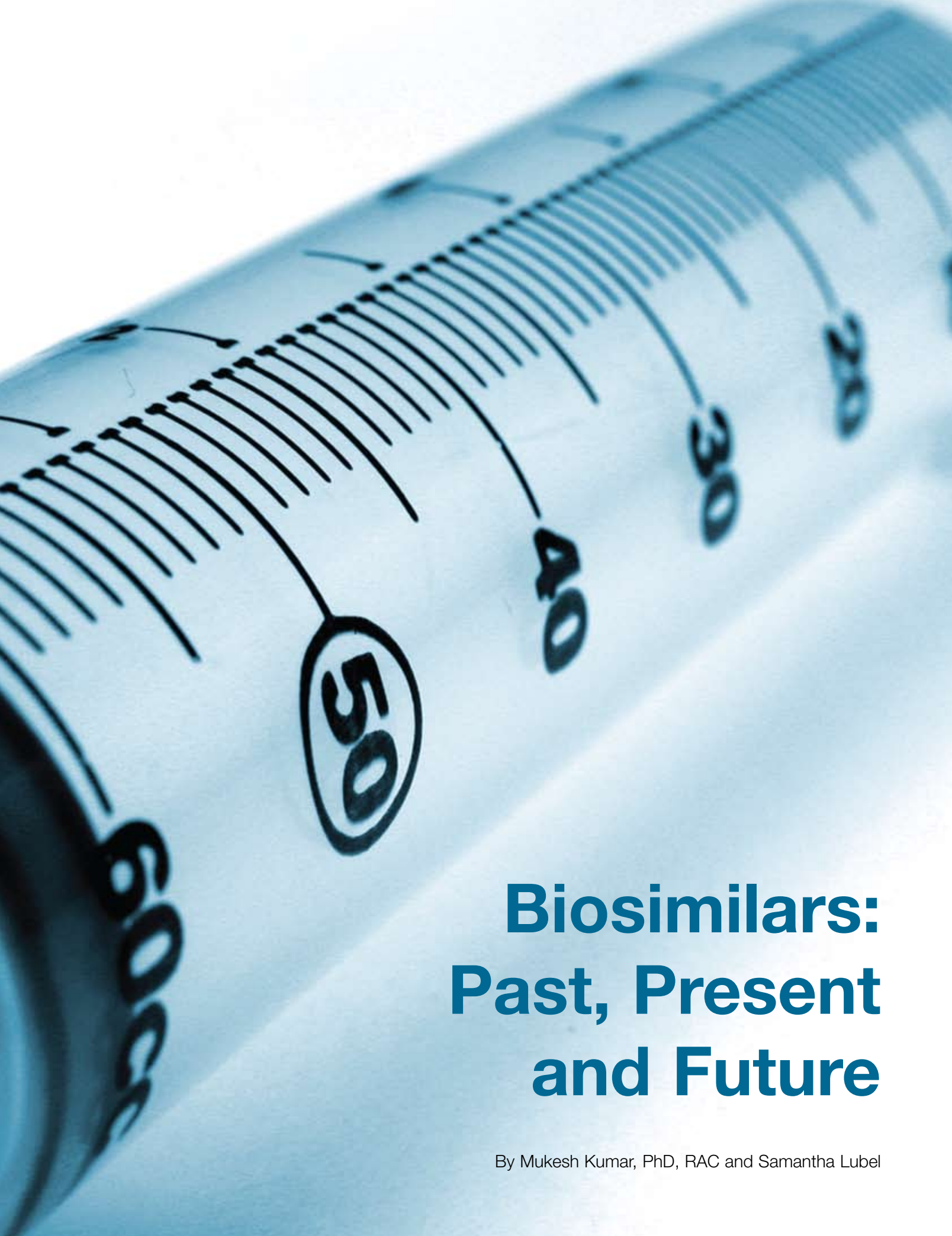

Biosimilars: Past, Present and Future

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Facing steep increases in healthcare costs, US legislators are making a concerted effort to find new ways to reduce them. One approach targets the high cost of biologics. Biologics are typically very expensive. While justifications for their price tags include the high cost of development and manufacture, higher risk of failure and limited markets, a key reason is lack of competition. Unlike drugs, there is no regulatory pathway for approval of generic versions of biologics in the US. Hence, a biologic can survive in the market for a longer time without fear of cheaper competitors.

