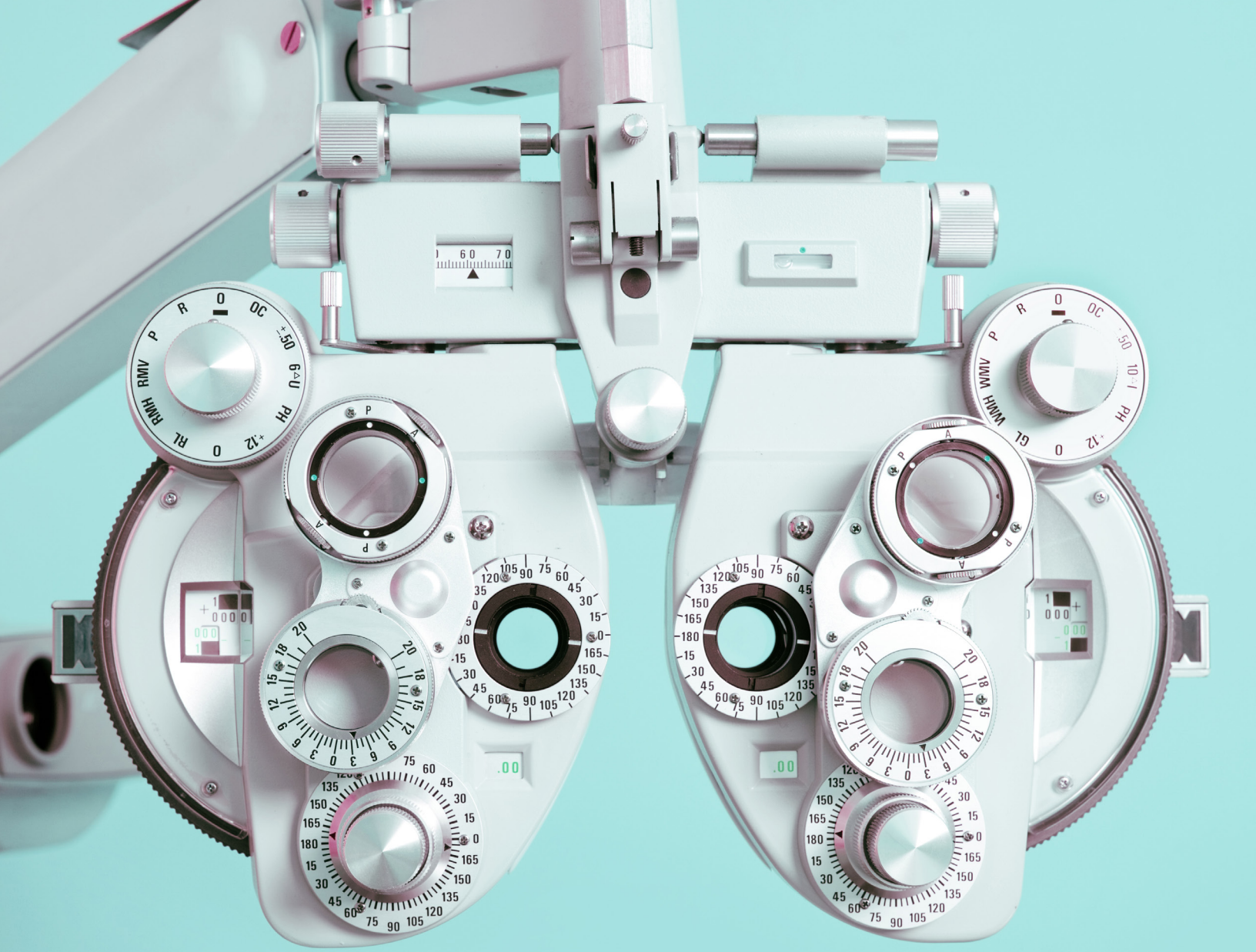

# Biosimilar Market Opportunities in Ophthalmology

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MATRIX GLOBAL ADVISORS

# Introduction

Biosimilars are biologic drugs that are highly similar to and have no clinically meaningful differences from existing reference products. Biologics, which are used to treat a variety of medical conditions, are synthesized from living sources such as human, animal, or plant cells. Because biologics are large and often complex molecules, the decades-old regulatory pathway for generic versions of traditional small-molecule drugs does not apply to biologics. In 2009, Congress created an abbreviated approval pathway specifically for biosimilars. The pathway allows pharmaceutical companies to develop, and the Food and Drug Administration (FDA) to approve, biosimilars at a lower cost than innovator biologics, and savings can be passed on to patients and payers.

