The Seybold Report
ISSN 1533-9211
DOI: 10.5281/zenodo.10153134

BIOSIMILARS IN OPHTHALMOLOGY: A REVIEW

JAWAHAR LAL GOYAL*

Professor and Head of Ophthalmology, SMS&R, Sharda University, Greater Noida, U.P.
*Corresponding Author Email: dr_jlgoyal@rediffmail.com

PREETI BHARDWAJ

Junior Resident, Department of Ophthalmology, SMS&R, Sharda University, Greater Noida, U.P.
Email: preetibhar1997@gmail.com

HOLMES NAOREM

Senior Resident, Department of Ophthalmology, SMS&R, Sharda University, Greater Noida, U.P.
Email: ace.hotahoris@gmail.com

PULKIT GANDHI

Assistant Professor, Department of Internal Medicine/ Nephrology, Lake Erie College of Osteopathic Medicine, Rochester, NY. Email: dr.pulkitgandhi@gmail.com

Abstract

There has been a parallel advancement in the field of biosimilars with other recent biologic medications like cell line science and protein expression science. These are molecules that are chemically similar to their already approved biological medication counterparts which enable a faster and more cost-effective production as they only require one clinical trial, unlike the reference product which has to usually undergo two. Recently, various biosimilars for ophthalmic use have been developed and studied in various parts of the world. Razumab, a biosimilar to Ranibizumab approved in India in 2015, has been extensively studied in clinical trials which has shown its effectiveness and safety in various chorioretinal vascular diseases. The future of the field of biosimilars is expected to be shaped by several factors like healthcare policies, increased market penetration, and competition. Hence, further studies and research need to be conducted in this lucrative field of biosimilars.

Keywords: Biosimilars, Ophthalmology, Razumab

INTRODUCTION

The development of biosimilars is progressing in parallel with advancements in cell line science, protein expression science, and bioengineering, mirroring the progress made in their corresponding biologic medications. Bio similar are molecules that bear a chemical resemblance to already-approved biologic medications, and offer a compelling alternative to their original counterparts, as pharmaceutical companies can create pharmaceuticals that are sufficiently equivalent in terms of safety and effectiveness to established biotherapeutics. They allow for faster and more cost-effective production compared to their original equivalents.[1,2]

The Biologics Price Competition and Innovation Act of 2009 introduced an expedited review process for biological products that demonstrated similarity or interchange ability with an FDA-approved biological product.[1] The primary objective of this pathway was to enhance patient access to a wider range of treatment options and potentially reduce healthcare costs.[3] Developing these complex molecules presents significant challenges, distinguishing

The Seybold Report
ISSN 1533-9211
DOI: 10.5281/zenodo.10153134

biosimilars from generic medications and subjecting them to a distinct approval process.

A biosimilar product is essentially indistinguishable from the reference product, except for minor differences in the inactive components called excipients. It shares the same level of safety, purity, and potency as the reference product, specifically within the indications stated on its label. The evaluation of biosimilars includes studies on human pharmacokinetics (exposure) and pharmacodynamics (response), along with an assessment of the clinical performance of biosimilars that have been compounded or repackaged. This comprehensive evaluation ensures that biosimilars maintain the necessary standards to be considered equivalent to the reference product.[4]

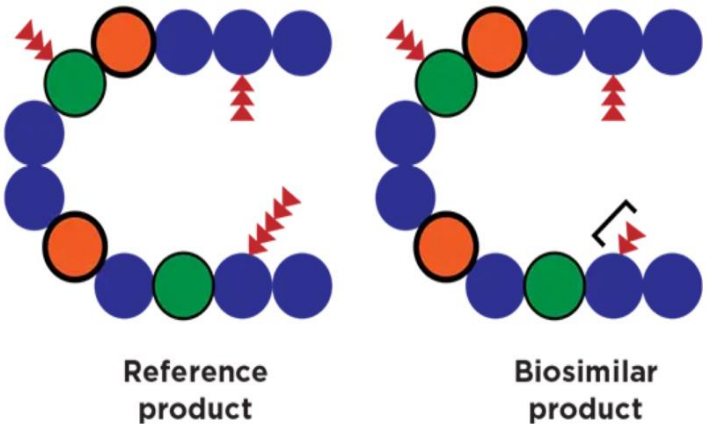


Fig 1: Biosimilar product is never exactly but nearly similar to reference product (Derived from FDA source.)

