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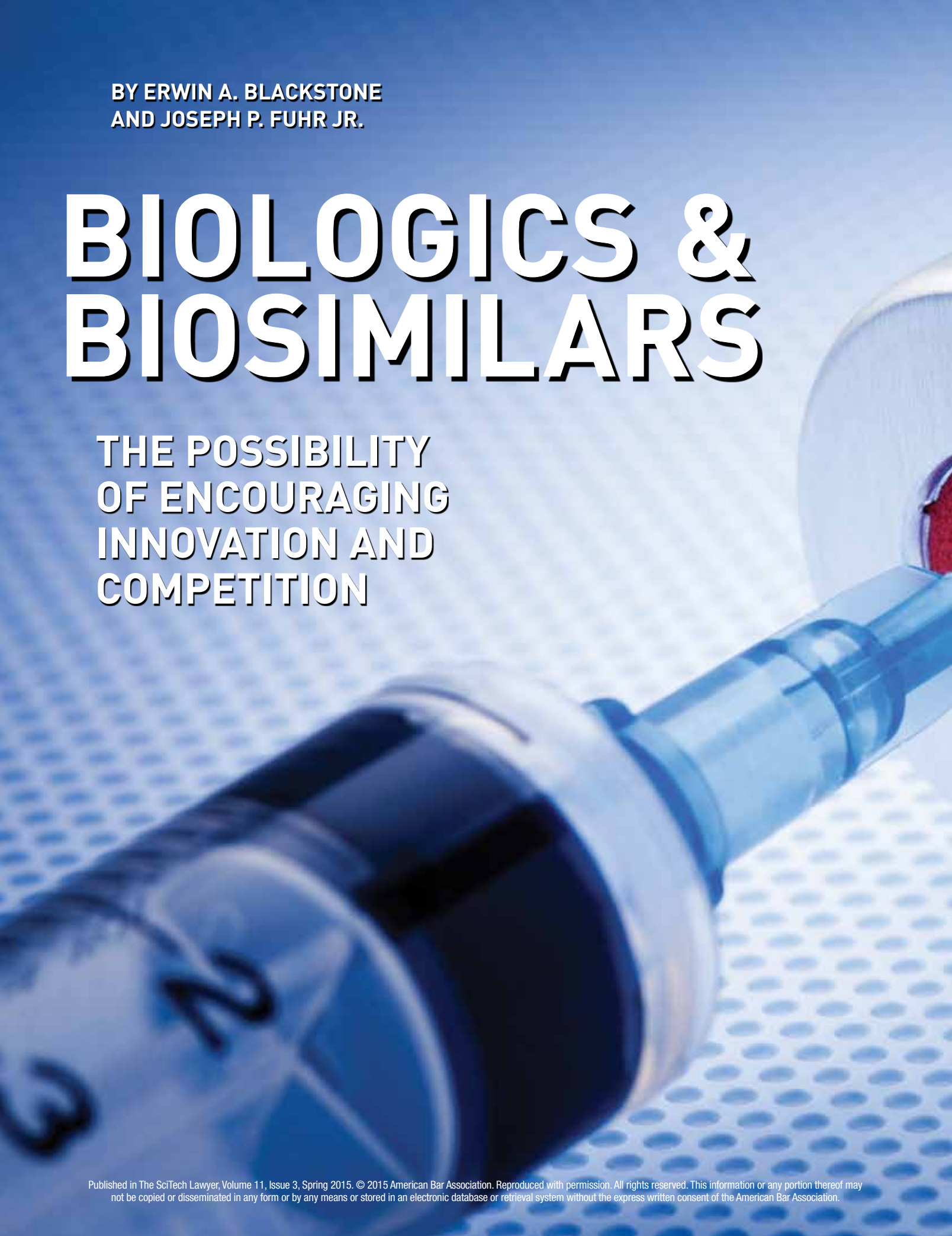
BIOLOGICS & BIOSIMILARS

THE POSSIBILITY OF ENCOURAGING INNOVATION AND COMPETITION



Medicines known as *biologics* represent an increasingly important part of the pharmaceutical industry. Unlike more familiar small molecule chemical drugs manufactured using biochemical processes (such as aspirin or heparin), biologics are large molecule drugs produced in living organisms.[1] Because biologics are produced using living organisms, a potential competitor of the developer of the original drug (the "originator") may be unable to replicate the reference biologic, even if the chemical structure of the originator's drug is known. In contrast, if the chemical structure of a small molecule drug can be determined, then once the patent expires on the original version of the drug, it is possible for competitors of the originator to make exact copies, commonly known as *generic* drugs. Because of this difficulty in developing and manufacturing an exact replica of an innovative biologic medicine, potential competitors of the originator are also challenged to give assurances that their *mimic* of the originator's drug is the same or that it will have the same biochemical effects when administered to humans.