The FDA has now approved 36 biosimilars, which compete with 11 reference biologics. These biosimilars, primarily for the treatment of cancer and autoimmune diseases, have increased patient access to valuable medications and reduced prices through competition. Popular ophthalmology treatments are among the next wave of biologics expected to face biosimilar competition.

To drive both swift adoption of ophthalmology biosimilars and the benefits they can bring, stakeholders will have to clear hurdles that exist for biosimilars generally as well as those unique to ophthalmology. The trajectory of current US biosimilars offers valuable lessons in how to overcome these barriers. These lessons include the importance of encouraging and incentivizing biosimilar utilization and the need for education for all stakeholders—from healthcare providers and patients to administrators and payers—on the safety and efficacy of biosimilars. Those who want to ensure ophthalmology biosimilars achieve their full potential should take the time to understand the economics of both ophthalmology practices and ophthalmology biologics in the United States.

# Ophthalmology in the United States

Many of the leading causes of blindness and damaged vision in the United States are age-related, which means that Medicare is a dominant payer in ophthalmology. There are an estimated 52 million annual visits to office-based ophthalmology practices in the United States (*CDC, 2021*). Approximately 57 percent of patients are 65 years of age or older, and Medicare is the primary source of payment for 47 percent of patients (*ibid.*).

Roughly 15 years ago, ophthalmology was revolutionized by the introduction of biologics known as anti-vascular endothelial growth factor (anti-VEGF) agents. Anti-VEGF drugs are intravitreal injections that treat leading causes of vision loss, including wet age-related macular degeneration (AMD), diabetic retinopathy, and retinal vascular disease (*Cornel et al., 2015*).

These drugs have had a large positive impact on patient outcomes (*Finger et al., 2020*). They also have significantly changed ophthalmology practice administration, as these products must be purchased and stocked at an ophthalmology practice in advance so that they can be administered when patients need treatment.

In 2018, 10 percent of total drug spending in Medicare Part B (which covers outpatient services and care) went toward treating ophthalmic conditions, and wet AMD alone accounted for 77 percent of ophthalmic Part B spending (*Avalere, 2020*).

Pronounced population aging over the next several decades will likely result in an increased occurrence of common age-related eye disorders and increased demand for ophthalmic therapies.

## OPHTHALMOLOGY PRACTICE DYNAMICS AND TRENDS

In the United States, there are more than 19,000 actively practicing ophthalmologists. Nearly 18,000 work in patient care, with others in teaching, research, or administrative positions (*AAMC, 2020*). Over the past decade, the number of active ophthalmologists has increased approximately 8 percent (*AAMC, 2012 and 2020*), which slightly outpaces US population growth but is significantly lower than the 65-and-older growth rate (*US Census Bureau, 2020*).

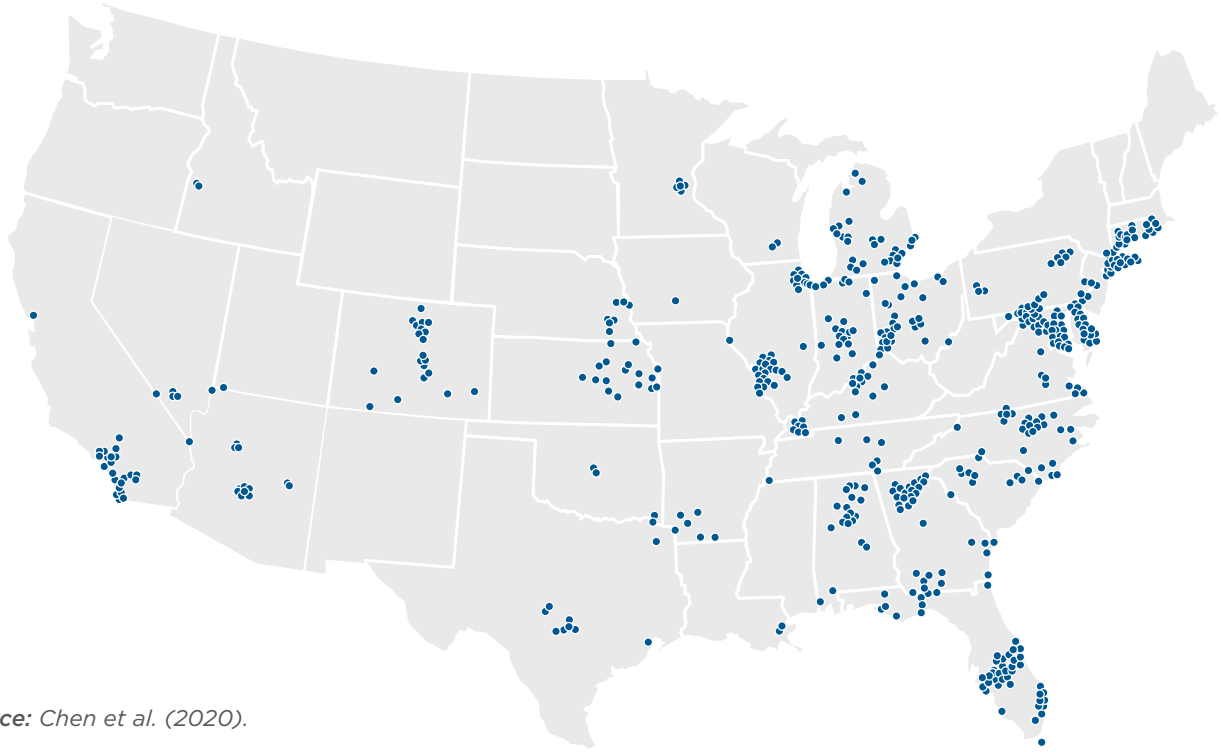
The urban-rural disparity in access to ophthalmology practices is considerable (*Feng et al., 2020*). Physician density is significantly correlated with healthcare infrastructure hubs and areas with greater numbers of college-educated residents (*ibid.*). The largest concentrations of physicians per 100,000 residents can be found in the District of Columbia, Maryland, Massachusetts, and New York (13.61–8.62 physicians per 100,000 individuals in 2020–2021). Access to ophthalmologists is most limited in Wyoming, New Mexico, Nevada, and Idaho (1.37–3.72 physicians per 100,000 individuals in 2020–2021) (*HRSA, 2021*).