To determine the safety and efficacy of ocular biosimilars, a comparative clinical study is necessary. These studies typically span nine months, with the duration potentially being longer for conditions like age-related macular neovascular degeneration.

While a reference product is typically required to undergo two clinical trials, biosimilars only need to conduct one comparative efficacy trial, whereas reference products must undergo two. Furthermore, a biosimilar must be compared specifically to the US reference product, rather than any anti-VEGF biologic or placebo.

Both the reference product and the biosimilar are evaluated for safety. At the conclusion of the dosage period, the effectiveness of the reference product is assessed. On the other hand, the comparative efficacy of a biosimilar is determined at a critical point on the efficacy curve, which is typically eight weeks, rather than the standard nine-month duration.

An interchangeable biosimilar product is one that meets more stringent requirements. A biosimilar product must demonstrate the same clinical outcomes as the reference product for any given patient, and switch between the products must not have any negative impact on patients.

The Seybold Report
ISSN 1533-9211
DOI: 10.5281/zenodo.10153134

In some regions, it is legally permitted to dispense an interchangeable biosimilar without explicitly informing the prescribing doctor.

To differentiate a biosimilar from the reference product, a four-letter suffix is added to the name of the biosimilar. This suffix is not applicable to non-living objects. For instance, recent innovator biologics like ranibizumab, aflibercept, and bevacizumab have been assigned a four-letter suffix.

The field of Ophthalmology, particularly the subspecialty focusing on the retina, has undergone a profound transformation with the introduction of anti-vascular endothelium-derived growth factors (anti-VEGF) over 15 years ago. This innovation has led to the development of approved and groundbreaking anti-VEGF treatments, including ranibizumab (Lucentis®; Genentech, Inc., South San Francisco, CA, USA), aflibercept (Eylea®; Regeneron Pharmaceuticals, Inc; Tarrytown, NY, USA), and the off-label use of bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA, USA). These molecules have played a pivotal role in revolutionizing the management of various retinal vascular diseases, bringing about a substantial positive impact.[5,6] The expiration of patents has marked the onset of a new era characterized by the emergence of biosimilars.[7]

In the United States, the introduction of biosimilars with FDA-approved ophthalmic applications took place in September 2021 when Byooviz got approved. Under certain conditions, manufacturers of existing biologics can choose to pursue the standard biologic licensing process and forgo the biosimilar pathway.

While biosimilars are relatively novel in the field of ophthalmology, their successful utilization has already been established in various other subspecialties. These include disciplines like rheumatology, dermatology, gastroenterology, oncology, and hematology, where biosimilars have demonstrated effectiveness.[8]

Biosimilars: Points to Consider

Safety and Effectiveness

The biosimilar approval procedure emphasises approximate equivalence rather than absolute identicality between the reference product and the biosimilar. For biosimilar certification, the FDA typically demands three major requirements: analytical verification of biosimilarity, animal tests to evaluate toxicity, and a succinct clinical study. A biosimilar is based on a reference product that has already been proven to be safe and effective. The manufacturer must demonstrate the biosimilar's resemblance in terms of absorption, excretion, levels achieved within the body, and in vitro activity ambiguity. While biosimilars are considered to be generally safe, there is some ambiguity when compared to identical twins.

