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REVIEW

Biosimilars: A cure to the U.S. health care cost conundrum?

Bradford R. Hirsch [a,b], Gary H. Lyman [c,d,*]

[a] Deparment of Medicine, Duke University Medical Center, USA
[b] Duke Clinical Research Institute, Durham, NC, USA
[c] Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, USA
[d] Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA

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ABSTRACT

As the cost of healthcare continues to rise and patents on biologics near expiration, biosimilars are gaining visibility as a mechanism for cost reduction. Yet, the introduction of biosimilars into the U.S. market will be complex, due to the related complexity of production, research requirements, and regulatory uncertainty. The purpose of this paper is to frame the relevant issues in order to provide context for stakeholders. It is particularly crucial that clinicians understand the scientific, regulatory, legislative and economic considerations involved in order to ensure that the path to approval is consistent with their needs and that appropriate utilization occurs, once approved.

1. Introduction

Healthcare costs are unsustainable and stakeholders are in search of ways to bend the cost curve. One change on the horizon with the potential to temper the rise in health care costs is in the introduction of biosimilars to the U.S. market. Biologic agents are unique from traditional therapies in that they are derived from living sources and often used to treat complex conditions such as cancer and rheumatoid diseases. A biosimilar, or follow-on biologic, is an agent in which the active ingredients closely resemble that of a previously approved biologic agent. There are numerous definitions of biosimilars throughout the world, a selection of which is shown in Table 1.

Despite having been approved for a number of years in Europe, a recent survey of 470 physicians in France, Germany, Spain, Italy and the United Kingdom demonstrated that almost a quarter of physicians either hadn't heard of biosimilars or couldn't define them [1]. Some stakeholders believe that biosimilars are the same as generic small molecules, which were introduced following the passage of the Hatch Waxman Act in 1984, while others understand that the complexities of their production make the introduction of biosimilars very different. Regardless, there remains a great deal of uncertainty as to the steps and requirements involved in their approval. Differences in aspects of their production, including the manufacturing process, source of the agent, and method of extraction mean that they cannot perfectly replicate the reference agent. It is estimated that it presently takes three to five years and between $1 and $5 million to bring a traditional generic drug to market while it is anticipated to take eight to ten years and $100 to $200 million to do the same for biosimilars [2]. This difference is driven by the complexity of production, research needs, and regulatory requirements.

Both are dwarfed by the cost of initial development. A systematic review published in 2011 on the cost of drug development reported a range of cash outlays for new therapies of $92 million for drugs developed in the 1960s and 1970s to $738 million in the 1990s and 2000s [3]. The capitalized costs range from $161 million to $1.45 billion. The cost of development for more recent agents has undoubtedly increased still further.

The potential impact and role of biosimilars in clinical practice in the U.S. are substantial. While they will not be as heavily discounted as generic agents, the involved savings are still potentially dramatic. In this manuscript, we outline the critical aspects of their assessment and introduction in order to help stakeholders make informed decisions about their use moving forward. In particular, we will discuss the economic considerations, evidentiary concerns, regulatory environment at the national and state levels, and international experience, and conclude by discussing the U.S. market.

2. Economic considerations

The fact that the growth in health care spending in the U.S. is unsustainable is not a new reality. At present, health care spending constitutes 18% of the overall gross domestic product [4]. While the rate of growth has slowed more than anticipated, the drivers of this change are not fully understood and are unlikely to be sustained. Of the $2.8 trillion spent on healthcare in 2012, 10% was spent on pharmaceutical agents (~$261 billion) [4]. Biologics in particular are expected to grow to a cost of between $200 and $210 billion by 2016 according to IMS Health [5], growing at a faster rate than the overall market and nearly equal to the total outlay today. The fields of hematology and oncology, in which biologics are disproportionately used, include 3 of the top 20 agents in

* Corresponding author at: 1100 Fairview Ave N, M3-B232, Seattle, WA 98019, USA. Tel.: +1 206 667 6670; fax: +1 206 667 5977.
E-mail address: glyman@fhcrc.org (G.H. Lyman).

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Table 1
Varying definitions of biosimilars among key organizations worldwide [34].

Organization	Definition
World Health Organization (WHO)	A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.
U.S. Food and Drug Administration (FDA)	A biosimilar is a biological product that is highly similar to a US-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.
European Medicines Agency (EMA)	A biosimilar medicinal product is a medicinal product which is similar to a biological medicinal product that has already been authorized (the 'biological reference medicinal product'). The active substance of a biosimilar medicinal product is similar to the one of the biological reference medicinal product. The name, appearance and packaging of a biosimilar medicinal product may differ to those of the biological reference medicinal product. It may also contain different inactive ingredients.

outpatient practices in 2013 by total revenue, including rituximab (Rituxan, IDEC Pharmaceuticals), bevacizumab (Avastin, Genentech) and trastuzumab (Herceptin, Genentech). It is further estimated that a substantial percentage of all new agents coming to the market over the next decade in hematology and oncology will be specialty pharmaceuticals.

