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Biosimilars

Biobetters: The Advantages and Challenges of Being Better

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The Biologics Price Competition and Innovation Act of 2009 (BPCIA) was passed as part of health reform signed into law by President Barack Obama in March 2010. The BPCIA created an abbreviated pathway for Food and Drug Administration approval of biologic medicinal products that are ''biosimilar'' to an already FDA-approved product. Because biologic drugs, also referred to as biologics, are complex molecules made in living organisms rather than chemically synthesized, biosimilars are not copies of an approved biologic product. Instead, the BPCIA requires a biosimilar to be ''highly similar'' to the approved product without any clinically meaningful differences in terms of safety, purity and potency.

The FDA recently approved the first U.S. biosimilar: Sandoz's biosimilar of Amgen's Neupogen, a blockbuster drug used to prevent infections in cancer patients. While the FDA currently is reviewing four other proposed biosimilars and additional applications for approval of biosimilar versions of some of the most successful biologic medicines are expected shortly, many innovators and biosimilar manufacturers are responding to the changing landscape for biologics by developing ''biobetters'': new and improved versions of biologic medicinal products.

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While biobetters require discovery and an original Biologics License Application (BLA) with a full complement of pre-clinical and clinical data for marketing approval, they also offer many advantages. By offering a superior or longer-acting medicine, biobetters provide a competitive advantage over biosimilar products. In addition, unlike biosimilars, they generally would be entitled to patent protection and 12 years of non-patent exclusivity under the BPCIA.

Biobetters

Biobetters can provide a substantial difference in clinical efficacy, safety or convenience and they may have fewer side effects or less frequent dosing. Amgen's Neulasta, an improved long-acting version of Amgen's Neupogen that was approved by the FDA in 2002, is one of the early examples of biobetters. Neulasta consists of Neupogen with a covalently bound polyethylene glycol (PEG) molecule that allows Neulasta to be administered less frequently. While Neupogen is administered once daily during a chemotherapy cycle, Neulasta is administered only once per chemotherapy cycle. U.S. sales in fiscal year 2014 for Neulasta were approximately $3.8 billion as opposed to only $880 million for Neupogen, reflecting the commercial value of a biobetter.

Biobetter Strategies

Manufacturers are employing a number of strategies to create biosimilars and many more biobetters are being developed in the face of impending biosimilar competition.

Pegylation (*i.e.*, the addition of PEG) is being used to create long-acting versions of successful biologics. In addition to Amgen's Neulasta, a number of companies have used pegylation to make biobetters of their own drugs or those of other innovators. For example, Roche created a pegylated biobetter of Amgen's Epogen that is sold as Mircera. In 2007, the FDA approved Mircera for once-monthly dosing to anemic patients as opposed to weekly dosing for Epogen. Last year, Biogen Idec obtained approval for Plegridy, a pegylated long-acting

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version of its own Avonex, a treatment for multiple sclerosis.

Innovators also are actively pursuing a number of strategies to create biobetters of some of the most successful antibody products. One such strategy is to prepare a fragment of the originator antibody that retains the efficacy of the antibody, but confers benefits in terms of delivery or safety. For example, Roche's Lucentis, approved to treat age-related macular degeneration and edema, is a fragment of Roche's Avastin antibody, a treatment for colon and other cancers. The antibody fragment may penetrate the eye's retina better than the full antibody and only Lucentis is approved for ophthalmic use.

Antibody-drug conjugates represent another approach to developing biobetters. Roche's Kadcyla, approved in 2013, is a recent example of that strategy. Kadcyla is a conjugate of a cancer-killing agent with Roche's Herceptin antibody, a blockbuster breast cancer treatment. The antibody inhibits a protein that is overexpressed in certain breast cancers. Kadcyla also delivers the cancer-killing agent site-selectively, a one-two punch.

Attempts to reduce a patient's unwanted immune reaction to chimeric antibodies, antibodies with mouse and human protein sequences, have led to the development of humanized biobetters, *i.e.*, antibodies where many of the mouse sequences are replaced with human ones. Roche, as an example, is developing ocrelizumab, a humanized analog of the chimeric Rituxan antibody for treatment of multiple sclerosis. This humanized version of Rituxan is now in phase III clinical trials.

In 2013, Roche obtained approval of another humanized antibody, Gazyva, a Rituxan biobetter that is also known as ''Son of Rituxan.'' Gazyva, a therapy for chronic lymphocytic leukemia, is also engineered to more efficiently trigger an immune response and clear cancer cells. The FDA gave Gazyva a breakthrough therapy designation based on clinical evidence indicating that it offers a ''substantial improvement'' over available therapies, such as Rituxan. If approved for other Rituxan indications, Gazyva is poised to take over the Rituxan market, potentially before biosimilar competition.

Advantages of Biobetters

Biobetters have the potential to offer tremendous commercial advantages over originator or biosimilar drugs as well as to receive patent protection and market exclusivity.

Commercial Value

By providing a more effective or longer-acting medicine, biobetters create the potential to take over and control the market prior to entry of biosimilars of the originator drug. For example, in Europe, where biosimilars of Neupogen are marketed at a 20 percent to 30 percent discount over Neupogen, Amgen has retained significant market share by having Neulasta to offer patients.[1] Neulasta, as a long-acting biobetter of Neupogen, provides advantages to patients that Neupogen or its biosimilars do not have. Similarly, although Granix, Teva's version of Amgen's Neupogen, has been on the U.S. market since 2013, Neulasta continues to be a blockbuster product in the U.S. due to the benefits it provides to patients.

