [34], and thus removing the disincentive to use them (until the coverage gap is phased out in 2020). Without this policy change, clinicians might decide to maintain patients on the reference medication, resulting in lower overall out-of-pocket costs and less administrative work for themselves.

Finally, policy changes were also made recently to coding used for Medicare reimbursement that differentiated reference and biosimilar products as part of Part B (office- or hospital-infused agents). Assuming that the ASP for the biosimilar was less than the ASP for the originator biologic, the provider infusing either would be paid an additional 6%, based on the ASP. The new policy now mandates that the ASP would be calculated as a group, so that biosimilars are not disadvantaged by lower reimbursements to providers [35].

4 Updates on Factors Influencing Biosimilar Uptake in the USA

4.1 Extrapolation

One of the critical factors in optimizing uptake of biosimilars involves their use in extrapolated indications. Extrapolation refers to the extension of regulatory agency approval of the biosimilar to indications for which clinical studies were not performed. In the USA, it is typical for the FDA to approve biosimilars for multiple indications based on the physiochemical and pharmacokinetic similarities as well as its performance in clinical trials involving one or two specific indications (i.e. called the "totality of evidence" approach) [36]. For example, the clinical program for an adalimumab biosimilar might study its use in rheumatoid arthritis, one of about a dozen current indications for the reference product. The FDA approvals for the adalimumab biosimilars approved in the USA extend to several autoimmune indications. Similar to any approved product, physicians may prescribe the adalimumab biosimilar for other indications for which the reference drug may be used. Additionally, depending upon economics and rebate structure, health plans may elect to allow biosimilar use across all indications of the reference product. Indeed, a survey of US payers revealed that more than half expect to reimburse biosimilar prescriptions across the spectrum of reference product indications [37]. This can have implications for upcoming biosimilar scenarios. In fact, in the case of the last approved US biosimilar (Celltrion's version of ritixumab), the manufacturer did not request approval for the reference product's immunologic indications (e.g. rheumatoid arthritis). It sought and obtained approval for Rituxan®/MabThera®'s oncology indications [i.e. non-Hodgkin's lymphoma (follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia)]. Based on the research by Brook and colleagues [37], payers may well reimburse for what could be non-approved uses in the USA.

4.2 Switching and Interchangeability

Single-switch studies are commonly performed by prospective biosimilar manufacturers [38–40]. Although the FDA has not approved any existing biosimilar as interchangeable to the corresponding reference drug, the agency can provide that designation following the completion of necessary multiple switching studies. The NOR-SWITCH study demonstrated that changing therapy between Remicade® and infliximab-dyyb [40] in patients with different disease states did not result in negative outcomes and has been published in peer-reviewed literature. These results have important

implications for interchangeability between biosimilar infliximab and the reference product.

It is not yet known when the first biosimilar will receive the interchangeability designation, although Boehringer Ingelheim is actively involved in such studies for its biosimilar version of adalimumab [41]. It could be a significant competitive advantage upon product launch; the lack of interchangeability among presently approved biosimilars limits payers' ability to shift away from the reference biologics. Thus, the use of approved biosimilars in long-term therapy is mostly limited to drug-naïve patients, unless a patient or physician specifically desires the biosimilar.

Most savings estimates do not fully account for a lack of drug interchangeability or when interchangeability may be a reality [6, 42, 43]. The full economic benefit of biosimilars cannot be realized without interchangeability or widespread switching.

To date, US payers have not yet applied many potential incentives to their policies that may incentivize provider adoption of biosimilars. One example is by reducing some of the administrative burden for the practices, such as prior authorization or precertification, while maintaining these requirements for reference products [44]. Another example is to widely employ biosimilar tiers with reduced cost sharing relative to the reference biologic. This could prompt patients seeking lower out-of-pocket costs to try the biosimilar agent.

4.3 Physician Comfort Level with Prescribing Biosimilars

An important barrier to gaining uptake of biosimilars could be physician concern over the formation of antidrug antibodies and their unproven use for extrapolated indications [42]. Danese and colleagues [45] found that physician comfort levels in Europe increased substantially after real-world practice experience was gained. A 2013 survey (before the launch of Europe's first infliximab biosimilar) found that only 13% of gastroenterologists were confident in biosimilar safety and effectiveness; this figure rose to 47% after just 2 years of experience [45]. At this time, it is unknown whether biosimilars for trastuzumab or bevacizumab for oncology treatment may encounter greater resistance from the physician community.

There have been various US reports of prescriber and patient concerns about biosimilars [46, 47]. Health plans realize the importance of education if they are to maximize uptake of these agents in the future. A survey revealed that health plans and insurers will target not only prescribers, but also patients with different educational modalities (Fig. 1) [37].