Biosimilars are becoming a central issue as more and more biologic agents near patent expiration. In the European Union (E.U.), a number of agents have already come off patent. However, the only agent to do so to date in the U.S. is Neupogen, which occurred in late 2012. While tbo-filgrastim, a competitor to Neupogen, was approved by the U.S. Food and Drug Administration (FDA) in 2012, patent litigation delayed its marketing. Tbo-filgrastim was subsequently introduced into the market by Teva Pharmaceuticals when the injunction was lifted in late 2013 [6]. While it is sold elsewhere in the world as a biosimilar, it was introduced in the U.S. through a full Biologics License Application (BLA), the same path used for approval of novel agents, as opposed to the abbreviated process intended for biosimilars. This occurred because of uncertainty as to the requirements for the new pathway. The full BLA process requires extensive information on the applicant, product and manufacturing along with extensive pre-clinical and clinical studies. Because this represents the initial approval of a novel agent, the requirements are stringent. The requirements for the abbreviated pathway are still being defined, as will be discussed subsequently. As such, no true biosimilar has been introduced using an abbreviated pathway. The earliest patent expirations for epogen occurred in 2013, which will be followed by pegfilgrastim and rituximab in 2015 and bevacizumab and trastuzumab in 2019 [7]. The increasing pace at which agents will be coming off patent in the next few years will likely include the first utilization of the pathway.

The potential impact of biosimilars is dramatic, yet quite different from that seen with generics. Generics are sold at a substantial discount to the reference, branded agent because of the relative ease of approval and production. This differs from biosimilars, which are anticipated to be discounted by only 20% to 40% compared to the reference agent. This is driven by the complexity and time commitment required to bring them to market. Generics can be produced in such a way that they closely reflect the reference product as they do not rely on a complex biologic pathway for production. Therefore, the required studies are limited. This is not the case with biosimilars, the introduction of which is complicated by the fact that the production process used for the originator agent is proprietary and that, even with full information, the biologic process cannot be perfectly replicated. However, the more limited discount associated with biologics does not undermine their economic relevance. If biologic agents attain 20% of sales of reference biologics, this would represent savings of $8 billion based on 2012 sales. As the market grows, this impact will begin to be realized.

The true economics in practice are complex. To better understand the implications at the practice level, consider a hypothetical situation as shown in Fig. 1. Practice X previously purchased Biologic Y at a list price of $1000 for each of its 100 patients. As a result of their relationship with the manufacturer and volume, the practice received a discount from the manufacturer of 25% off the listed price for the agent. Subsequently, Biosimilar Z was released at a 40% discount to the reference agent and 20% of patients within the practice were transitioned to its use. Because of the change in volume for Biologic Y, the manufacturer chose to discontinue the discount in order to maintain revenue. Now 80 patients are being charged $1000 (list price for Biologic Y) and 20 are being charged $600 (list price for Biosimilar Z). Despite the introduction of the biosimilar, costs have increased from $75,000 to $92,000 for the practice and its patients. In this very simple example it is clear that there are a number of factors at play in the market such as discounts and market penetration that will determine the economic impact of biosimilars. It is also likely that the manufacturer of the reference agent will decrease the price to maintain market share, potentially undermining the case for investment in biosimilars. These factors lead to uncertainty as to the true market potential and extent of cost savings.

3. Regulatory environment

The regulatory considerations related to biosimilar uptake remain ill-defined and lead to some of the uncertainty as to their impact. While the primary focus to date has been on the FDA, there are state regulatory and other considerations of importance as well. As part of the Affordable Care Act in 2010 [8], the Biologics Price Competition and Innovation Act introduced the pathway for biosimilar approval. Within it, biosimilarity was defined as being "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and it was stipulated that "no clinically meaningful differences exist" in terms of "safety, purity, and potency." This was followed by draft guidance from the FDA in 2012 on quality [9] and scientific [10] considerations and in 2013 by guidance on the type of meetings [11] the FDA plans to hold. Despite these areas of progress, the specifics remain elusive. In a New England Journal of Medicine editorial by Dr. Woodcock et al. [12], they stated that a "one size fits all" approach is unlikely in the near term because of the variability between agents. As such, it will be left to those who pursue initial approval to take part in defining the process regarding the pre-clinical and clinical evidentiary requirements that would lead to approval via the abbreviated pathway.

The E.U. has experience in developing related pathways to approval for biosimilars, although the E.U. experience is unlikely to be fully replicated in the U.S. In 2005, legislators in the E.U. released a "guideline on similar biological medicinal products" which was followed by specific guidelines on safety and efficacy, as well as quality [13]. These were further clarified with guidelines on specific categories of agents such as erythropoietins [14,15], granulocyte colony stimulating factors [16,17], and human growth hormones [18]. As discussed subsequently, this approach has led to a number of approvals and widespread uptake, and has not resulted in widely publicized safety events.

3.1. Substitution

Despite this focus on federal regulations, many important activities are occurring in parallel at the state level in the U.S., which will impact uptake. The two primary issues are around substitution and naming. Substitution refers to whether pharmacists can freely substitute a

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