



## POLICY STATEMENT

### *The Use of Biosimilars in Ophthalmic Practice*

#### Background

Congress, through the Biologics Price Competition and Innovation Act (BPCI Act) of 2009, created an abbreviated approval pathway for biological products that are demonstrated to be biosimilar to or interchangeable with a Food and Drug Administration (FDA)-approved biological product.<sup>1</sup> This pathway was established to provide additional treatment options for patients, increase patient access, and potentially lower health care costs. Manufacturing these large molecules is complex.<sup>2</sup> Biosimilars are not generic drugs and are approved via a distinct pathway.

A biosimilar product has no clinically meaningful differences in terms of safety, purity, and potency to the reference product for its labeled indications, except for differences in inactive components, termed excipients. This is best demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, and an assessment of clinical immunogenicity. The excipients --- including the stabilizer or buffer -- may differ from what is used in the reference product. There should be studies demonstrating safety of those excipients for the approved indication and the target tissue (e.g., the eye). An example was the occurrence of cases of sterile inflammation when the first biosimilar of ranibizumab approved in India was introduced; this problem was addressed through a revised drug formulation.<sup>3</sup>

Biosimilars may be approved for all or a subset of the approved indications for the reference product. Any differences between the proposed biosimilar product and the reference product are evaluated by FDA to ensure the biosimilar meets the FDA's approval standards for safety and efficacy. The FDA does not study the safety or potency of the off-label use of biosimilars or of compounded/repackaged biosimilars.

For ophthalmic biosimilars, systemic pharmacokinetics are not predictive of safety or efficacy, so that, in addition to an analytic similarity comparison, a comparative clinical trial is required. These comparative trials are of similar duration (9 months or more for neovascular age related macular degeneration). Biosimilars require only one comparative efficacy trial, whereas a reference product typically is expected to submit two clinical trials. A reference product can be compared to any anti-VEGF biologic or placebo, but a biosimilar must be compared to the US reference product. The safety for the reference product or the biosimilar is evaluated throughout the duration of the trial (9 months). The efficacy of a reference product is evaluated at the end of the dosing period, typically 9 months, while the comparative efficacy of a biosimilar is made at the most sensitive portion of the efficacy curve, 8 weeks.

An interchangeable product is a biosimilar product that meets additional stringent requirements. The manufacturer needs to show that an interchangeable product is expected to produce the same clinical result as the reference product in any given patient. Data need to show that patients can be switched back and forth with no adverse effects. Under law, an interchangeable biosimilar product may be dispensed without notifying the prescriber in some states.

A biosimilar is identified by a four-letter suffix attached to its name to distinguish it from the reference product. Newer innovator biologics also include a four-letter suffix, but ranibizumab, aflibercept and bevacizumab reference products do not. Biosimilars with FDA-approved ophthalmic indications are anticipated in 2022 in the US. Manufacturers under some circumstances for an existing biologic may pursue normal biologic licensing authority and not follow the biosimilar pathway.

## Recommendations

### *Prescribing Biosimilars*

State rules vary for pharmacist substitution of biosimilars and should be reviewed by each treating ophthalmologist. In cases where a different biosimilar is suggested by the pharmacist or the insurer, the ophthalmologist needs to review the FDA-approved biosimilar's approved indications. For off-label use of biosimilars in the eye, the Academy strongly recommends against biosimilar substitution until there is robust clinical use data available for those indications. The ophthalmologist should assess any medico-legal risk associated with use of biosimilars lacking FDA-approval for intravitreal use.

### *Economics of Biosimilar Use in Eye Care*

Biosimilars may reduce health care costs if they are priced less than the reference product, but should be used only if there is clinical evidence and an FDA-approved indication supporting their use. In ophthalmology, a biosimilar may not be the least expensive option on the market. For example, off-label use of (repackaged) bevacizumab may continue to be less expensive than use of other on-label reference products and new biosimilars.

