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EDITORIAL

Factors influencing the economics of biosimilars in the US

Introduction

In 2010, the Biologics Price Competition and Innovation Act (BPCIA) was passed as part of the Patient Protection and Affordable Care Act[1]. As part of the BPCIA, the Food and Drug Administration (FDA) was directed to develop a section 351(k) approval pathway for biologic biosimilar drugs to speed their development and approval in the US, as part of a wide recognition that biologic drug spending was rising; the dominance of biologic agents in the pharmaceutical pipeline signaled not only a tide of innovation, but also higher costs[2].

Biosimilars are reverse-engineered, inexact copies of highly complex biologic molecules. A biosimilar is developed to have a chemical structure and pharmacologic and pharmacodynamics properties that do not vary significantly from the biologic reference or originator product. The medication must also demonstrate in clinical trials to not yield any clinically meaningful differences in safety and effectiveness (in at least one indication) compared with the reference product[3].

Since 2006, European countries have approved 36 biosimilars[4]. Whereas marketing approval and pricing varies by country[5], significant cost savings have been realized[6–8]. In the US, only three biosimilars have been launched: infliximab-dyyb in September 2015[9], infliximab-abda in July 2017[10], and filgrastim-sndz in December 2016[11]. Additionally, adalimumab-atto and etanercept-szzs are FDA approved[12], but not yet marketed as of early August 2017. Differences in how the drugs are regulated/approved, purchased, priced, and distributed makes it difficult to extrapolate Europe's experience to the US. In Europe, biosimilar marketshares and pricing discounts have varied by country[13,14]. At this time, too little experience is available to assess how biosimilars actually affect the rising biologic spend in the US.

However, the potential for biosimilar cost savings is undeniable and highly anticipated. In 2014, the RAND Corporation predicted a cumulative saving as a result of biosimilars of $44.2 billion over 10-years ending 2024[15]. Express Scripts, the US's largest pharmaceutical benefit manager (PBM), prior to any US-biosimilar approvals, estimated savings by 2024 of $250 billion if 11 biologics were approved[16], and biosimilars for infliximab and filgrastim would account for $22 billion in savings by 2024[17]. In 2016, IMS Health predicted US and European biosimilar savings in eight categories of $110 billion cumulatively by 2020[18]. IMS Health calculated its figures based on a minimum discount of 20%.

Assessing how much biosimilars may actually save in the future is a mix of highly variable pricing assumptions, marketing considerations, payer actions, patent litigation, Medicare reimbursement policy, and the FDA (i.e. interchangeability designations).

Assumed discounts to net price

Net price paid by health plans, insurers, and PBMs is based on manufacturer-negotiated discounts on the wholesale acquisition cost (WAC) and rebates. Rebate contracts are common and shift payers overall concerns to net costs, not WAC pricing.

The WAC discount offered by Pfizer and Sandoz on their respective biosimilars was 15% in both cases[19]. Market research revealed that most payers expected initial pricing discounts for biosimilars of at least 25%; at this level, they would seriously consider preferred formulary positioning[20]. At the actual WAC discounts offered, payers might not want to incur the resources necessary for an organized switch from the reference product to the biosimilar. Stronger downward price pressure is anticipated only when multiple biosimilars become available for the same reference products. With the announcement by Merck in July 2017 that it will begin to market the second infliximab biosimilar (infliximab-abda) at a 35% discount to the reference product[10], infliximab prices may now drop significantly and rapidly.

The rebate trap

In multiple product classes, manufacturers gain preferred positioning in exchange for greater rebates. This may also involve exclusivity arrangements that reduce competition. Placing a biosimilar on a preferred tier may conflict with existing arrangements, where the payer receives a high rebate if their product is only "1 of 2" drugs with preferred formulary positioning. Large health plans may see multimillion-dollar budget reductions if biosimilars are placed in a preferred position, jeopardizing the rebate stream from products with the lion's share of revenue[21]. Hakim and Ross[21] called this "the rebate trap", in which considerable rebates on highly utilized reference agents, like etanercept or adalimumab, may be lost if only a portion of the plan population is switched to the biosimilar. The plan may pay a greater amount as a result, even with significant (but not complete) biosimilar adoption.

Designation as an interchangeable biosimilar would help resolve this situation. In that case, plans can rapidly advance biosimilar marketshare through automatic substitution (where allowed), replacing the lost reference drug rebate revenue with new biosimilar rebate revenue.

Medicare coverage gap and biosimilars

Under the Affordable Care Act, biosimilars used by Medicare beneficiaries are reimbursed in the coverage gap in the same

manner as generics (rather than biologics)[1]. Without legislation to amend this problem, patients will pay more out-of-pocket for the biosimilar than the reference brand until the Part D coverage gap is phased out in 2020[22]. In 2017, biologic manufacturers provide a 50% discount, health plans cover 10%, and patients pay 40%. For biosimilar (and generic) drugs, there is no manufacturer discount. Patients pay 49% of the cost, the health plan covers the remaining 51%.

This may alter the dynamics of biosimilar prescribing for Medicare patients, as those requiring biologic medications will likely reach the coverage gap. Rather than switching patients from a biosimilar to a brand upon reaching this threshold, clinicians may decide on a simpler strategy: to maintain patients on the reference medication, resulting in lower overall out-of-pocket costs and less administrative work for themselves.