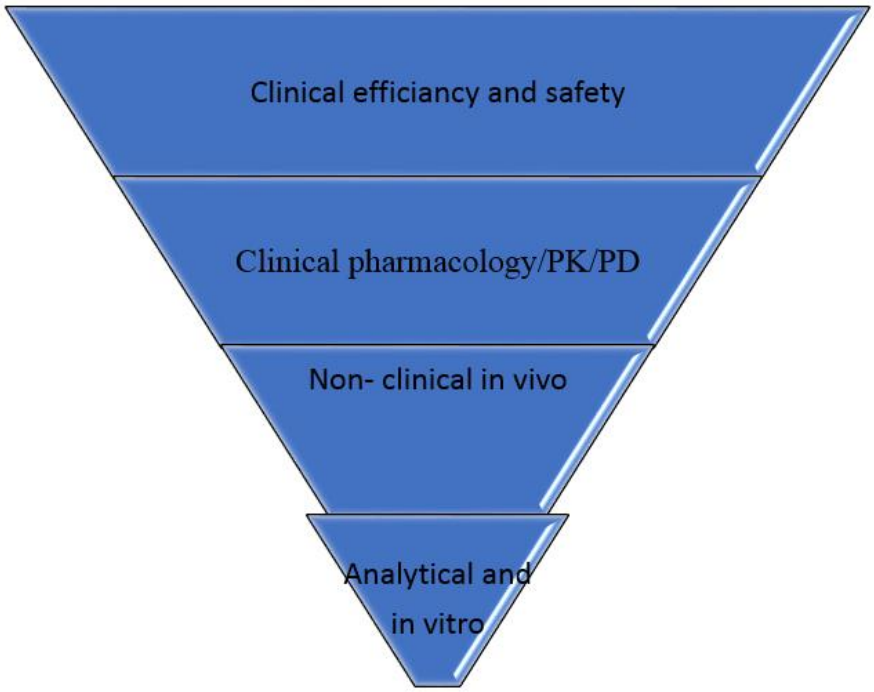
The goal is to show similarities to the original product, for which a benefit-risk profile has already been established, rather than to re-establish a product's efficacy/safety profile. A pharmacological comparison (non-clinical comparability) comes next, followed by a determination of similarity in terms of quality (physicochemical and biological), and clinical comparability (clinical trials) comes last.[9] According to Fig. 2 [10] The initial (analytical) step of

The Seybold Report
ISSN 1533-9211
DOI: 10.5281/zenodo.10153134

establishing that the biosimilar is chemically, structurally, and physiologically very similar to the originator molecule receives the majority of regulatory attention in the case of biosimilars. The biosimilar will only be subjected to further examination in research involving people if these requirements are satisfied. The determination of the pharmacokinetic (PK) profile is typically the first step in this process. It should be noted that phase I studies for biosimilar candidate items used to treat retinal vascular diseases have not been conducted due to the minimal significance of systemic pharmacokinetics and pharmacodynamics brought on by intravitreal delivery.

These studies are carried out in a patient population that is representative of the approved therapeutic indications for the reference product and that will be sensitive for detecting potential differences between the reference and the biosimilar, with the aim of excluding clinically meaningful differences in efficacy, safety, and immunogenicity.[11] The most common design is an equivalency one with symmetric inferiority and superiority margins.[12]

Like with all biological products, producers of biosimilars must offer regulatory agencies comprehensive post-approval risk management strategies and pharmacovigilance initiatives to characterise, reduce, and identify a drug's significant risks when administered to a larger patient population.[13]