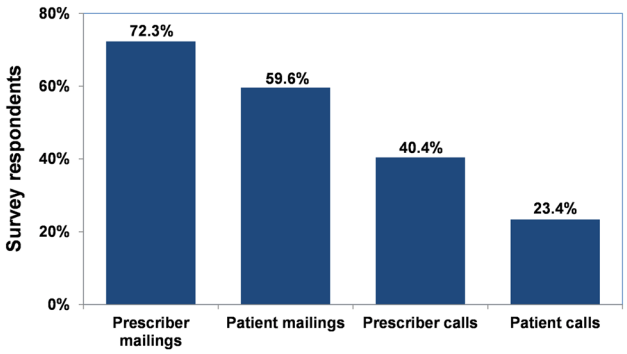

Fig. 1 Health plans and insurers' preferred modes in disseminating biosimilar education to prescribers and patients. Source: Brook 2018 [37]

4.4 Savings in the USA: Real and Anticipated

With the delayed access to biosimilars in the USA, health plans and insurers have been less sanguine regarding the savings they expect to see. A survey of US payers [37] demonstrates that expectations of savings of greater than 20% cannot accrue until after 2023, when the adalimumab biosimilars will be first available for prescription.

By mid-2018, limited experience had been compiled in the USA to reliably assess the way in which biosimilars actually affect the rising biologic spend. There is evidence that the use of filgrastim-sndz has resulted in savings to a payer or individual health system. Grewal and co-workers [48] used a financial model to estimate a 5-year cost savings from filgrastim [granulocyte-colony stimulating factor (GCSF)] of $256 million, of which 18% (US$47 million) are from reduced patient out-of-pocket costs, 34% (US$86 million) are savings to commercial payers, and 48% (US$123 million) are savings for Medicare. These estimates were based on publicly available data on disease incidence, treatment patterns, market share, and drug prices and incorporated regulatory policies, provider and patient perception, pricing, and payer policies.

Furthermore, the authors' analysis of Medicare ASP payments from July 2015 to January 2019 (unpublished data, from https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles.html) found that the availability of infliximab biosimilars has resulted in lower net costs of the reference product to health plans and insurers by 11% from a peak of US$85.81 per 10 mg in January 2018 to US$76.65 per 10 mg in January 2019 (a 68-kg patient will require > 200 mg/dose). Without biosimilar competition, Abbvie has been free to implement annual price increases, and the first adalimumab biosimilar may not be marketed in the USA until 2023. This could mean that the reference product Humira will cost 54% (assuming a 10% annual price

increase) more in 2023 than in 2018. A biosimilar made available today could nullify this cost escalation [10].

In the past few years, a few payers and PBMs (e.g. CVS Caremark [49], UnitedHealthcare [50], and Veterans Affairs [51]) have excluded reference products from coverage, except for patients currently receiving the agent. Instead, they substituted a biosimilar (filgrastim-sndz) and follow-on biologic insulin glargine (Basaglar®) for the reference brands. Although the agreements are considered proprietary, it can be assumed that significant savings were obtained in exchange for these replacements. The extent to which formulary replacements increase the utilization of biosimilars is not yet clear.

4.5 Reference Drug Makers' Attempts to Fend Off Biosimilar Competition

In a previous article by the authors [6],[1] the fictional example was given where reference biologic manufacturers will be reluctant to cede their market to biosimilar manufacturers, particularly when they can still hold on to multibillion annual revenue. To forestall this loss of market share, reference drug manufacturers can simply increase their rebates or lower WAC price to approach the initial WAC discount to entice plans and pharmacy benefit managers not to accept biosimilars onto their formularies.

Aggressive patent litigation strategies have been well documented and result in a complicated "patent maze" or "patent thicket" for prospective competition, delaying biosimilar market entrants. Although the primary patent may have expired, other patents may extend exclusivity for years [52]. Abbvie's defense of adalimumab is only one example. It has now signed patent settlements that include royalties paid back to the reference manufacturer, which prevent several manufacturers from marketing their biosimilars before 2023 [53]. Although this avoids further legal costs for the biosimilar manufacturers, the royalty costs are likely to be passed on to the drug purchasers. As a result of the patent litigation, biosimilar makers seem to be waiting on the sidelines for either patent expirations or settlements with the reference manufacturers.

Amgen, in its role as reference drug manufacturer, has exemplified another possible approach. In its defense of its pegfilgrastim market share, it has separate patents for the Neulasta® Onpro® patch, which provides patient benefits over the injectable form of the originator drug Neulasta®. Although biosimilar competition for the injectable formulation of pegfilgrastim is beginning to rise in the USA, Amgen reported in an earnings conference call this year [54] that it has succeeded in moving at least 60% of its pegfilgrastim use to the patch form. This would leave the biosimilar competitors a far narrower slice of the estimated $4 billion US annual revenue for the pegfilgrastim market.

5 Concluding Thoughts

Despite the success in introducing biosimilars into the EU marketplace, the USA risks missing opportunities to save significant dollars on high-cost biologic products. With the biosimilar market potential for products like adalimumab, infliximab, pegfilgrastim, and other agents with multibillion-dollar sales revenue, the US government needs to identify and implement innovative avenues for increasing access to biosimilar drugs.

Unlike several European countries, the US market comprises multiple payers with regulations that vary by state, for both commercial and government programs. Recent changes to CMS reimbursement policies may reduce government expenditures; however, the US commercial market is still driven by confidential rebates providing reference manufacturers, and PBMs, means to maintain profitability and stifle competition. Should rebate (and PBM) transparency occur, the market will be more likely to benefit from biosimilar competition.

In the near term, switching by US payers or the designation of an interchangeable product may not have a significant effect on biosimilar uptake and prescription in the near future. However, acceptance of extrapolation by providers and the comfort levels of physicians with their use do not seem to be the challenging barriers they appeared to be a few years ago.

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Compliance with Ethical Standards

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