Most US ophthalmology practices are small. In 2016, 32 percent of American Academy of Ophthalmology members were in solo practice, and 60 percent practiced in one- to three-person groups (*Parke, 2016*). But evidence suggests that group practices are increasing in prevalence. Data from Ophthalmic Mutual Insurance Company show that group policies more than doubled from 2005 to 2016 (*AAO, 2017*). The next generation of ophthalmologists seems less inclined toward solo practice—among ophthalmologists in training, only 3 percent of those surveyed expressed interest in practicing on their own (*ibid.*). Financial hardships induced by the COVID-19 pandemic may also drive solo and small practices toward consolidation or co-management with optometry practices.

Private equity and venture capital firms are changing the practice landscape as well. As alluded to in the previous section, the rise of anti-VEGF drugs over the past 15 years has changed the business model of ophthalmology practices, requiring more upfront capital and more robust systems for billing, medication management, and ordering (*Stoneback, 2017*). While larger groups and consolidated practices can have some downsides, they have a greater advantage in a capital-intensive business model than solo and small-group practices. Coordinated networks of physicians can more easily control patient feed, devote staff to regulation and billing compliance, and invest in high-cost equipment, which appeals to investors and physicians alike.

Between 2012 and 2019, private equity firms publicly disclosed acquisitions of nearly 140 ophthalmology practices (*Chen et al., 2020*). These practices, with an average of seven ophthalmologists in each, include 841 clinical locations and nearly 1,000 physicians. (**See Figure 1.**) Private equity acquisitions have been accelerating in recent years, particularly in major metropolitan areas, but remain a small share overall.

**FIGURE 1.** OPHTHALMOLOGY CLINICAL LOCATIONS ACQUIRED BY PRIVATE EQUITY FIRMS, 2012–2019



***Source:*** *Chen et al. (2020).*

# Ophthalmology Biologics

**Anti-VEGF biologics used to treat age-related vision loss:**





At present, four anti-VEGF biologics are used to treat age-related vision loss. Eylea® (approved in 2011) is currently the market leader among all drugs in total Medicare reimbursement, with Part B spending on the drug totaling more than $2.9 billion in 2019 (*CMS, 2020*). Lucentis® (approved in 2006) is sixth in total Part B reimbursement, with nearly $1.3 billion in Part B spending in 2019 (*ibid.*). Beovu® (approved in October 2019) is the newest anti-VEGF biologic indicated to treat wet AMD. The FDA updated the Beovu® label in 2020 to include warnings of vision-related side effects. Its market potential is uncertain, as its current usage is effectively halted.

Avastin® is a biologic approved to treat metastatic colorectal cancer, non-small cell lung cancer, glioblastoma, and cervical cancer, but retinal specialists have used Avastin® off-label to treat wet AMD since 2005.[1] A single-use vial of Avastin® can be repackaged by compounding pharmacies into dozens of doses for ophthalmic treatment. One intravitreal injection of Avastin® costs approximately $50, or 30–35 times less than Eylea® and Lucentis® (*Mukamal, 2020*). According to a 2018 survey of nearly 800 retinal specialists, Avastin® was used in 70 percent of wet AMD treatments (*Mehr, 2021*). However, some ophthalmologists prefer to administer, and some patients prefer to receive, drugs with full FDA approval.