Generic drug prices are much less than innovator drugs due to their lower cost of manufacture and marketing. Therefore, it is assumed that the availability of more generic drugs can reduce overall costs. Creating a similar regulatory pathway for generic biologics is expected to reduce consumer costs and expand patient access to these therapies as well. However, the effort to create regulatory pathways for generic or similar versions of biologics has been fraught with one issue after another, from scientific and financial to political. Over time, the term "biogeneric" has been replaced by more politically correct terms such as "biosimilar" or "follow-on biologic" (FOB). This article discusses the past, present and future of biosimilars or FOBs. More specifically, it reviews the regulatory history, new proposed development pathways, realities and myths about biosimilars, the politics involved and, finally, what the future holds.

Generic Drugs Are Well Received by Patients and Regulators

The safety and efficacy of generic drugs are recognized, as is their substitution for their innovator drugs. A generic version of a drug is interchangeable at the pharmacy level, meaning that a pharmacist can dispense a generic drug instead of a brand-name product without needing a separate prescription. Usually, both patients and insurance companies prefer generic drugs because of their lower cost.

Generic drugs go through an abbreviated review process: the US Food and Drug Administration (FDA) requires only bioavailability and bioequivalence (BA/BE) studies in humans comparing the generic product to the innovator. The safety and efficacy of the generic drug are assumed based on studies conducted for the innovator product, to which FDA can refer to without needing permission from the innovator drug manufacturer provided no patents are infringed. As a result, generic drugs take far less time to develop and require less financial investment, leading to the lower costs. Also, because the generic drug benefits from the established market for the innovator product, no separate marketing is required. For any given innovator product, there may be multiple generic versions. The increased competition for market share reduces the retail price even further. Generic drugs have about 25 years of regulatory history and there now are roughly 25 times more generic approvals by FDA than new drug approvals. Generic drugs account for about 65% of the US pharmaceutical market, which is the world's largest generic drug market with 45% of global sales.[1]

For all of these reasons, a process to create follow-on versions of biologics is very attractive to all stake holders: the generics industry, the insurance industry, consumers and legislators.

Biosimilars Are Not Generic Biologics

Unlike drugs, which are well-defined molecules, it is very hard to create a similar product for biologics. Because they are derived from living organisms using biological processes, very minor changes in the process could lead to major changes in the product. Biologics generally exhibit high molecular complexity and may be quite sensitive to manufacturing process changes. It is often stated that for biologics, "the process is the product." There is a strong debate in the scientific community about whether technology exists to create and validate a copy of a product made through complex biological processes.

In the beginning of this debate, the term "biogeneric" was used by proponents of copies of biologic products. They assumed that generic versions of biologics could be created by following a regulatory pathway very similar to that for generic drugs. Biogenerics approval would require only BA/BE studies comparing them to the innovator product, and would be substitutable at the pharmacist level. Over time, it became clear that neither the scientific community nor FDA was comfortable designating a biogeneric as a substitutable replacement for the innovator product.

The science to fully characterize most biologics is questionable at best. Large proteins cannot be chemically synthesized outside living cells with accurate folding and side groups. Complex biological processes can best be replicated only in living organisms. The innovator biologics go through an extensive process that includes characterization of the growth conditions for living organisms, harvesting the active ingredient, purification, stabilization, packaging and storage.

Many of these steps are not described in patents but instead are protected as proprietary trade secrets. FDA is not allowed to publicly disclose this information. Hence, the process of reverse engineering these products without the help of the original manufacturer also includes extensive recharacterization of all the processes, validation and retesting (clinical and nonclinical trials) before the product can be considered similar. That makes it virtually impossible to make an interchangeable substitute. Therefore, over time, the term biogeneric has been replaced by biosimilar or FOB to emphasize that while these products are similar to the innovator product, they cannot be considered analogous to generic drugs.

All stakeholders have now accepted the term biosimilar or FOB indicating a general understanding that generic biologics are neither possible nor desired at this time, due to the many scientific and regulatory issues involved. Instead, current efforts are focused on developing a formal regulatory pathway for approval of biosimilars in the US.

FDA Has Approved Biosimilars

In the US, biologics are regulated under the *Public Health Service* Act (*PHS Act*) and, thus, differently than chemical drugs. Although there are similar regulatory processes, such as IND applications, for biologics, there are also many differences, for example no review processes are defined for biologic products that are copies of existing products. Every biologic is considered new and is regulated as such. Hence, applications for biologics similar to existing products are reviewed by FDA as though they are brand-new products. There are cases where FDA has waived specific clinical and nonclinical studies, on a case-by-case basis, if there is sufficient justification based on information available in the public domain.[2] To date, FDA has approved between 15 and 20 biosimilar products using this approach.[2] Most of the approved applications for similar biologics required clinical studies, comparability studies and safety and efficacy studies, as well as extensive chemistry, manufacturing and controls (CMC) characterization information. None of these products is considered substitutable; all require a product-specific prescription.