ISSN 1533-9211

DOI: 10.5281/zenodo.10153134

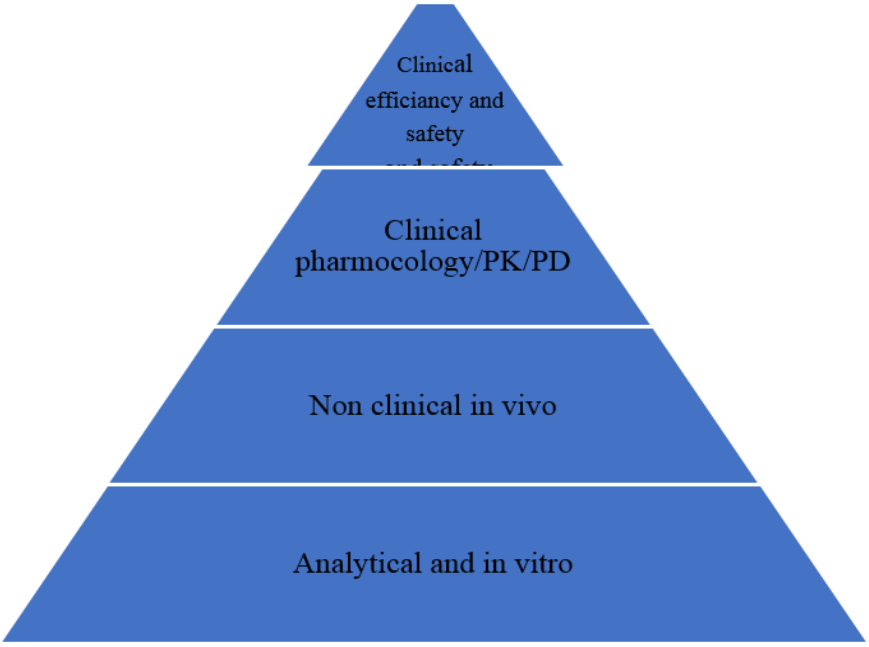


Fig 2: A comparison of the development processes for reference biologics and biosimilars (Reproduced from Future Oncol. (2021) 17(19), 2529–2544)

However, it is critical to note that biosimilars are not needed to demonstrate independent safety and efficacy, which offers some challenges.

The FDA does demand proof demonstrating safety and effectiveness comparability between a biosimilar and the reference medication. It is understood, however, that the data collected with the biosimilar will never be completely equal to that obtained with the original product.

To achieve a high level of purity and prevent toxicity, critical purification stages are used in the manufacture of antibodies, particularly during the injection of the material. These purification stages are critical for ensuring the biosimilar's safety and effectiveness. While the biosimilar strives to reach a comparable level of purity, it is acknowledged that due to the nature of the manufacturing process, there may be some discrepancies between the biosimilar and the reference product.

Cost-Effectiveness

Statistics are difficult to get because of the nature of the biosimilar approval process. Although just two RZB biosimilars have been licenced, a huge number are in development and might substantially reduce the cost of this vital treatment. From 2008 to 2021, RBZ and Aflibercept accounted for more than 10% of all Medicare Part B expenditures, with an average cost of $1,673.59 and $1,385.95 per 0.5 mg therapy, respectively. The current Medicare allowed payments for accessible biosimilars are $1805.99; we must utilise the Medicare authorised payments for each reference drug and compare them to the biosimilars' wholesale acquisition costs (WACs), as their Medicare permitted payments are currently unavailable as of November

The Seybold Report
ISSN 1533-9211
DOI: 10.5281/zenodo.10153134

12, 2020.[4] The WACs for RZB-nuna 0.5 mg, RZB-earn 0.3mg, and RZB-earn 0.5mg are $1130, $816, and $1360, respectively. Medicare payments of 83.104% and 21.2% of the average sales price (ASP) are used to calculate the patient cost.

Medicare would save $132 million and patients would save $33.6 million if all patients currently receiving RZB 0.5 mg, RZB 0.3 mg, or Aflibercept 2 mg were switched to a lower-cost biosimilar.[3] In order to stimulate the adoption of biosimilars, the 'Inflation Reduction Act' boosts the "add-on" for certain qualifying biosimilars from 6% to 8% of ASP for a five-year period commencing in October 2022.

The consequences of this payment mechanism are uncertain. Biosimilars are frequently seen as more cost-effective substitutes for their reference biologic items. Because biosimilars are often priced lower than reference biologic drugs, healthcare systems, payers, and patients benefit from cost savings. Biosimilar competition can lead to price reductions for both the biosimilar and the reference product.[14]

Access: The emergence of biosimilars can improve patient access to biologic medicines by providing more economical alternatives. This increased availability may result in better patient outcomes as more people obtain critical therapies.

Market Competition: The entrance of biosimilars onto the market causes firms to compete. This competition has the potential to bring down prices and encourage cost-cutting solutions, benefiting both healthcare systems and patients.

Potential Cost reductions: The use of biosimilars has the potential to result in considerable cost reductions for healthcare systems and payers. These savings can be utilised to fund other healthcare activities or to increase healthcare access.

Several variables, including the particular biosimilar, the therapeutic area, the pricing strategy, and the regional healthcare environment, might affect how cost-effective a biosimilar is. The cost-effectiveness of biosimilars in particular contexts is often evaluated through comparative studies and health economic analyses.

Ultimately, decision-makers must take into account a variety of aspects when assessing the value and possible savings of biosimilars because it is a complicated and developing topic.