Biosimilars are generally covered under Medicare Part B not Part D, because they are office-administered biologics. Medicare Part B payment policy for biosimilars has also been criticized, as current policy dictates that biosimilars for each reference product will get a J-code that is different from the reference product, resulting in different payment rates. Alternative models have been suggested by the Medicare Payment Advisory Commission and others[23,24], which could increase savings.

Incentives to prescribe biosimilars

An important barrier to gaining uptake of biosimilars is physician hesitation to prescribe them for the biosimilars' extrapolated indications[25]. This may be alleviated through experience with prescribing them, according to European surveys[26]. A 2013 survey (prior to launch of Europe's first infliximab biosimilar) revealed that only 13% of gastroenterologists were very or totally confident in biosimilar safety and effectiveness, rising to 47% after 2 years of experience[26].

In the US, payers can incentivize provider adoption of biosimilars by reducing some of the administrative burden for the practices, such as prior authorization or pre-certification, while maintaining these requirements for reference products[25].

Interchangeability designations and utilization of biosimilars

The FDA's January 2017 draft interchangeability guidance[27] requires adequate switching studies (i.e. the reference product to/from the biosimilar). Moots et al.[28] identified more than 50 switching studies worldwide involving biosimilars. The NOR-SWITCH study on the interchangeability of infliximab-dyyb[29] in patients with different disease states has received a great deal of attention and is one of the few studies where the full results have been published in peer-reviewed literature. However, FDA action to enable this agent to be automatically dispensed at the pharmacy, as is routinely done for generics, is purely speculative at this point.

It is not yet known when the first biosimilar will receive this designation. The lack of interchangeability among presently approved biosimilars limits payers' ability to shift away from the reference biologics. The utilization of these biosimilars may be 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[5,17–19]. The full economic benefit of biosimilars cannot be realized without interchangeability or widespread switching.

Reference drug makers' options to forestall loss of market share

It is unlikely reference drug manufacturers will cede their markets to biosimilar makers, as regularly occurs when multiple generic competition is launched. Consider a reference biologic that generates $6 billion in sales in 2017. If biosimilar competition shrinks the total market to $4.5 billion in 2019, the reference drug maker's 30% market share would still account for $1.35 billion in revenues. However, the drug maker will resist the annual loss of $4.65 billion in any case. To block market access and maintain market share, reference drug manufacturers can simply increase their rebates (i.e. the rebate trap) or lower the WAC price to approach the initial WAC discount.

Aggressive patent litigation strategies can create a difficult and time-consuming "patent maze" for prospective competition, delaying biosimilar market entrants. To protect intellectual property, manufacturers often file several product patents, including primary patents on the molecule and manufacturing, and patents on formulations, delivery devices, or even absorption. Although the primary patent may have expired, other patents may extend exclusivity for years[30]. Since the threat of biosimilar competition, Abbvie has filed more than 60 patents in defense of adalimumab, possibly delaying competition until 2022[30]. This patent maze delayed the launch of several approved biosimilars, despite having complied with the 180-day notification period recently struck down by the US Supreme Court[31]. In its decision, the Supreme Court did not rule on the validity of the exchange of patent and manufacturing information, known as "the patent dance", that was detailed in the BPCIA[1].

Drug manufacturers may decide to settle biosimilar patent litigation in exchange for royalties[32], avoiding legal costs and providing biosimilar maker's faster access to revenue. Royalties may also inflate the biosimilar's price. Infliximab-dyyb is the only biosimilar launched before the settlement of patent litigation, leaving Pfizer liable for stiff penalties if its challenges to Janssen's patents are unsuccessful.

Payer actions that may influence biosimilar savings

A few payers and PBMs (e.g. CVS Caremark[33], UnitedHealthcare[34], and Veterans Affairs[35]) have excluded reference products from their formularies by substituting a biosimilar (filgrastim-sndz) and follow-on biologic (Basaglar) for Neupogen and Lantus, respectively. Although the agreements

are unpublished and 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 unclear.

Despite not having an interchangeable designation (which does not apply to Basaglar, because it is not technically considered a biosimilar, nor is it bioequivalent), biosimilar products like filgrastim-sndz may be switched for non-medical reasons (by physicians), particularly if physicians' practices would require administrative action to ensure that patients currently prescribed the reference product continue to receive it.

Conclusions

There is little doubt that biosimilars will result in savings. Attempts to quantify those savings have perhaps been premature, based on the slow evolution of numerous factors affecting biosimilar development, approval, and adoption (and, therefore, greater competition). The recent Supreme Court ruling eliminated the 180-day notification period, which could help speed biosimilar products to the market, but the practicality of interchangeability, an end to prolonged patent litigation, and revised incentive strategies affecting the market adoption of biosimilars still need to be addressed. The greatest savings will likely occur with the entry of multiple biosimilars for the same reference product, as is now occurring in the infliximab category. Therefore, over time, the opportunity for economic savings from biosimilars should increase.

Transparency

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Declaration of financial/other relationships

SRM is principal of Biosimilars Review and Report and president of SM Health Communications. He consulted for Boehringer Ingelheim in 2016. **RAB is** head of Retrospective Analysis, vice president of The JeSTARx Group, and principal of Better Health Worldwide. He consulted for Sandoz, Inc in 2016. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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