The 20-year clock on drug patents begins ticking upon the invention of a drug, rather than upon drug approval by the U.S. Food and Drug Administration (FDA). The process of FDA approval is lengthy: pushing a novel medication through phase 1, 2, and 3 trials can often approach 8 or more years. Just over a decade ago, the dawn of the anti-vascular endothelial growth factor era ushered in a dramatic change in the treatment of a number of major retinal diseases, now including exudative age-related macular degeneration, vein occlusion, diabetes, and myopic choroidal neovascularization.

The twilight of the patent and exclusivity periods covering Lucentis (ranibizumab; Genentech, South San Francisco, CA) is now upon us, with an expiration date in June of 2020 for the United States and 2022 for the European Union, and Eylea (aflibercept; Regeneron, Tarrytown, NY) is not far behind. This opens the door to the introduction of biosimilar medications, which have the potential to offer significant cost savings to patients, insurers, and society. However, are biosimilars similar enough? As ophthalmologists, we have seen a number of examples of generic drugs that do not perform quite like their branded compatriots in either efficacy or side effects. Biologic drugs are far more complex to produce than small molecules, with greater chance for dissimilarities in effect.

Szilard Kiss, MD, and Jennifer Krawitz, MD, both of Weill Cornell Medical College in New York City, tackle the issues surrounding the introduction of biosimilars in the treatment of retinal disease. This timely review is of high importance due to the impending avalanche of changes to our drug armamentarium.

Coming of Age: Biosimilars

by Szilard Kiss, MD; and Jennifer Krawitz, MD

During the last 10 years, the use of intravitreal anti-vascular endothelial growth factor (VEGF) therapy has tremendously increased and plays an integral role in the treatment of numerous retinal diseases. These medications are considered to be biologics as they are produced in living cells as compared to traditional small-molecule medications that are synthesized through a chemical process. Ranibizumab (Lucentis; Genentech, South San Francisco, CA) and aflibercept (Eylea; Regeneron, Tarrytown, NY) are two U.S. Food and Drug Administration (FDA)-approved biologic agents that are approved to treat neovascular age-related macular degeneration (AMD), macular edema following retinal vein occlusion, diabetic macular edema, and diabetic retinopathy. Just recently, ranibizumab was also approved for myopic choroidal neovascularization. Bevacizumab (Avastin; Genentech, South San Francisco, CA), which is an FDA-approved biologic for the treatment of colon cancer, has also been used as an off-label alternative to ranibizumab and aflibercept for the treatment of these retinal diseases. As of now, these three anti-VEGF agents are the main intraocular therapies used to treat retinal disease; however, this will likely change in the next few years as biosimilars enter the market. This article will address the development and the potential impact biosimilars may have in ophthalmology.

EXCLUSIVITY PERIODS

Currently, drug compounds produced in the United States have a defined exclusivity period during which only the company who manufactured the drug can market it. After the exclusivity period has ended for branded, small-molecule medications, generic medications can be produced to compete with the original medication. Similarly, after the exclusivity period has ended for branded biologic medications, biosimilar medications can be produced and sold. Importantly, the exclusivity period is set to expire for ranibizumab in June 2020 and for aflibercept in June 2027, and there are already many companies developing biosimilar medications to compete with these popular ocular medications.

One of the reasons pharmaceutical companies are investing in biosimilars is because they are a lot less costly to develop.
than bringing a new biologic to market. It is estimated that the cost to develop a new biologic is close to $800 million, whereas the cost to develop a biosimilar ranges from $75 to $250 million. In 2015 alone, Lucentis generated $3.6 billion and Eylea $2.7 billion in global sales, highlighting the reason why biologic companies are interested in entering the ocular biologic marketplace.

One of the reasons for the lower developmental costs has to do with the ability for biosimilars to be approved through an expedited pathway known as the Biologics Price Competition and Innovation (BPCI) Act of 2009, which is part of the Affordable Care Act (Figure 1). In comparison to the development of a new biologic, which focuses on defining efficacy and safety through clinical trials, biosimilar development focuses more on scientific testing and proving that the two agents are similar, with the understanding that similar molecules will produce similar reactions in the body (Figure 2).