FDA approved biosimilars:

As per a recent survey carried out by the Vitreo Retina Society of India, the adoption of ranibizumab biosimilars has exhibited a consistent upward trajectory following their introduction in the Indian market.[15]

Biosimilars to Ranibizumab that have been approved by the FDA are being developed by a number of different manufacturers; some of these products have already achieved this status, while others are currently in the research and development stage. For their medicine Razumab, Intas Pharmaceuticals Ltd. has received approval in India. Additionally, the South Korean company Samsung Bioepis recently received approval for its biosimilar drug Byooviz (SB11) from both the US FDA and the EMA.

The Seybold Report
ISSN 1533-9211
DOI: 10.5281/zenodo.10153134

Six other biosimilars, including FYB 201 from Germany, Xlucane from Sweden, R-TPR-024 from India, SJP-0133 from Japan, LUBT010 from India, and CKD-701 from South Korea, are also undergoing advanced clinical trials.

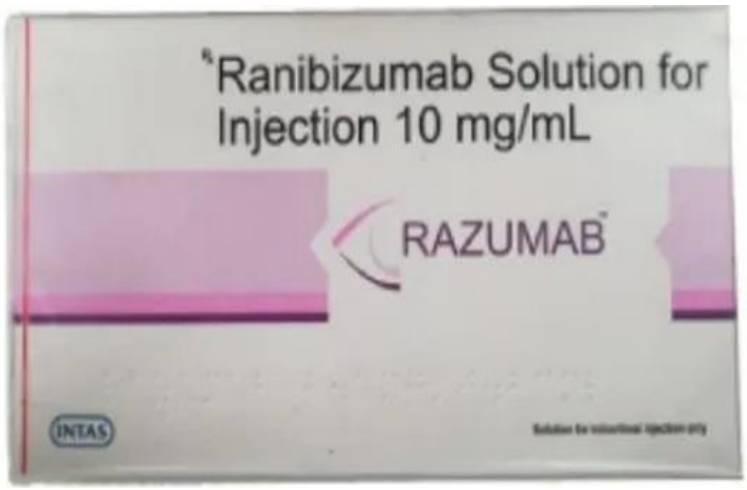


Fig 3: Razumab (Intas Pharmaceuticals Ltd., India): A biosimilar of Ranibizumab

Ranibizumab biosimilar Razumab® (Intas Pharmaceuticals Ltd., India) was authorised in that country in 2015. It has been thoroughly investigated in clinical trials, including one with 104 Indian patients with wet AMD in the third phase. Its effectiveness and safety in treating various chorioretinal vascular illnesses have been demonstrated in a number of retrospective and prospective investigations, including the RE-ENACT trial and the CESAR research.[16,17,18] The biosimilar has equaled the success of the original biologic in terms of popularity and sales. Adverse medication reactions were once a source of concern, however these issues were resolved thanks to improved production techniques.

Numerous additional biosimilars of ranibizumab have been introduced to the Indian market in recent times, including products like RanizuRel™ by Reliance Life Science, headquartered in Mumbai, India.[19]

Biosimilar to Aflibercept

Aflibercept's biosimilar is called MYL-1701P (Momenta Pharmaceuticals and Mylan NV, USA). In September 2021, a randomised, double-blinded, active control study involving 324 individuals with central DME and diabetes mellitus was finished. Participants in the research were randomly randomised to receive intravitreal therapy with MYL-1701P or Eylea® (the reference aflibercept) in a 1:1 ratio. The goal of the producers was to receive marketing permission in USA by 2023.

Phase 3 clinical trials for the treatment of neovascular age-related macular degeneration (AMD) are now being conducted with Amgen's A BP-938.566 participants with neovascular age-related macular degeneration (AMD) will be randomly assigned to receive either ABP-938 or the innovator drug aflibercept every eight weeks in the randomised multicentre trial. Patients

The Seybold Report
ISSN 1533-9211
DOI: 10.5281/zenodo.10153134

receiving aflibercept will be randomised once more in a 1:1 ratio after 16 weeks, with 50% of them switching to injections of ABP-938. A follow-up phase of 52 weeks will come after a 48-week therapy session. By July 2023, the study should be finished.