## ECONOMICS OF OPHTHALMOLOGY BIOLOGICS

As noted above, ophthalmology practices purchase anti-VEGF biologics directly and stock them on site. After an ophthalmologist administers a biologic to a patient, the practice seeks reimbursement from the insurer (Medicare or a commercial payer). This system is known as "buy and bill."

[1] Avastin® became a widely accepted treatment option after two National Eye Institute–sponsored studies, one published in 2011 (*CATT Research Group, 2011*) and another in 2015 (*Diabetic Retinopathy Clinical Research Network, 2015*), showed Avastin® to be as effective as Lucentis®. A more recent National Institutes of Health–funded clinical trial showed Avastin® to be as effective as Eylea® (*NEI et al., 2021*).

For Medicare patients, physician-administered drugs are paid through Part B, and the reimbursement amount is set at the drug's average sales price (ASP) plus 6 percent (a formula known as ASP+6).

Sequestration of Medicare spending, triggered by the Budget Control Act of 2011, reduced Medicare payments by 2 percent, which set reimbursement at ASP plus 4.3 percent. The CARES Act, legislation passed in 2020 to provide pandemic-related relief, suspended sequestration for Medicare spending from May 1, 2020, through December 31, 2021. The suspension was later extended through March 31, 2022.

Effective July 1, 2022, through September 30, 2022, the Medicare reimbursement limit (ASP+6) for a 0.5-milligram injection of Lucentis® is $1,376. The reimbursement limit for a 2-milligram Eylea® injection is $1,826 (*CMS, 2021*).

Assuming practices can obtain doses of both Lucentis® and Eylea® at their ASP ($1,298 and $1,723, respectively) and Avastin® at $50, they are incentivized to stock and administer the most expensive drug, Eylea®, for which the "+6" is largest ($103 for Eylea®, $78 for Lucentis®, and $3 for Avastin®). For a single patient receiving a typical treatment in both eyes (a single injection in each eye once per month for three months), practices that purchase products at the ASP would be reimbursed an additional $618 for Eylea®, $468 for Lucentis®, and $18 for Avastin®. Practices able to negotiate for prices lower than ASP would receive additional income.

## INNOVATIONS IN OPHTHALMOLOGY BIOLOGICS

The manufacturers of Lucentis® and Eylea® are both working on innovations to their current products. Genentech is gearing up to launch a port-delivery system (PDS) with applications for Lucentis®, and Regeneron is developing a high-dosage form of Eylea®.

Genentech's PDS is a continual-release eye implant designed to eliminate monthly injections of Lucentis®. A doctor would instead refill a patient's PDS device twice a year with a slightly modified version of Lucentis®. In June 2021, the FDA accepted a Biologics License Application under priority review to consider approval for PDS treatment with Lucentis®.

Regeneron recently announced Phase 2 data for a high-dosage form of Eylea®. Phase 3 trials are ongoing. Other efforts to produce advanced versions of Eylea® have been less successful. In 2021, Regeneron ended its collaboration with Ocular Therapeutix to develop a sustained-release formulation and an extended-delivery system like Genentech's PDS.

## OPHTHALMOLOGY BIOSIMILARS

Biosimilars are poised to increase competition significantly in the anti-VEGF market. The first biosimilar of Lucentis®, from Biogen and Samsung Bioepis, launched in June 2022. Byooviz™ is priced 40 percent lower than the Lucentis® list price.

The next wave of ophthalmology biosimilars is expected to enter the market in the latter half of 2023. Bausch + Lomb and Coherus are developing products referencing Lucentis®, and their candidates have already completed Phase 3 trials (**see Table 1**). Amgen, Biogen, Formycon, and Mylan have active or completed Phase 3 trials for biosimilars referencing Eylea® (**see Table 2**).

Biosimilar entrants in the anti-VEGF market are poised to increase competition significantly in the ophthalmology space.

