

# BIOSIMILARS: NOT YOUR TYPICAL GENERIC

Although the role for this category of medicine in retina is not yet clear, cost will likely be a significant factor.

BY S.K. STEVEN HOUSTON III, MD



The Apple iPhone and Range Rover Evoque are well known and successful products. Wanting to claim a part of that success, other companies have come out with their own versions of each of these products. In the world of ophthalmology, the anti-VEGF drugs ranibizumab (Lucentis, Genentech) and aflibercept (Eylea, Regeneron) are also

well known and successful products, and now companies are developing anti-VEGF biosimilars in attempts to get a foothold in the anti-VEGF market, currently valued at \$7.5 billion and predicted to grow over the coming decade.

This article looks at the anti-VEGF biosimilars arms race and examines what effect it may have on the ophthalmic industry and profession.

## BIOSIMILARS: A PRIMER

What is a biosimilar, and how does it differ from a generic drug? Biosimilars are medicines that are similar to existing, approved biologics. Biosimilars must have no significant differences in quality, effectiveness, or safety when compared with their approved reference biologic.

Calling a large-molecule biosimilar a copycat is not fair because these large-molecule agents are much more complicated to develop than small-molecule generic drugs. The generic drugs most people are familiar with are small molecules developed through chemical reactions. They are 1/1,000th the size of biosimilar molecules, which are developed by modified cellular processes. Furthermore, biosimilars such as monoclonal antibodies can degrade over time and can have significant immunogenicity. As a result, biosimilars are much more complex to design and manufacture than generic drugs.

Technically, bevacizumab (Avastin, Genentech) qualifies as a biosimilar to the approved ophthalmic anti-VEGF agent ranibizumab. However, bevacizumab is used off-label for ophthalmic indications, and it is likely destined to remain off-label despite the CATT study showing its comparative effectiveness with ranibizumab. Off-label use of bevacizumab, as shown in the 2016 American Society of Retina Specialists (ASRS)

Preferences and Trends survey, approaches 75%, and it has been used by retina specialists since 2006.<sup>1</sup> So bevacizumab may be seen as the original disrupter, but new anti-VEGF biosimilars appear poised to make waves in this space.

## The Approval Process

The enactment of the Biologics Price Competition and Innovation Act in 2009 opened the door for biosimilars in health care. In 2015, filgrastim-sndz (Zarxio, Sandoz) was the first biosimilar approved by the US Food and Drug Administration.<sup>2</sup>

Following the precedent of this first approval, biosimilars from several other companies have also been approved (see sidebar The Approval Process in a Nutshell). Once the patents have expired on the reference biologic, a biosimilar can be approved as an interchangeable product for the same indications. US regulatory approval requires a head-to-head comparison of the biosimilar with the reference biologic with respect to safety, quality, and efficacy.

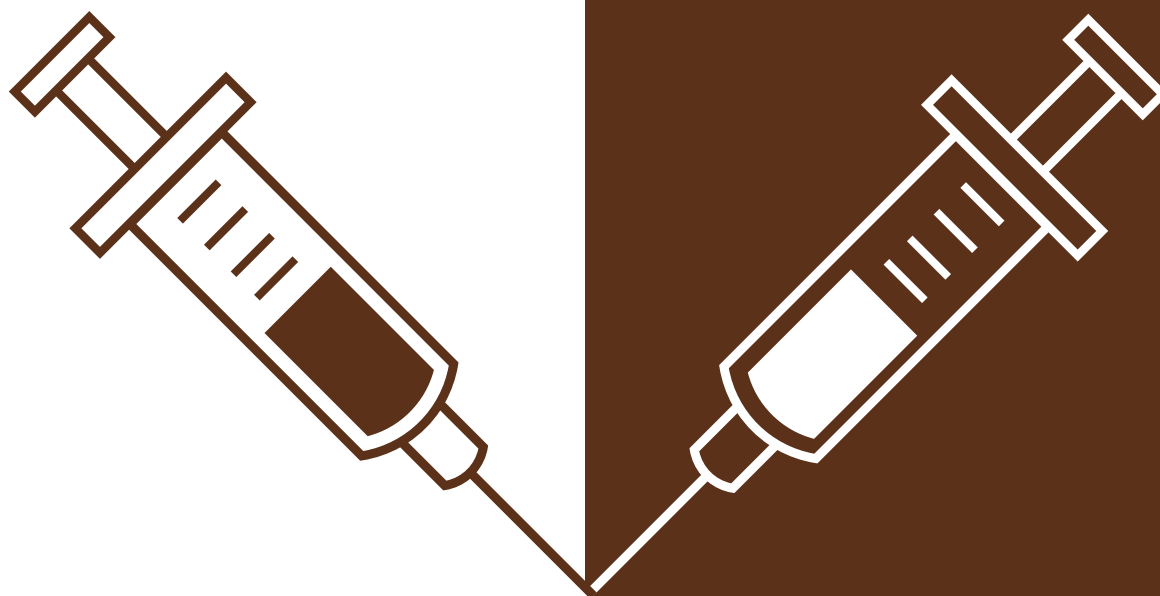
## Biosimilars in the Retina Space

The US patents for ranibizumab and aflibercept will expire in 2020, and European patents will expire for ranibizumab in