**APPROVAL AND DEVELOPMENT OF BIOSIMILARS**

Since the passage of the BPCI Act, a total of seven biosimilars have been approved in the United States, and more than 60 are in development, including many ophthalmologic biosimilars of both ranibizumab and aflibercept. In terms of ocular biosimilars, the company Formycon is furthest along with FYB201.
which is a biosimilar of ranibizumab. The company is currently enrolling patients in a phase 3 clinical trial to compare the safety, efficacy, and immunogenicity of FYB201 to ranibizumab. The company is also in the early stages of development of FYB203, a biosimilar of aflibercept.6,7,8

However, Formycon is not the only company targeting the ocular biosimilar market; Pfenex, Coherus BioSciences, Siam Bioscience, Samsung Bioepis, and Xbrane have all started the development process of a biosimilar to ranibizumab.9

Although ocular-specific biosimilars still remain in the developmental stages in the United States, other countries have already started to incorporate them into their armamentarium. In 2015, India became the first country to approve an ocular anti-VEGF biosimilar, Razumab by Intas Pharmaceuticals was approved as a biosimilar to ranibizumab for the treatment of wet AMD, edema associated with retinal vein occlusions, degenerative myopia, and diabetes. In India, it is offered at a 25% discount compared to Lucentis (Razumab sells for $240 vs. $340 for Lucentis). Unfortunately, Razumab struggled initially with maintaining the quality of its batches, which led to a high rate of ocular inflammation in up to 10% of patients. Once the manufacturing process was revised, no significant adverse events have been reported. Similar to Lucentis, initial reports of Razumab show an improvement in macular thickness and best-corrected vision.6,10,11

HESITATION TO SWITCH

Razumab’s initial struggles highlight the fragility of biologics and is just one of the reasons why practitioners may be hesitant to incorporate new biosimilars into their practice. Another reason why physicians may not be eager to switch to biosimilars has to do with the cost. Biosimilars will be priced lower than their branded counterpart; however, they will still not be cheaper than off-label bevacizumab. Bevacizumab, on average, costs approximately $50 per treatment, whereas Eylea and Lucentis cost approximately $2,000 per treatment.17 If ocular biosimilars follow the same pattern as other biosimilars released in the U.S., we could expect an estimated savings of 15% to 30% off a ranibizumab and aflibercept bio-

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**Figure 2.** The development of a new biologic medication requires significant time and funding to support multiple, large clinical trials to prove efficacy and safety. This is in contrast to the development of biosimilars, which focuses more on the analytical and preclinical studies to demonstrate that the biosimilar is in fact “similar” to the original molecule. Based on the understanding that similar molecules will behave similarly and produce similar results, there is a smaller focus on phase 2 and 3 clinical trials for biosimilars as compared to new biologics. Biosimilar development begins with extensive analytical and functional studies on multiple batches of the original biologic medication. Through reverse engineering, a biosimilar product is created, and its manufacturing process is perfected to produce highly similar medication in each batch. Preclinical functional studies are then performed to verify the same mechanism of action followed by phase 1 pharmacokinetic and pharmacodynamic studies in humans to determine bioequivalence. Lastly, phase 3 clinical studies are done to confirm safety and efficacy.5
similar. However, even with those savings, the final cost of biosimilars would still be nowhere near the cost of bevacizumab. As such, for those physicians who primarily prescribe bevacizumab switching to an ocular biosimilar will only potentially increase one’s costs.

The main demographic that will be impacted by the advent of biosimilars will be those ophthalmologists that frequently prescribe ranibizumab and aflibercept. Like all of us, these physicians have developed their own practice patterns and brand loyalty, so they may not be so eager to switch to a new biosimilar agent. However, with the way health care is changing, physicians may not have a choice but to incorporate biosimilars into their practice.

**POTENTIAL IMPACT**

More than ever, insurance companies are looking for ways to cut costs and save money. Biologics are part of a $7.5 billion industry, and if insurance companies can save 15% to 30% of those costs, it will result in significant savings. Insurance companies are looking at the cost of care by individual providers, which may result in physicians becoming more compelled to choose an FDA-approved biosimilar. Patients may also begin receiving push back from their insurance companies who may only agree to reimburse a biosimilar, forcing those who want a brand name product to pay the difference. Physicians may also need to begin justifying why a patient needs a “brand name only” product over a biosimilar equivalent to obtain coverage.

Although we cannot predict for certain how biosimilars will affect ophthalmology, we know that biosimilars will undoubtedly have a large impact on the United States health care system. Biosimilars will offer an FDA-approved, lower-cost biologic medication that should not compromise on quality, efficacy, or safety standards. Although this may force physicians to incorporate new medications into their practice, hopefully these biosimilars will truly offer an equivalent safety and efficacy profile.

Biosimilars should drive competition while providing savings for patients, providers, and the health care system as a whole, which hopefully will go into the development of the next generation of medications.

**REFERENCES**