Biobetters also have the potential to reduce healthcare costs due to greater therapeutic efficacy or by having to be administered less frequently, as in the case of Neulasta. Also, unlike biosimilars, biobetters are not faced with the burden of having to be similar to the originator biologic. This frees companies to use more modern and potentially less costly manufacturing methods. In addition, as a better or more convenient medicine, biobetters offer a marketing advantage over the originator biologic or its biosimilars.

Patents

Biobetters also are likely eligible for patent protection. Patents can potentially be obtained for the biobetter itself, a pharmaceutical composition of the biobetter, a method of treatment or manufacture. Biobetters may be eligible for all of the same types of patent protection available for originator biologics. Amgen, for example, obtained patent protection for its Neulasta biobetter. Similarly, Roche obtained patent protection for Mircera (a biobetter of Amgen's Epogen), Gazyva (a biobetter of Roche and Biogen's Rituxan antibody) and Kadcyla (a biobetter of Roche's Herceptin antibody).

Regulatory Advantages and Non-Patent Exclusivity

Biobetters, just as any new biologics, allow manufacturers to avoid the complex litigation provisions, a 12-year bar to final FDA approval and regulatory uncertainty associated with the BPCIA. Because biobetters are approved through submission of a full BLA rather than an abbreviated BLA (aBLA), they are not subject to the litigation provisions of the BPCIA and are not blocked by the originator biologic's 12 years of non-patent exclusivity provided in the BPCIA. Under the BPCIA, a biosimilar cannot receive final regulatory approval from the FDA and cannot be marketed until the reference biologic has enjoyed 12 years of marketing exclusivity from the time it was first licensed. By contrast, the FDA can approve biobetters at any point in time, and therefore biobetters can enter the market prior to the marketing of any biosimilars.

Further, while approval of a biologic through a traditional BLA with a full complement of pre-clinical and clinical data is much more costly than approval through submission of an aBLA, the BPCIA is still a largely untested regulatory pathway. To date, only Sandoz's biosimilar of Neupogen, known as Zarxio, has been approved through the BPCIA regulatory pathway. While Zarxio's approval earlier this year was a milestone event, it is unlikely to offer significant insight into the regulatory requirements for obtaining approval of complex biologics due to its simplicity. Zarxio is a small protein made in bacteria with no glycosylation (attached sugars). Biobetters, by being approved through submission of a traditional BLA, benefit from a more certain and established regulatory approval pathway.

As with other new biologics, the BPCIA provides a significant advantage to biobetters. Biobetters have the potential to receive their own 12 years of market exclusivity from biosimilar competition. The BPCIA automatically provides biobetters with that advantage if the regulatory application is filed by a company that is not related to or a licensee of the company that applied for

[1] Henry Grabowski *et al.*, *Biosimilar competition: lessons from Europe*, Nature Reviews: Drug Discovery, 13, 99-100 (Feb. 2014).

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or manufactured the originator biologic. When the company that applied for approval of the originator biologic seeks FDA approval of a biobetter of its own product, the biobetter will likely receive 12 years of market exclusivity as long as it is a true biobetter, *i.e.*, it is (1) structurally different from the originator biologic and (2) provides a change in safety, purity or potency as compared to the originator product.[2]

Guidance from the FDA confirms that biobetters likely will be entitled to their own 12-year exclusivity.[3] The FDA considers any of the following differences to be a structural modification of the originator biologic for purposes of the 12-year exclusivity provision of the BPCIA: ''any differences in amino acid sequence, glycosylation patterns, tertiary structures, post-translational events (including any chemical modifications of the molecular structure such as pegylation), and infidelity of translation or transcription, among others.'' The typical biobetters strategies, discussed above, all meet this requirement.

In assessing whether such structural differences result in a change in safety, purity or potency as compared to the originator product, the FDA intends to make a case-by-case determination based on information provided by the biobetter applicant about a ''measurable effect (typically demonstrated in preclinical or clinical studies and shown by relevant methods such as bioassays).'' The FDA recommends that the biobetter applicant present ''evidence that the change will result in a meaningful benefit to public health, such as a therapeutic advantage or other substantial benefit when compared to the previously licensed biological product.'' Since the goal of biobetter development is to provide a superior medicine that is meaningfully different in terms of safety, purity or potency, this further requirement should be readily met, providing the biobetter with 12 years of non-patent exclusivity against biosimilar entrants.

Challenges of Biobetters

Biobetters also pose formidable challenges. As with originator biologics, biobetter development is fraught with risk and requires significant research and development. Biobetters are bound to have a higher success rate than originator biologics due to a validated target for the biologic, but an improved biologic is far from certain and may require significant experimentation. In addition, biobetters may have new and unexpected side effects that are different from that of the originator biologic. Approval of a biobetter also requires a traditional BLA with a full complement of pre-clinical and clinical data. As a result, research and development costs for biobetters will be significantly greater than that for a biosimilar of an originator biologic and approach that of an originator biologic. But the development of the biobetter benefits from the established efficacy of the originator biologic and validated target.

Outlook

Biobetters are here now, but, as biosimilar competition looms, biobetters may become the better approach for all biologics manufacturers. With the promise of 12 years of market exclusivity, the possibility of patent protection and the hope of capturing a market before competition arrives, the most important consequence of the BPCIA may not be the introduction of biosimilars, but the incentive for biobetters.

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[2] 42 U.S.C. §§ 262(k)(7)(A) & (C).

[3] FDA, Draft Guidance for Industry: Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (Aug. 2014), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM407844.pdf.