The first formal regulatory pathway for biosimilars was proposed by the European Medicines Agency. In its *Guidance Document on Similar Biological Medicinal Products*, released in 2005,[3] the agency proposed approving similar biological products based on comparability data and reduced clinical and preclinical evidence provided the following conditions are met:

- These products will be considered similar, not identical to innovator biologics.
- Studies of comparability to innovator products, along with complete CMC information, must be submitted for review.
- Similar products will be considered only for well-characterized products, such as single protein products, but not for vaccines, allergens or multi-active ingredient products.
- Biosimilars will not be substitutable for innovator products.

The European regulatory pathway does not create substitutable biosimilars, but product dossiers include a review package much more like one for a new product than for a generic one. FDA has repeatedly defended its current policy of case-by-case application review, citing lack of legislation to support a formal process for biosimilars or FOBs. Both FDA and the European Medicines Agency treat biosimilar products as innovator products while granting waivers from certain clinical and nonclinical studies when appropriately justified.

A Formal Regulatory Process for Biosimilars Has Been Proposed

Since 2006, several bills have been proposed in the US Congress to create a formal regulatory pathway for biosimilars. Most include similar review processes and give FDA discretionary power to determine what studies are required to support a biosimilar application on a case-by-case basis. However, they differ in the length of market exclusivity offered to the innovator product. Market exclusivity is considered one of the most important incentives offered by US regulations: its provisions prevent competing products from being introduced onto the market for a certain period after the innovator product is approved, regardless of patent status. For drugs, market exclusivity varies from three to seven years (three years for 505(b)(2) products, five years for new chemical entities and seven years for orphan products). For biologics, five to 14 years of market exclusivity before biosimilars can be introduced in the market have been proposed. At present, there seems to be agreement on about 12 years of market exclusivity for biologics. Recently, the pending biosimilar bills were merged with the healthcare reform bills in both the House of Representatives and the Senate. However, due to the political issues involved with healthcare reform, there is a move to try to pass the biosimilar legislation by itself as originally proposed.

The proposed pathway for biosimilar review is very much like that for 505(b)(2) drug products. The biosimilar product sponsor would be required to provide complete chemistry information comparing it to the innovator product. FDA might request additional characterization information on a case-by-case basis, based on its experience with the innovator product. Initially, only biosimilars for simpler, well-characterized biologics such as single or few protein formulations would be allowed. However, with

increasing regulatory experience, more-complex products might also be pursued.

The sponsor for a given biosimilar product would be allowed to claim FDA's previous findings of safety and efficacy for the reference product; however, in addition to BA/BE studies, FDA would mostly likely require additional clinical and nonclinical studies in support of the biosimilar. Just like a 505(b)(2) drug product, the biosimilar could claim additional benefits over the innovator product and would not be considered substitutable for the innovator reference product. For this reason, the biosimilar product sponsor would have to launch an independent marketing campaign to encourage doctors to specifically prescribe the biosimilar.

As with generic drugs, the first biosimilar to be approved would have market exclusivity (currently proposed to be about a year) over other biosimilars for the same reference product.

There are many intellectual property issues concerning biologics that would affect biosimilars. Most biologics are covered by multiple patents. A sponsor is unable to begin developing a biosimilar product until all patents on the innovator product have expired. Additional challenges are introduced if the manufacturing processes are covered by trade secrets or involve proprietary information. If a trade secret is used in a process, FDA can never use that information to approve another product. So, the biosimilar developers would have to develop their own processes without the benefit of help from FDA about innovator product trade secrets.

Benefits of a Formal Biosimilar Regulatory Pathway are Questionable

While there is general agreement that a formal regulatory pathway for creating biosimilars will eliminate existing legal ambiguity for sponsors, the tangible benefits of these products to patients and sponsors are questionable at best. For consumers and legislators, biosimilars hold the promise of a lower-cost alternative to expensive biologics. There have been several analyses by academic centers, industry groups and government groups such as the Government Accountability Office and the Federal Trade Commission indicating varying financial benefits of biosimilars in reducing healthcare costs. Estimated cost reductions range from $4 billion to $70 billion over 10 years.