## AT A GLANCE

- Biosimilars are medicines that are similar to other already approved biologics and must have no significant differences in quality, effectiveness, or safety.
- Biosimilars, like the biologics they mimic, are large molecules that are developed by modified cellular processes, whereas small molecule generics are developed through chemical reactions.
- Bevacizumab (Avastin) was the original disrupter, but anti-VEGF biosimilars appear poised to make waves in this space.



2022 and aflibercept in 2021. Several companies are developing biosimilars for these two anti-VEGF agents.

Intas Pharmaceuticals developed Razumab as a biosimilar to ranibizumab. Razumab was approved in India in 2015. Following approval, the first three batches of drug showed an ocular inflammation rate of 10%.<sup>3,4</sup> The issue was resolved by revising the manufacturing process. This incident highlighted the significance of biologic stability and of maintaining the quality of each batch of drug. Following this initial setback, positive experiences with Razumab were presented at the ASRS meeting in 2016, with presenters describing short-term improvement in visual acuity and reduction in central retinal thickness in treatment of neovascular age-related macular degeneration (AMD), diabetic macular edema (DME), and cystoid macular edema secondary to retinal vein occlusion.<sup>5,6</sup> Intas Pharmaceuticals is applying to conduct phase 3 clinical studies of Razumab in

the United States.

Formycon, collaborating with Santo Holding, has developed FYB201 as a biosimilar to ranibizumab and FYB203 as a biosimilar to aflibercept. A phase 3 study (NCT02611778) is enrolling patients to compare the safety, efficacy, and immunogenicity of FYB201 with those of ranibizumab. Planned enrollment is 650 patients across more than 80 centers, comparing the two agents head-to-head for treatment of wet AMD. Final data collection for the primary outcome measure is expected in March 2020.

Another company, Pfenex, collaborating with Pfizer subsidiary Hospira, has developed PF582 as a biosimilar to ranibizumab. A phase 1/2 study has been conducted, with 25 patients (13 receiving PF582, 12 receiving ranibizumab) treated with intravitreal injection each month for 3 months. Results of this small pilot study showed no meaningful

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## The Approval Process in a Nutshell

- ✓ The approval process for biosimilars allows the submission of a biological license application for a biosimilar or interchangeable biological.
- ✓ The process requires a biosimilar applicant to demonstrate that there are no clinically meaningful differences in safety, purity, or potency between a biosimilar product and the branded product. A demonstration of biosimilarity requires analytical data, animal testing, and clinical studies, unless a requirement is determined to be unnecessary.
- ✓ The process allows approval of a biosimilar product as interchangeable either at the time of initial approval or after a supplemental approval. An interchangeable product is a biosimilar product that can be substituted for the branded product without the intervention of the health care provider who prescribed the branded product. A demonstration of interchangeability requires evidence that the biosimilar product will produce the same clinical result as the branded product in any given patient and that it presents no additional risk if a patient is switched between products.



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differences in visual acuity, central retinal thickness, or local and systemic safety measures between the two agents. Immunogenicity was also comparable. Long-term studies with more patients are needed to demonstrate the efficacy and safety of PF582 compared with ranibizumab.

Two other companies are developing biosimilars to bevacizumab: Hetero, developing cizumab, and Reliance Life Sciences, developing bevacirel.

### IS THERE A FUTURE FOR BIOSIMILARS IN RETINA?

The role of biosimilars in retina will likely be considerably less than in other fields of medicine that use biologics, mainly because of the established use of bevacizumab and the plethora of data indicating its comparable efficacy to ranibizumab and aflibercept for the treatment of patients with DME and wet AMD. In addition, the cost of bevacizumab is closer to the 80% to 90% reduction common for generic drugs, compared with the 15% to 30% reduction common for biosimilars. Because most retina surgeons already use bevacizumab as first-line therapy in many instances, and physicians have extensive experience with ranibizumab and aflibercept over several years, it will be difficult to convince these physicians to switch to a biologic that has not yet gained their trust.

However, the elephant in the room is the shifting health care landscape, with the transition from the Affordable Care Act to whatever may replace it. For insurance companies, use of a biosimilar that saves 15% to 30% of \$7.5 billion will represent significant savings. We are already starting to see cost factored into future payment reimbursements from Medicare, and insurance companies are paying attention to cost of care by individual physicians. Only time will tell what role biosimilars end up playing in future retina practice. We can look forward to following these developments as we approach the year 2020. ■

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