Biosimilar is the name given to a biologic that is highly similar in chemical structure to an originator's biologic and, to the extent scientifically measureable, produces the same medical effect as the originator. A biosimilar (by definition) is not an exact copy of the originator's drug. The originator can continue to enjoy monopoly power for the innovative drug beyond the life of the originator's patent until a biosimilar enters the market. Indeed, some biologics that already have lost patent protection in the United States still do not face competition from biosimilars because an approval process for biosimilars has only recently been created.

For chemical drugs, in 1984 Congress passed the Drug Price Competition and Patent Term Restoration Act, commonly known as the Hatch-Waxman Act (H-W) in an effort to bring more price competition to the drug industry and hold down the rising cost of these drugs. H-W provided a pathway for drug companies to obtain approval of generic versions of small molecule drugs without having to incur the enormous costs of replicating the patient studies that the originator of the drug was required to undertake.

However, until adoption of the Biologic Price Competition and Innovation Act (BPCIA) of 2009, as part of the Patient Protection and Affordable Care Act of 2010 (commonly referred to as the ACA or the Affordable Care Act), no process existed for obtaining FDA approval of a biosimilar. The goal of the BPCIA was to provide for biosimilars a pathway similar to the pathway created by H-W for nonbiological generic drugs while still preserving enough economic incentives for originators to continue to develop innovative biologic drugs. This article examines the biosimilar market that has begun to evolve in the United States as a result of the BPCIA and its possible effects on consumers and health care costs.

Unique Characteristics of Biologics

Biologics are far larger and more complex than small molecule drugs. For example, the biologic Epogen has a molecular weight 168 times that of a small molecule drug aspirin.[2] Such size and complexity make manufacturing more difficult, complicate methods of administration, and increase the health risks of use. Even small changes in their manufacture can lead to serious health consequences. And because large molecules have difficulty passing through the intestinal wall, pills to deliver biologics have proven problematic. As a result, biologics are more often infused or directly administered by a health professional than are chemical drugs.

The development of a new biologic is a long and difficult process, taking on average between 10 and 15 years, with many of these efforts ending in failure. Research and development (R&D) costs for one originator biologic have been estimated to be between $1.3 billion and $1.9 billion in the 2012–13 period, with some suggesting that, when taking failures into account, the costs for those biologics reaching the market could be considered to be as much as $5 billion each.[3] Further, spending on R&D for biologics exceeds the R&D spending for all but a few other product categories. In 2013 the industry spent 21.3 percent of its $71.9 billion of sales on research and development. Some of the small companies that actually get a biologic product to market spend about 75 percent of their revenues on R&D.[4]

Partly as a result of these enormous development costs, biologics are often among the most expensive drugs. For example, in 2014 the annual per patient expense for Soliris, a biologic for treatment of a blood disease, was $536,269.[5] Some other expensive biologics are Neglazyme for Maroleaux-Lamy Syndrome and Kalydeco for cystic fibrosis, with annual patient costs, respectively, of $485,747 and $299,592. Of the revenues for the 10 best-selling drugs, in 2001 biologics accounted for only 7 percent but by 2013 that percentage had grown to 71 percent.[6] Five of the top 10 revenue-producing drugs in 2012 were biologics, an increase from two of the top 10 in 2008.[7] Further indicative of the economic importance of biologics is the fact that they represent 18 percent of global pharmaceutical industry revenues in 2012 and that revenues for biologics are growing at twice the rate of global drug revenues overall.

Hatch-Waxman and Chemical Drugs

The impetus for the BPCIA came in part from the success of the H-W in encouraging the entry of generics into the market for chemical drugs. Prior to the adoption of H-W, many chemical drugs faced limited competitive pressure to reduce prices after their patents had expired. For example, only 35 percent of such drugs that lost patent protection had generic competition.[8] H-W encouraged the development of generics by providing incentives to challenge patents and requiring only chemical equivalency for approval of generics. In an effort to provide some compensation to originators for the anticipated reduction of their revenue streams as a result of the increased

competition, H-W also provided the possibility that originators could extend patents on an innovative drug for five years beyond their normal 20-year lives when FDA drug approval took an inordinate amount of time.

H-W has generally been successful, with more than 80 percent of prescriptions for small molecule drugs now being filled by lower-priced generics (sometimes priced as much as 90 percent lower). Yet the incentives for new chemical drug development have been maintained. The issue is whether the BPCIA can do the same for biologics, a subject to which we now turn.