Additionally, FYB203, created by the German company Formycon AG/Bioeq, is undergoing Phase 3 clinical studies to treat AMD. For the first three doses of the MAGELLAN-AMD research, which started recruiting participants in March 2020, 400 patients were intravitreal injections of FYB203 once every four weeks. Thereafter, injections were given once every eight weeks until the study's conclusion. For the treatment of AMD, SB-15 is presently conducting Phase 3 clinical studies, while SOK583A19 is also undertaking these trials. The MYLIGHT research compares the effectiveness, safety, and pharmacokinetics of SOK583A19 against Eylea in a parallel, double-blind, randomised fashion. Phase 3 clinical studies for Celltrion's CT-P42, which treats diabetic macular oedema, have begun 300 individuals randomly assigned recipients will either get CT-P42 or the control product.

An ongoing randomised, double-masked, multicenter trial comprising 446 patients was started in the study in June 2020. For the first three months, participants were randomly assigned to take SB-15 or aflibercept every four weeks; thereafter, every eight weeks until Week 48. After week 32, participants in the aflibercept group was divided into two groups through rerandomization; one group was given SB-15, and the other group was kept on aflibercept. Up until week 48, the individuals will receive the prescribed treatment once every eight weeks. Week 56 will mark the conclusion of the study. At 8 weeks, the change in best-corrected visual acuity (BCVA) will be assessed as the primary outcome. Phase 3 clinical trials for the treatment of AMD are now being conducted using drug 5 SOK583A19 (Sandoz, Switzerland). The ongoing MYLIGHT research, which was started in May 2021, compares the effectiveness, safety, and pharmacokinetics of SOK583A19 against Eylea in 460 participants from 20 different countries. Clinical studies for CT-P42 (Celltrion, South Korea) have begun in Phase 3 for the treatment of diabetic macular edoema (DME). The randomised, active-controlled, double-masked study, which got underway in February 2021, compares the effectiveness and safety of CT-P42 with Eylea. The primary outcome will be the clinical response in BCVA using the ETDRS chart, with a total of 300 participants being randomised 1:1 to receive either CT-P42 or the reference product.

Phase 1 clinical trials were launched by ALT-L9 (Alteogen, South Korea) to compare the effectiveness of Bevacizumab with Ranibizumab. Bevacizumab biosimilars have previously received approval in a number of cases. Although this medication's primary use is in oncology, it has grown in popularity as an off-label medication used in ophthalmology. Bevacizumab is now being used more frequently in ophthalmological treatments as a result of this. Currently, Outlook Therapeutics is developing ONS-5010, a brand-new bevacizumab biosimilar. The company's investigational new drug application for ONS-5010 has been approved by the FDA. Patients with neovascular age-related macular degeneration (AMD) are being enrolled in phase 3 clinical trials to compare ONS-5010's efficacy with Bevacizumab utilising the PIER dosage regimen.[7] If authorised, ONS-5010's intravitreal formulation could eliminate the need for compounded Bevacizumab, albeit this could push

The Seybold Report
ISSN 1533-9211
DOI: 10.5281/zenodo.10153134

up the price of the drug. A bioequivalent to Adalimumab (Humira®) Certain patients with noninfectious uveitis who are commonly treated with the three medications described above in the field of ophthalmology can benefit from an affordable biosimilar of adalimumab.[20]

The first Ranibizumab biosimilar, Razumab® (Intas Pharmaceuticals Ltd., India), received Indian regulatory approval in 2015 and has since grown in popularity and sales success to par with the original biologic. Adverse medication reactions were once a source of concern, however these issues were resolved thanks to improved production techniques. Razumab® (Indian company Intas Pharmaceuticals Ltd.) Ranibizumab's biosimilar, which was licenced in India in 2015, has equaled the original biologic in terms of popularity and sales performance. Its effectiveness and safety in treating a variety of chorioretinal vascular disorders have been demonstrated through considerable research in clinical studies. The biosimilar has equaled the success of the original biologic in terms of popularity and sales. Initial worries about negative medication effects surfaced, however these were resolved by better manufacturing procedures. It has been thoroughly investigated in clinical trials, including one with 104 Indian patients with wet AMD in the third phase. Its efficacy and safety in treating various chorioretinal vascular diseases have been demonstrated in a number of retrospective and prospective investigations, including the RE-ENACT trial and the CESAR study.[21] The biosimilar has equaled the success of the original biologic in terms of popularity and sales. Initial worries about negative drug reactions were raised, however they were resolved by better production procedures.