**TABLE 1. LUCENTIS® (RANIBIZUMAB) BIOSIMILARS**

| COMPANY | DRUG | PHASE 3 COMPLETION* | STATUS |
|---|---|---|---|
| Biogen-Samsung Bioepis | Byooviz™ (SB11) | Dec. 2019 | Launched in US June 2022 |
| Coherus-Bioeq | FYB201 | June 2018 | Application scheduled for FDA review Aug. 2022 |
| Bausch + Lomb-Xbrane | Xlucane | Nov. 2021 | Application to be resubmitted after FDA request for more information |

**According to www.clinicaltrials.gov*

**TABLE 2. EYLEA® (AFLIBERCEPT) BIOSIMILARS**

| COMPANY | DRUG | STATUS* |
|---|---|---|
| Biogen-Samsung Bioepis | SB15 | Phase 3 completed Mar. 2022 |
| Mylan | MYL-1701P | Phase 3 completed Apr. 2022 |
| Formycon-Bioeq | FYB203 | Phase 3 active (not recruiting) |
| Amgen | ABP 938 | Phase 3 active (not recruiting) |

**According to www.clinicaltrials.gov*

Several biosimilars referencing Avastin® are already approved, and others are in development. It is unclear, however, what role these biosimilars may have in ophthalmology. Biosimilars referencing Avastin® (Zirabev™ from Pfizer, Mvasi® from Amgen, and Alymsys® from Amneal) have not gained ground in ophthalmology. In fact, the American Academy of Ophthalmology issued a statement opposing the use of these products because they have never been tested in the eye and are not indicated for ophthalmic use (*AAO, 2021*).

## ECONOMICS OF OPHTHALMOLOGY BIOSIMILARS

Increased competition within the large and lucrative ophthalmology market could generate significant cost savings for Medicare and other payers. Evidence from other biosimilar markets in the United States indicates two channels through which cost savings materialize: biosimilars launch at a discount to the reference biologic, and the reference biologic reduces its price in response to competition (*Brill and Ippolito, 2019a*).

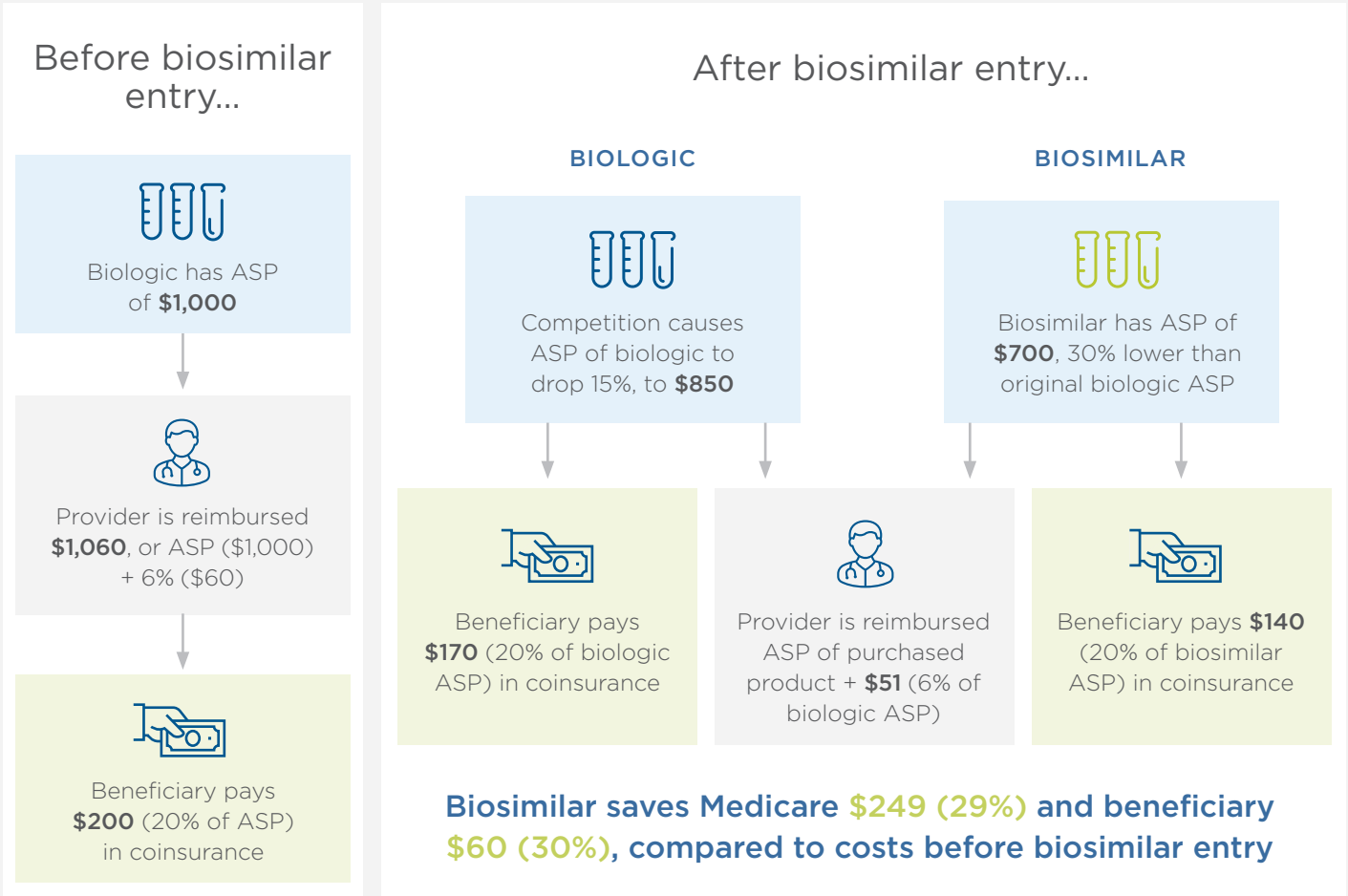
For example, upon market entry of the first FDA-approved biosimilar, Zarxio, its reference product, Neupogen®, saw a significant net price reduction. By 2019, biosimilar competitors of Neupogen® reported ASPs 30–41 percent lower than that of Neupogen® (*Brill and Ippolito, 2019b*). The market entry of more recent biosimilars for other originator biologics has resulted in similar trends.