Framework for Analysis of the BPCIA

At the outset, we acknowledge that without innovative biologics, there could not be biosimilars. We would not suggest that the originator of such innovative drugs should not have adequate compensation for risk-taking. Indeed, if we had to err, we would err on the side of providing strong incentives for innovation given the great societal benefits often provided by the originator's drugs. Some have argued that patents would provide inadequate protection and thus insufficient opportunity for the innovator to recoup its very high investment.[9] However, we subscribe to the view that, once patents expire, consumers deserve the benefits of competitive pricing. The BPCIA seeks to strike a balance by providing 12 years of market exclusivity from the date of FDA approval, regardless of patent expiration. This means that the FDA could approve a biosimilar for that drug, but it cannot be marketed during that 12-year period. Such exclusivity cannot be challenged in court as patents can. Therefore, it can provide a stronger incentive for innovation and risk-taking than do patents.

It is also noteworthy that the prospect of competition from biosimilars may actually facilitate bringing originator drugs to market. Because the prices charged for originator biologics tend to be very high, obtaining approval for reimbursement by third-party payers could become problematic. By holding out the promise of eventual competition from lower-cost biosimilars, the BPCIA may make it more likely that biologics will be approved for reimbursement. Indeed, given their high cost and their increasing share in pharmaceutical expenses, not permitting competition could well have reduced innovation by making it more difficult for originator drugs to qualify for reimbursement.

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Biosimilar Opportunities

Biosimilars represent a tremendous business opportunity, as many originator biologics either have lost patent protection recently or may do so in the near future. Many of these have sales of more than a billion dollars. These include Aranesp and Copaxione, which were scheduled to lose protection in 2014, Neulasta and Rituxan in 2015, Humira in 2016, Avastin and Herceptin in 2019, and Lucentis in 2020. The 2013 global sales of the above-mentioned biologics totaled $45.65 billion. Because the United States accounts for about one half of global biologic sales, we estimate the US sales to be almost $23 billion. This makes the US market highly attractive to biosimilar firms.[10] If biosimilars were able to reach the market and replace the corresponding originator drugs, and if the effect were to reduce spending on those biologic drugs by 20 percent, annual savings for patients and insurers could be $4.6 billion.

Barriers to Entry

There are many hurdles to overcome for potential biosimilar entrants, including entry barriers quite distinct from those for chemical generics. First is the cost of development. Developing a chemical generic (that only requires showing safety and equivalency to the originator drug in order to obtain regulatory approval) requires spending only $1 million to $5 million. Approval of such generics generally does not require expensive and time-consuming clinical trials. On the other hand, biosimilar development is expected to cost between $100 million and $200 million per drug and take between eight to 10 years.[11] For example, Celltrion has invested $112 million in the development of Remsima, which is a biosimilar to the reference product Remicade.[12]

To date, the FDA has not established firm guidelines as to exactly what will be required for approval as a biosimilar. The FDA draft guidance for biosimilar approval considers a totality of evidence and case-by-case approach, which provides little specificity for prospective entrants and therefore increases uncertainty and inhibits entry.[13] However, the FDA appears to be on the verge of setting a possible precedent with staff and advisory committee approval of the biosimilar Zarzio. In January 2015, the staff of the FDA and an FDA advisory committee recommended approval of Zarzio, developed by Sandoz as a biosimilar for Amgen's reference product Neupogen. Full FDA approval was granted in March 2015. This is the first biosimilar approved for use in the United States. There are currently three other biosimilar applications under consideration, including one by Celltrion. However, as discussed below, the complexity of certain patent issues (which were raised prior to the Sandoz and Celltrion applications) may well complicate biosimilar entry even after approval by the full FDA is obtained.

Entry into the biosimilar market also requires establishing manufacturing facilities that must meet FDA requirements regarding "good manufacturing practices" or GMP. Such approved manufacturing facilities cost approximately $250 million.[14] In addition, biosimilars are likely to encounter more storage and handling issues than chemical drugs.

Because biosimilars are not identical to the reference originator drug and because of the risks of immunogenicity arising from the introduction of a foreign biological substance into the human body, at least some clinical trials are almost certainly going to be required.[15] These tests are costly and carry some of the same development and clinical risks as the trials for the originator drug. Even after approval, the threat of malpractice lawsuits should there be a problem with a biosimilar may encourage health care providers to remain with the originator.