For the developers, the regulatory requirements for biosimilars could vary extensively based on FDA's experience with the innovator biologic. This means that the process of creating a biosimilar will most certainly be much longer and more expensive than for a generic drug. It would involve a much larger investment of time and financial resources and carry a much higher risk of failure than for conventional generic drugs. A manufacturer would not only require expensive chemical and biological characterization but also need to conduct several long clinical and nonclinical studies just like those for new products. The need for a marketing campaign would add to the cost of doing business. Hence, the cost to patients is expected to be not much lower than that of the innovator product. Estimates of cost reduction of 10% to 20% for biosimilars have been suggested. However, given the high cost of many biologics, even a modest cost reduction could mean significant savings for patients.

Due to the extensive amount of time and huge investment required to develop biosimilars, only sponsors with significant resources will be able to create such products, leading to much less competition than is usual for generic drugs. Typically, several generic drugs are introduced within a short time after patent expiration of the innovator product, leading to a price depression of up to 80% compared to the innovator product.

For patients, besides the modest price reduction, the major benefit seems to be the availability of alternate therapies leading to greater access to treatments. However, due to the overall hurdles in developing biosimilars, it is expected that only biologics with a large market share will be pursued. This has been evident with several biosimilars being pursued for anemia, interferons and influenza vaccines. Many biologics target indications with smaller market size, i.e., fewer patients. Such biologics would not be attractive to biosimilar sponsors, thereby giving the innovator products unlimited market exclusivity for all practical purposes. This long market exclusivity would allow the innovator companies to develop a much stronger brand and their own improvements to the initial product, thereby constantly maintaining an advantage in the market.

Practical Strategy for Sponsors of Biosimilars

Due to the complexity of current and proposed regulatory processes, sponsors interested in developing biosimilars need a comprehensive strategy. A good strategy would include identifying appropriate reference products to target, developing regulatory expertise specifically in understanding the FDA review process and developing scientific expertise in the characterization of the active ingredients and the final product. Companies should be prepared for a higher risk of failure to get marketing approval, in addition to longer development time, greater financial investment and large, complex clinical trials.

A simpler, well-characterized biologic with one or a few ingredients and a well-characterized manufacturing process that can be compared to that of an already approved biologic would be the best candidate. The development strategy, including the studies required, resource allocation and CMC considerations, should be carefully planned. FDA discussions are very

beneficial, especially for a biologic, due to the risk associated with these products. Once a biosimilar successfully navigates the regulatory maze, it will be faced with strong competition from the well-established innovator biologic. The innovator of the product has had 12 years of exclusivity to build a strong brand for which the biosimilar is not a substitute. Hence, it will not be possible to "piggyback" on the innovator's existing market. Unless there is a significant cost advantage, consumer and insurance company acceptance of a new product over a well-established product may be questionable at best.

A better strategy seems to be to develop a biosimilar as a new product. It would benefit the sponsor to use scientific rationale and its own nonclinical and clinical testing, most of which will be required anyway, to develop its product as a unique biologic and get the benefit of extended market exclusivity.

Conclusions

Biosimilars have been the subject of extensive publicity with projections of huge benefits for the consumer and industry alike. However, in reality, the benefits to all stakeholders appear to be modest. A few biologics would be very attractive targets for biosimilar development due to their large revenues. However, most biologics with smaller markets will not be affected by the proposed biosimilar regulatory pathway for practical reasons.

It is not possible to create a simplified general scientific pathway for developing biosimilars. Most products will have to go through a long, expensive and risky development process. Because they will not be substitutable for innovator biologics, biosimilars would be more like competing innovator products than price-cutting generics. Gaining market share for a biosimilar could be challenging when there is no added benefit over the innovator and insignificant cost savings. Lastly, it is highly unlikely that a formal regulatory pathway for biosimilars would benefit the small biotech industry. The small biotech industry is better served by creating clear innovator biologics than trying to develop biosimilars with questionable returns.

It is expected that the US will soon have a formal regulatory pathway for biosimilars very much like the 505(b)(2) pathway for generic drugs. It is also probable that innovator biologics will enjoy much longer market exclusivity periods of about 12 years postapproval and that biosimilars will not be substitutable products. In our opinion, these make the biosimilar pathway, as proposed, fraught with too many issues to be practically useful. On the contrary, once the pathway is approved, if FDA decides to classify new products as biosimilars—thereby keeping most of the regulatory requirements but taking away the market exclusivity—it may stifle innovation.

Before delving into an uncertain and complex product development arena, a sponsor must understand the pros and cons of the process and make a prudent judgment. In the end, these decisions will always be made on a case-by-case basis.

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