When the biosimilars pathway was established more than a decade ago, it was accompanied by a unique reimbursement policy in Medicare Part B intended to prevent a disincentive for biosimilar utilization. Specifically, Part B reimbursement for biosimilars is set at the biosimilar's ASP plus 6 percent of the reference product's ASP instead of 6 percent of the biosimilar's ASP (**see Chart 1**).

Consider the example in an earlier section, where ophthalmology practices can obtain doses of Lucentis® and Eylea® at their ASPs ($1,298 and $1,723, respectively). In this scenario, the "+6" for a biosimilar of either product would be the same as the originator—$78 and $103, respectively—regardless of the biosimilar's ASP (if its ASP is lower than the reference product). The intent of this policy is to create neutrality between the add-on payment for a biosimilar and its reference product.

Despite this policy, ophthalmology biosimilars will face other hurdles that may challenge their competitive potential unless stakeholders make a concerted effort to overcome these obstacles.

**CHART 1. EXAMPLE OF BIOLOGIC AND BIOSIMILAR REIMBURSEMENT IN PART B**




***Note:*** *This example is intended to illustrate reimbursement for a Part B biologic for an average Medicare beneficiary. It does not represent actual ASPs or price discounts.*

# Unlocking the Potential of Ophthalmology Biosimilars

Given the billions of dollars spent annually on ophthalmology biologics in the United States, there is tremendous savings potential in ophthalmology biosimilars. But barriers exist to patients and payers realizing these savings. Some barriers arise because biosimilars are relatively new in the United States and not yet available for on-label use in ophthalmology.

But there are additional barriers specific to the ophthalmology market. One is the small size of many ophthalmology practices, requiring numerous unique decisions by solo practitioners or small-group practices to stock and use biosimilars. Another is the potential for Eylea® and Lucentis® innovations that are in the works to draw market share away from biosimilars.

Despite these hurdles, there is hope for ophthalmology biosimilars. The experience in other biosimilar markets suggests that education campaigns that fill biosimilar knowledge gaps and incentives to encourage biosimilar utilization are effective. For example, see the case studies in this paper on US oncology biosimilars (**below**) and European biosimilars (**page 12**).

In short, widespread early adoption of ophthalmology biosimilars will hang on ophthalmologists' and patients' perceptions of the safety and efficacy, as well as the anticipated financial benefits, of biosimilars.

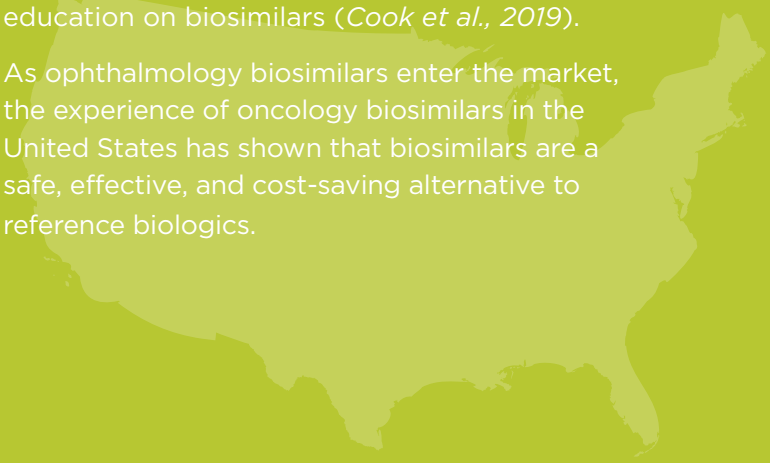
## LESSONS FROM US ONCOLOGY BIOSIMILARS

Of the 36 biosimilars currently approved in the United States, 20 are labeled for oncology use. An increasing number of oncology biosimilars are in the approval pipeline, and the use of biosimilars for cancer patients is increasing rapidly.