Overcoming physician reluctance to

switch to biosimilars will also require significant sales and promotion efforts. Such sales efforts are likely to add substantially to the cost of entry. Indeed, a typical drug firm may devote about 25 percent of its revenues to sales promotion and other overhead activities.

In addition, the large number of companies working or planning to work on biosimilars targeting a particular originator drug could discourage some companies from entering because a given biosimilar market may be too small to accommodate many competitors.

In the generic market, there was little response from the originator to generic competition, and prices decreased in some cases by as much as 90 percent. However, given the higher costs of biosimilars, one would not expect prices to decrease as much as in the chemical generic market. In the EU biosimilar competition has resulted in price decreases of around 20 to 30 percent. The experience in the EU has been that the originator cuts its prices in response to biosimilar entry and may also try to produce second-generation originator biologics that offer various benefits over the first generation biologics, such as ease of administration and less frequent dosing. For example, Neulasta is administered once a week, compared to Neupogen, which is given daily.[16]

Biosimilars have enjoyed modest success in most of the developed foreign markets. For example, in 2010 total biosimilar sales in the EU, Canada, Australia, and Japan were $235 million out of a market total for biologics of $134 billion.[17] Biosimilars have been available in the EU since 2006. Prices in the EU were generally about 30 percent lower for biosimilars than their reference products. On the other hand, Zarzio has now become the first biosimilar in the EU to garner more prescriptions than the originator or reference drug, Neupogen.[18]

The gains to society from biosimilars could be substantial. Our analysis suggests that even after approval, biosimilars are unlikely to result in the same percentage declines in price or to experience the same percentage increase in market shares as those experienced from the introduction of generics into the chemical drug market. Nevertheless, the actual dollar benefit for consumers might be even greater for biosimilars than it has been for generics. A 20 percent price reduction on a drug whose annual patient cost is $200,000 generates annual savings of $40,000. A chemical or small molecule drug like Lipitor during its patent protection period in 2010 had annual patient cost of about $1,640 for a 20 mg tablet.[19] Even if the price of Lipitor were reduced by 80 or 90 percent, annual per patient savings would be at most about $1,500. The potential cost savings from generics, when expressed in dollars rather than percentages, may be equaled or exceeded by savings from the introduction of biosimilars. A recent RAND study estimated the cost savings from biosimilars over the next 10 years could be more than $44 billion.[20]

Finally, in terms of the safety of biologics, the experience to date has generally been good, albeit with one notable exception. This occurred when Johnson and Johnson made a small change in its manufacturing process for Eprex. Patients using the drug after the manufacturing change experienced immune system problems that resulted in pure red cell aplasia.[21] However, the biosimilar experience in the EU has shown little if any safety issues. In any event, awareness of the possible negative impact of an adverse event on the ultimate success of biosimilars in the marketplace, the FDA is likely to be cautious and require adequate clinical trials and postapproval monitoring to assure safety.

Additional Legal Issues

Under the BPCIA, a biosimilar producer and the originator are supposed to exchange information about any patents that may be at issue concerning the biosimilar entry. This provides opportunities for communication and shared information between competitors. However, such information sharing by competitors has traditionally raised antitrust concerns that will require biosimilar producers to rely on legal counsel for advice regarding such exchanges.

Next, *pay-for-delay* issues may well arise similar to those challenged by the FTC in the generic markets. Pay-for-delay agreements are arrangements in which the maker of the originator's drug pays the maker of the potential generic version not to produce the lower-priced generic, at least for some period of time. The delay of entry could have benefits for both the originator and the biosimilar maker at the expense of consumers, because the price of the originator's biologic is able to be maintained at an elevated level, and some of the profits are shared with the biosimilar producer.[22] The practice has been defended on the ground that the risk of losing a patent case that results in shortening the exclusivity period during which the originator enjoys profits is likely to reduce the incentive to produce new drugs. This may harm consumers in the long run. It has also been argued that such agreements can be procompetitive because they could allow for biosimilar entry before patent expiration. The Supreme Court and FTC have looked at the possible anticompetitive effects of pay-for-delay in the generic markets. However, without the 180-day exclusivity that the first successful generic filer obtains under H-W, this strategy may not be as profitable, because other biosimilars could enter the market. The delay of entry by first filers essentially forecloses other generics from entering the market. This will not occur in the biosimilar market.

In addition, the patent situation for biologics is exceedingly complex. For example, it is a general rule that patents claiming laws of nature or natural phenomena are invalid. On the other hand, artificial manipulation of naturally occurring genetic substances can result in an invention or discovery that qualifies as a patentable product.[23] Another patent-related issue is whether a patented production method could be used by the maker of a biosimilar to examine the question of similarity.[24] The uncertainties involved could provide additional justification for the 12-year market exclusivity for originators. In any event, the patent situation increases uncertainty, which could imperil innovation and impact consumers.