Off Label Use of Biosimilars

For uses or patient populations that have not been officially approved by regulatory authorities, biosimilars can be used off-label in ophthalmology. By providing cheaper purchase prices, they can increase therapy accessibility and widen treatment options. Despite their clinical efficacy, many bio-originators are frequently prevented from receiving licences for less common inflammatory disorders due to the high costs involved in getting marketing authorisation.[20] Biosimilars can improve access to biologics for off-label use in treating these patients by providing cheaper acquisition costs.[20] Furthermore, they can provide doors for investigating off-label therapies in circumstances where biologic therapy is not yet well-established. Although it is necessary to maintain post-marketing surveillance, it is critical to recognise that off-label prescribing may expose patients to risky and inefficient treatments. This surveillance is essential for creating long-term proof that guarantees patients' safety and efficacy.

Future Expectations

Forecasting the trajectory of biosimilars within ophthalmology presents a challenge at this juncture. This is attributed to the unique characteristics of ophthalmology that set it apart from other medical specialties, a distinction magnified by the diverse factors that distinguish developing nations from their developed counterparts.[22]

Several elements, including rising market penetration, escalating market rivalry, and healthcare regulations, are anticipated to have an impact on the future of biosimilars. Expanding Clinical Applications: Biosimilars are entering new clinical applications in ophthalmology,

The Seybold Report
ISSN 1533-9211
DOI: 10.5281/zenodo.10153134

dermatology, neurology, and other areas where biologic treatments are commonly employed. As more biosimilars are approved for a wider range of uses, competition may grow and more people may have access to more treatment alternatives. Regulatory developments: To provide clearer pathways for development, licencing, and interchangeability, regulatory bodies around the world are improving rules and regulations for biosimilars. The adoption of biosimilars may increase as a result of ongoing regulatory process improvements that increase patient and provider confidence. Interchangeability and Substitution: The ability to swap between a biosimilar and its reference product without sacrificing safety or effectiveness is referred to as interchangeability. Healthcare systems may introduce rules to ease their usage, such as automatic substitution at the pharmacy level, as more biosimilars prove their interchangeability. This could result in a greater acceptance of the technology and cost savings.

Biobetters and Next-Generation Biosimilars: These upgraded versions of reference biologics, which offer enhanced features such greater efficacy, safety, or convenience, are known as biobetters and next-generation biosimilars. Next-generation biosimilars can have cutting-edge delivery methods as well. These developments could increase the value proposition of biosimilars even more and boost their market share. Ildong Pharmaceuticals is developing a biobetter that uses Ranibizumab to treat age-related macular degeneration, while Genentech is creating a port-based delivery system for Ranibizumab. Due to an improved manufacturing procedure, Alteogen is creating a biosimilar version of aflibercept that delivers noticeable enhancements in terms of shelf life and heat resistance. Biobetters hold the potential to be a significant disruptive force. However, at present, the absence of well-defined regulatory frameworks for biobetter approval poses a challenge.[23]

CONCLUSION

There has been a massive advancement in biosimilars in recent years. Owing to their high index of safety, effectiveness and, more importantly, cost-effectiveness and increased accessibility, these ever-evolving fields promise immense benefits to the healthcare system and patients. Hence, more studies need to be dedicated to this lucrative field of biosimilars and biobetters.

References

1) Biosimilars. U.S. Food and Drug Administration. https://www.fda.gov/druqs/therapeutic bioloqics-applications-bla/biosimilars. Accessed on July 2, 2023.

2) Sharma A, Kumar N, Parachuri N, Bandello F, Kuppermann B, Loewenstein A. Biosimilars for retinal diseases: An update. Am J Ophthalmol. 2021; 224:36–42.

3) Calvo B, Gorostiaga M, Echevarria E. The surge in biosimilars; considerations for effective pharmacovigilance and EU regulation. *Therapeutic Advances in Drug Safety* 2018;9(10):607-608.

4) Sharma A, Kumar N, Kuppermann B, Bandello F, Loewenstein A. Ophthalmic biosimilars and biologics - role of endotoxins. *Eye* 2020; 34:614-615.