Oncology providers are sensitive to the cost of biologics, as high and increasing spending on cancer treatments has created accessibility barriers and disparities in clinical outcomes. Some qualitative data on early adopters of oncology biosimilars suggest that adoption of oncology biosimilars has been driven at the hospital or facility level (*Oskouei, 2021a*).

Some studies suggest that cost is a key factor for individual oncology physicians choosing to prescribe biosimilars (*Kim et al., 2017*), while others find that oncologists need further education on biosimilars (*Cook et al., 2019*).

As ophthalmology biosimilars enter the market, the experience of oncology biosimilars in the United States has shown that biosimilars are a safe, effective, and cost-saving alternative to reference biologics.



## EDUCATING STAKEHOLDERS ON OPHTHALMOLOGY BIOSIMILARS

Education about biosimilars for ophthalmologists, Medicare beneficiaries, and ophthalmology societies is of utmost importance. In particular, with many ophthalmologists in the United States working in small groups and solo practices, the choice to switch to biosimilars will often rest with individual physicians who have to make an active choice about which drug(s) to purchase, stock, and administer.

Ophthalmologists may be less familiar with biosimilars than other specialists are, given that most approved biosimilars are oncology and immunology therapeutics or treatments for inflammation and diabetes, but ophthalmologists appear willing to consider a biosimilar once one is available. In a small survey of retina specialists (37 respondents), Cardinal Health found that 31 percent of respondents "are not very familiar with biosimilars," but 83 percent said they "perceive biosimilars as fitting into the treatment armamentarium to help keep drug costs down" (*Oskouei, 2021b*).

Proactive education initiatives developed by federal agencies and manufacturers will build confidence in biosimilars and encourage uptake. Education campaigns targeting ophthalmologists and their patients should highlight the safety and efficacy of biosimilars and how biosimilar utilization generates savings. Several similar programs currently exist in the United States. (See page 12 for examples in European markets.)

For example, the FDA has been promoting biosimilar adoption with its Biosimilar Education and Outreach Campaign and the more recent Biosimilars Action Plan (*FDA, 2018*). The Biosimilar Education and Outreach Campaign was targeted primarily at prescribers of early approved biosimilars—oncologists, rheumatologists, and gastroenterologists, among others—and focused on definitions and the new FDA approval pathway (*Christl, 2018*).

A key focus of the more robust Biosimilars Action Plan stressed the development of effective communications to promote biosimilars among all stakeholders. The result is a suite of resources and educational materials for healthcare providers and patients available on FDA's website (*FDA, 2021*). In April 2021, the Advancing Education on Biosimilars Act became law, requiring the FDA to expand and maintain education programs informing healthcare providers about biosimilars.

Efforts to educate stakeholders about biosimilars should not be limited to public agency efforts. In fact, manufacturers of biosimilars have launched their own education programs that highlight the technology and manufacturing of specific biosimilar products (*Pfizer, 2021*).

## INCENTIVIZING OPHTHALMOLOGY BIOSIMILAR UTILIZATION

When presented with drugs that are similar in safety and efficacy, as is the case with biosimilars and originator biologics, prescribers do not have a direct incentive to move away from products with which they are familiar. While indirect effects such as a patient's lower out-of-pocket cost-sharing responsibility may encourage physicians to utilize biosimilars, this might not be sufficient to promote their widespread use.

As previously discussed, ophthalmology practices are currently incentivized to stock and administer the most expensive originator biologic or its biosimilar, for which Medicare Part B's "+6" payment is largest. (Recall that the +6 payment for a biosimilar is the same as for the originator if the biosimilar's ASP is lower than the originator's ASP, as illustrated in **Chart 1** on **page 8**.) But this neutrality between the add-on payment for a biosimilar and its reference product does not promote biosimilar utilization.

One opportunity to incentivize the use of ophthalmology biosimilars is through a shared savings model. In the context of Medicare,

this type of payment model aligns physician reimbursement incentives with Medicare's savings objective, benefiting not only Medicare, but also beneficiaries, physicians, practices, biosimilar manufacturers, and ultimately taxpayers who bear the burden of excess costs to the Medicare program.