### *Formulary Inclusion of Biosimilars*

The Academy believes that a biosimilar alternative being added to coverage or preferred coverage status by an insurer for an ophthalmic condition must include robust clinical literature supporting its use for ophthalmic diseases because small variations in excipients can lead to significant and potentially blinding inflammatory complications when injected intravitreally. Alternatively, the biosimilar should be listed in the FDA Clinical Outcome Assessment (COA) Compendium and include robust clinical literature supporting safety and efficacy.

### *Step Therapy using Biologics*

Step therapy is a widely used tool by insurers to reduce health care costs by requiring use of the least expensive treatment first, moving to a more expensive alternative if there is an inadequate response. The Academy does not support step-therapy; the choice of treatment should be that of a patient and their ophthalmologist. A clinical pathway for treatment of eye diseases may include the use of a biosimilar prior to the reference product or another biologic. Insurers promoting such policies need to limit such requirements to appropriate biosimilar products with FDA approved indications and demonstrated safety and efficacy for the eye disease being treated.

Bevacizumab became an accepted off-label ophthalmological therapy for a wide variety of ocular diseases -- most commonly age-related macular degeneration and diabetic retinopathy -- only after extensive studies evaluating its efficacy and safety were completed and prior to development of biologics specifically approved for eye disease. This unique history is not likely to be repeated. Insurers should recognize the situations described below when developing step-therapy programs.

### *FDA-approved biosimilars for ocular therapy*

These biologics will have been tested for safety, purity, and potency in the eye. Byooviz® (ranibizumab-nuna) is the first biosimilar to receive FDA-approval for treatment of neovascular age-related macular degeneration,<sup>4,5</sup> myopic choroidal neovascularization, and macular edema following retinal vein occlusion. Other biosimilar products for eye disease under development and with pathways to licensing in the US include those for aflibercept and bevacizumab.

### *Bevacizumab biosimilars used off-label in the eye*

Bevacizumab is FDA-approved for systemic administration for the treatment of several cancers. Bevacizumab is not FDA-approved for ocular use. It is repackaged by compounding pharmacies as an off-label product. Bevacizumab has been widely studied for eye disease and in 2020 was used in about half of intravitreal injections in the US. It has a favorable ten-year safety profile following the pivotal Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) in 2011.<sup>6</sup>

Bevacizumab biosimilars have been developed for use in the oncologic space including MVASI® (bevacizumab-awwb) and Zirabev® (bevacizumab-bvzr). Certain payers are including these in their

formularies and suggesting their use for ocular indications in place of the reference product, bevacizumab. However, neither available biosimilar has been studied for ophthalmic indications and their inactive ingredients have not all been approved for use in the eye. The Academy strongly recommends against including these in step therapy regimens and/or as replacement for the reference product, bevacizumab, in the absence of sufficient clinical studies for eye disease.

#### *FDA-approved biologics for ocular therapy*

The Academy supports inclusion of biologics FDA-approved for ophthalmic indications in coverage policy for beneficiaries with eye disease. Because patients may respond more favorably to one biologic over another, the choice of agent should remain a decision of the physician and their patient.

## **Conclusions**

The American Academy of Ophthalmology recognizes the potential societal value of biosimilars for improving care of patients with eye disease. Biosimilars should have sufficient research demonstrating their safety and effectiveness for treatment of eye diseases before they are routinely recommended for ophthalmologic use. When used, the choice of biologic product -- reference, biosimilar, or interchangeable -- should be that of the treating ophthalmologist and their patient. The successful and cost effective off-label use of bevacizumab for eye disease for over 15 years represents a unique history of a well-studied biologic agent injected into the eye, which has yet to be duplicated for bevacizumab biosimilars.

Before a biosimilar is required to be used for treatment or included in a step therapy regimen, it should be FDA-approved for the ophthalmic indication. Such a pathway ensures there is evidence of safety -- including for any excipients -- and efficacy for its use in the eye. If that pathway is not possible, the treating ophthalmologist should review the published evidence of safety and effectiveness for any biosimilar proposed for treatment with each patient to determine if it is the best clinical option.

## **References**

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## **Approvals**

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