Incentivizing Market Acceptance

Conventional wisdom suggests that in the United States biosimilars are likely to encounter greater difficulty

(especially initially) in competing with originators than generics did in the case of small molecule drugs. Even in the case of generics, time passed before they gained acceptance. Biosimilar uptake in the EU has been successful when stakeholders have the right incentives. High biologic prices could lead to pressure by payers to switch to lower priced biosimilars. For example, Germany has encouraged the use of biosimilars and has experienced some of the highest market shares for biosimilars.[25] In the United States, a bidding process for exclusive arrangements could be utilized to encourage more competition and might lead to more rapid expansion of the use of biosimilars, similar to the hepatitis C chemical drug market described below. Bundling of payments for providers so that they receive a fixed price for treatments would encourage the use of less-expensive inputs, including biosimilars. Similarly, the growth of Accountable Care Organizations, encouraged by the ACA, where providers earn higher profits for cutting costs, would seem to encourage the use of biosimilars. Reference pricing, which make patients pay out-of-pocket for prices above the insurance reimbursement rate, can encourage patients to seek biosimilars. Accordingly, the use of biosimilars could proceed faster than the experience in the EU and other developed markets.

One model may be evolving from the recent controversy over the price that Gilead has been charging for its hepatitis C drug, Sovaldi. Even though it is not a biologic, Sovaldi was priced at $84,000 for a course of treatment, which raised concern among payers. Recently, AbbVie came out with a newly approved hepatitis C drug, Viekira Pak, and in exchange for a discount entered into an exclusive agreement with Express Scripts so that Viekira Pak will be the only hepatitis C drug in the Express Scripts formulary. In response Gilead signed an exclusive agreement with CVS to discount Sovaldi. Such exclusive agreements could be employed in the biologic markets to encourage a greater uptake of biosimilars.

Implications and Conclusions

The potential benefits are substantial for exploiting the new pathway for biosimilars provided by the BPCIA. At the same time society should ensure that sufficient incentives remain for originators to develop new drugs. The market exclusivity provision of the BPCIA could and should provide a reasonable balance between encouraging innovation and competition. We anticipate that biosimilars will have only modest success for some time until they become recognized as acceptable substitutes for the reference products. The high entry barriers and cost for biosimilars will limit the growth of the biosimilar market. However, given the possibility of exclusive arrangements as well as other incentives, market uptake may be quicker. In any case, safety concerns dictate caution in the approval process to avoid the risk that a safety problem could derail the future of biosimilar competition. We suspect that the case-by-case approach of the FDA will eventually make the guidelines clearer. ◆

Endnotes

1. Jason Kanter & Robin Feldman, *Understanding and Incentivizing Biosimilars,* 64 Hastings L.J. 57 (2012).

2. *Id.*

3. *Biotechnology,* Standard and Poor's Industry Surveys, Sept. 2014.

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5. *Id.*

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10. Kantner & Feldman, *supra* note 1; and Rickwood & Di Biase, *supra* note 7.

11. Blackstone & Fuhr, *supra* note 8.

12. Celltrion v. Janssen, Celltrion's Opposition to Janssen's Motion to Dismiss for Lack of Subject Matter Jurisdiction, Case No. 1:14-cv-11613 (D. Mass., July 7, 2014), available at http://www.hpm.com/pdf/blog/REMICADE%20%20Celltrion%20Opp%20to%20Janssen%20MTD%20DJ%20Complaint.pdf.

13. Blackstone & Fuhr, *supra* note 8.

14. *Id.*

15. Kantner & Feldman, *supra* note 1.

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17. *Id.*

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21. Blackstone & Fuhr, *supra* note 8.

22. Erwin Blackstone & Joseph Fuhr, *Unintended Consequences: Generic Competition in the Prescription Drug Market,* Medicare Patient Mgmt., Mar./Apr. 2006, at 25–43, available at http://www.medicarepatientmanagement.com/issues/01-02/MPM01-02_Generics.pdf.

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24. Jeffrey Mann and Stephen Mahinka, *Biosimilars: Patent Challenges and Competitive Effects,* Legal Media Group Life Sciences 2014 at 33–36 (2014), available at http://www.morganlewis.com/pubs/LMG_Mann-Mahinka-BiosimilarsPatentCallenges_sept2014.pdf.

25. Rickwood & Di Biase, *supra* note 7.