Suppose ophthalmologists have the choice between obtaining and administering Lucentis® with its ASP of $1,298 or some lower-cost biosimilar entrant. Under the current Part B reimbursement design, ophthalmologists are not incentivized to choose the lower-cost biosimilar. They may decide to continue administering Lucentis®, with which they are more familiar. Medicare, meanwhile, would forgo the savings. It makes sense, then, for Medicare to actively incentivize ophthalmologists to use biosimilars.

There are many ways a shared savings model could be designed. Ophthalmologists choosing to use the lower-cost biosimilar could receive a specified dollar amount or a percentage of the savings generated, with Medicare retaining the remainder. Thresholds and benchmarks for biosimilar utilization could be considered as well, choices that may add efficiency but also complexity.

In a continuation of the example used above, consider a policy that gives ophthalmologists a 10 percent share of Medicare's savings from utilization of a biosimilar instead of an originator biologic. Ophthalmologists choosing to administer the lower-cost biosimilar would be reimbursed an additional $50 (10 percent of the $500 in Medicare savings), raising the total add-on payment to $140 (6 percent of $1,502 plus 10 percent of $500). Medicare's share of the savings would be $450 ($500 minus the 10 percent share paid to the prescriber).

A successful shared savings model for Medicare could be readily implemented by the Center for Medicare and Medicaid Innovation and rely on the existing billing infrastructure for Medicare Part B (*Brill, 2020*). Commercial insurers could also benefit from implementing shared savings models to advance their own cost-saving priorities without jeopardizing patient care.

There are other ways to construct financial incentives for ophthalmologists to use biosimilars. Another option is for a payer to provide ophthalmologists with a more generous reimbursement for biosimilars than for originator biologics. One such proposal is to temporarily reimburse biosimilars at their ASP plus 8 percent of the reference product's ASP (instead of the current system of the biosimilar ASP plus 6 percent of the reference product's ASP). The ASP+8 proposal was featured in the Prescription Drug Pricing Reduction Act of 2019 introduced by Senator Chuck Grassley (R-IA) as well as more recent proposals.

A successful shared savings model for Medicare could be readily implemented by the Center for Medicare and Medicaid Innovation.

## LESSONS FROM EUROPEAN BIOSIMILARS MARKETS

Europe approved its first biosimilar in 2006, four years before an approval pathway was enacted in the United States. Today, the European Medicines Agency has approved more than 80 biosimilars.

European policymakers and stakeholders have put significant effort into both education campaigns and incentives targeting physicians and patients.

Germany, for example, has focused on educating physicians about biosimilars in development. Regional physicians' associations use discussion forums to build physician trust in biosimilars (*IMS Institute, 2016*). Physicians are also incentivized to use biosimilars, which help meet certain budget requirements (*CADTH, 2018*).

In the United Kingdom (UK), national health and regulatory agencies published guides highlighting the safety, efficacy, and cost benefit of biosimilars. UK hospitals and the National Health Service (NHS) also disseminate materials on biosimilar successes and hospital use–cases to promote awareness (*ibid.*).

Several European countries have further incentivized biosimilar uptake by creating programs to share savings with providers. NHS England offers 1 percent of a drug's contract value to providers if they start 90 percent of new patients on a biosimilar and switch 80 percent of existing patients to a biosimilar (*ibid.*). Ireland offers hospitals 500 euros for each patient switched from Humira and Enbrel to lower-cost biosimilars (*GaBI, 2019*).

While there are many lessons to highlight from Europe's successful experiences with biosimilars, some European practices should not be adopted in the US market. For example, US policymakers should avoid price controls for pharmaceuticals, which risk discouraging potential manufacturers —innovators and competitors alike—from entering the market.

## Conclusion

The first wave of ophthalmology biosimilars is poised to enter the US market. These treatments for common retinal vascular disorders have the potential to generate significant savings for the US healthcare system and increase access for patients. Stakeholders should anticipate—and work in advance to overcome—barriers to market uptake of these products. Educating ophthalmologists, practice administrators, payers, and patients on the safety and efficacy of biosimilars will help support their early adoption. And reforms or payment models that improve alignment of physician, patient, and payer incentives are well suited to promote ophthalmology biosimilar utilization and savings.

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## ABOUT MGA

MGA is a boutique economic policy consulting firm in Washington, DC. Founded in 2007, MGA specializes in healthcare, tax, and fiscal policy. Drawing on years of policy experience, the MGA team uses analytics to help identify, quantify, and solve economic policy problems. On behalf of clients, MGA conducts original data analysis, constructs economic models, conducts research, writes white papers and expert reports, and offers strategic advice.

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