5) Finger R, Daien V, Eldem B, Talks J, Korobelnik J, Mitchell P et al. Anti-vascular endothelial growth factor in neovascular age-related macular degeneration – A systematic review of the impact of anti-VEGF on patient outcomes and healthcare systems. BMC Ophthalmology. 2020; 20:294.

The Seybold Report
ISSN 1533-9211
DOI: 10.5281/zenodo.10153134

6) Yorston D. Anti-VEGF drugs in the prevention of blindness. Community Eye Health. 2014; 27:44–6

7) Sharma A, Reddy P, Kuppermann B, Bandello F, Loewenstein A. Biosimilars in ophthalmology: "Is there a big change on the horizon?" Clinical Ophthalmology. 2018; 12:2137–2143

8) Hemmington A, Dalbeth N, Jarrett P, Fraser A, Broom R, Browett P, Petrie K. Medical specialists' attitudes to prescribing biosimilars. Pharmacoepidemiol Drug Safety 2017; 26:570–577.

9) Declerck P, Farouk Rezk M. The road from development to approval: evaluating the body of evidence to confirm biosimilarity. Rheumatology. 2017 Aug 1;56(suppl_4): iv4-13.

10) Kiss S, Krawitz J, Fine HF. Coming of age: biosimilars. Ophthalmic Surgery, Lasers and Imaging Retina. 2018 Mar 1;49(3):162-5.

11) European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, 2014. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf. Accessed 04 May 2021.

12) Food and Drug Administration. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry, 2015. https://www.fda.gov/media/82647/download. Accessed 25 Feb 2021.

13) Monés J, Srivastava SK, Jaffe GJ, Tadayoni R, Albini TA, Kaiser PK, Holz FG, Korobelnik JF, Kim IK, Pruente C, Murray TG. Risk of inflammation, retinal vasculitis, and retinal occlusion–related events with brolucizumab: post hoc review of HAWK and HARRIER. Ophthalmology. 2021 Jul 1;128(7):1050-9.

14) Zhao S, Nair JR, Moots RJ. Biosimilars: from extrapolation into off label use. Current Pharmaceutical Design 2017;23(44):6746-6751.

15) Sheth J, Stewart M, Khatri M, Shashank G, Shobhit C, Rajendran A, et al. Changing trends in the use of anti-vascular endothelial growth factor (anti-VEGF) biosimilars: Insights from the Vitreoretinal Society of India Biosimilars of Anti-VEGF Survey. Indian J Ophthalmol. 2021; 69:352–356

16) Sharma A, Kumar N, Kuppermann B, Bandello F, Loewenstein A. Biologics, biosilimars, and biobetters: Different terms or different drugs *Eye* 2019;33:1032–4.

17) Verma L, Thulasidas M, Purohit A, Gupta A, Narula R, Talwar D. Clinical efficacy and safety of Razumab®(CESAR) study: Our experience with the world's first biosimilar Ranibizumab. Indian Journal of Ophthalmology 2021;69(2):347.

18) Sameera VV, Apoorva AG, Joshi S, Guruprasad AS. Safety and efficacy of Razumab–the new biosimilar in India: our experience. Kerala Journal of Ophthalmology 2016;28(3):180-5.

19) Sharma A, Arunaprakash J, Das A, Nayaka A, Kumar N, Parachuri N et al. Ranizurel safety evaluation in real-world -(RaSER) study. Am J Ophthalmology Case Rep. 2022; 25:101358

20) Kapur M, Nirula S, Naik MP. Future of anti-VEGF: biosimilars and biobetters. International Journal of Retina and Vitreous 2022;8(1):1-8

21) Brown D, Wobst H. A decade of FDA-approved drugs (2010–2019): trends and future directions. Journal of medicinal chemistry 2021;22;64(5):2312-38.

22) Sharma A, Kumar N, Parachuri N, Regillo C, Bandello F, Kuppermann B. Retina: A unique subspecialty in the biosimilar landscape. Eye (Lond). 2022; 36:1145-1146.

23) McNeely W. Biosimilar vs Biobetter – a two-horse race? Available at: https://media.springernature.com/full/springercms/rest/v1/content/15588272/data/v4 Accessed on 7 March 2022.