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Biosimilar Essentials: Insights on Development, Approval, and Real-World Data

Announcer:
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This medical industry feature, titled "Biosimilar Essentials: Insights on Development, Approval, and Real-World Data" is sponsored by Amgen.

Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to ReachMD. I'm Dr. Charles Turck and joining me today to help dispel some common myths around biosimilars are Drs. Carl Awh and Leah Christl. Dr. Awh is a retina specialist in Nashville, Tennessee, and Dr. Christl is the Head of Regulatory Affairs and Regulatory Policy for Biosimilars at Amgen.

So why don't we start with you, Dr. Christl, and focus on how biosimilars are developed and approved. Can you give us an overview of how this process differs from other products?

Dr. Christl:
So, the regulatory and development requirements for biosimilar products is different, and appropriately so, from those of originator biologics, and I think everyone has really good familiarity with how innovative our originator products are developed and approved.

The intent of that development program and the data that is collected during that development program is to independently demonstrate the safety and effectiveness of a new product, a novel molecule, with substantial evidence, and that typically includes one or more adequate and well-controlled clinical trials, or phase 3 trials.

A biosimilar program, on the other hand, is not intended to independently demonstrate the safety and effectiveness of the product. It's intended to demonstrate biosimilarity, and what that means is that the product is highly similar on a structural and functional level to that originator product called the reference product, and that there are no clinically meaningful differences between the biosimilar and its reference product.

So, within the development program, the same types of data are collected, but all of the data is comparative. It's comparing your biosimilar candidate to the reference product.

Once we have that foundation, we'll then look at the clinical portion of a development program, and these safety and efficacy assessments, again, are that more final step that comes towards the end of the program, but here, unlike with an innovative program, where you have what we refer to as the phase 3 pivotal safety and efficacy studies, we don't have any pivotal study that's in a biosimilar program.

It's what's referred to as the totality of the evidence, so all of this comparative data that's making similarity connections between the biosimilar candidate and the reference product come into play, and all of this has to meet the standards for being, again, highly similar with no clinically meaningful differences. You can't fail in one place, pass in another, and still be approved. You have to pass all of it.

Dr. Turck:
With all that in mind, can you tell us about the role of clinical studies in biosimilar development?

Dr. Christl:

So the nature and scope of the studies will really depend on the extent of uncertainty that you have. So, what differences did you see in those critical quality attributes? Regulators generally expect adequate clinical PK comparisons for products where systemic PK is not relevant. You may be then looking at additional clinical studies, other types of studies. If pharmacodynamics are relevant, there's an expectation manufacturers will collect data on pharmacodynamic comparisons.

Also, an assessment of immunogenicity and an assessment of safety. Again, all clinical studies will require safety and immunogenicity comparisons as a part of them.

If we do have an additional clinical study looking at comparative safety and efficacy, this is typically the design that will be used. It's an equivalent study design, because again, we're looking for no clinically meaningful differences, so the product is neither inferior within a specified margin, nor superior within a specified margin, so it's a not a bio-better.

Equivalence studies are designed to again look at any clinically meaningful differences. So with that, you need to have sensitive endpoints and sensitive patient populations. So, what we're focused on in terms of sensitivity is the ability to detect differences between the products, should they exist, so we look for a more homogenous study population that's going to be enrolled.

Dr. Turck:
Now if we zero in on a certain aspect of biosimilar approval, what does the term “extrapolation” mean?

Dr. Christl:
So, one of the hallmarks of a biosimilar program is the concept of extrapolation. So, extrapolation is the approval of a biosimilar for use in an indication that's held by that originator reference product that is not directly studied by the biosimilar manufacturer.

What's important to understand about extrapolation is that we're not extrapolating safety and efficacy from the studied indication to other indications, so for example, you're not conducting a comparative clinical study in wet AMD and then extrapolating the safety and efficacy in wet AMD to DME.

You're extrapolating the finding of biosimilarity, and really actually extrapolating the safety and efficacy finding from the reference product to the biosimilar through all of that comparative data that’s been generated.

Dr. Turck:
And before we hear from Dr. Awh, is there anything else we need to know about biosimilars, Dr. Christl?

Dr. Christl:
One last thing to talk about is the concept of substitution, switching, and interchangeability, and the key thing in here is that terminology matters, and that these words do not mean the same thing; but yet, they get used, for lack of a better term, interchangeably.

So, pharmacy substitution is a practice where one drug is dispensed in place of another at the pharmacy level without consulting the prescriber. That can happen with biological products per state law, and we'll talk about how that happens.
Switching, on the other hand, is where a physician may elect to prescribe one medicine in place of another with the same therapeutic intent. So you can have switching that occurs, prescriber-led switching, from the reference product to a biosimilar.

In Europe, the term, interchangeable, has been used synonymously with the term, switching, and it has created some global confusion. All biosimilars in Europe are considered to be interchangeable, but what they mean by that is that they can be switched by prescribers and expect the same safety and efficacy outcome. It is not relevant to substitution. This is important, because in the US, we have a legal definition for an interchangeable biosimilar, and that is one that may be substituted at the pharmacy without the intervention of the prescriber.

So really, interchangeability in the US is only relevant, or should only be relevant to outpatient-dispensed products, so pharmacy-dispensed products that are self-administered by the patient or their caregiver.

It does not imply anything about the quality of the product. There's no quality difference between a biosimilar and an interchangeable biosimilar. An interchangeable biosimilar is not safer, it's not more efficacious, there's no difference in the quality, so that's really important to understand. The only distinction is that there’s been an additional assessment made by a regulatory authority in the US, the FDA, that that product can be safely substituted by the pharmacist to the patient.

Dr. Turck:
Thank you, Dr. Christl, for breaking all of that down for us.

And for those just joining us, you’re listening to ReachMD. I’m Dr. Charles Turck, and I’m speaking with Drs. Carl Awh and Leah Christl about biosimilars.

So if we turn to you now, Dr. Awh, can you tell us about the available biosimilars in the ophthalmology space and your experience with them as a retina specialist?

Dr. Awh:
For ophthalmology, there's the anti-TNF alpha biosimilars. Those are used by our uveitis colleagues, and the anti-VEGF biosimilars, some of which have now been approved, and others in development, and there will be many of these entering the market within the next year or two.

So, we began using biosimilars, anti-VEGF biosimilars, in our practice, Tennessee Retina, and in a lot of my colleagues' practices, during the last year. And even though we were aware of all that Dr. Christl just said, that these are supposed to be the same, you still get nervous when a drug has a different name. So our question really was, are there any unanticipated clinical outcomes associated with these anti-VEGF biosimilars, even though they are FDA-approved?

Dr. Turck:
Now as I understand it, you recently conducted a study to help address that question. So for some background, how was this study designed?

Dr. Awh:
The objective of this study was to understand if there are any unexpected outcomes from treatment with new commercially available anti-VEGF biosimilar agents. This was a retrospective, non-randomized, consecutive case series of eyes receiving commercially available anti-VEGF biosimilar agents at a large consortium of retina practices across the US.

So, we've reviewed records for each patient treated with a biosimilar, with follow-up of at least 28 days following the first injection with the agent. And we looked at the diagnosis, the number of prior anti-VEGF injections, visual acuity, and of course, what we were really looking for were new findings of inflammation, anterior chamber or vitreous cells, and ophthalmitis, uveitis, of course, vasculitis, we all have our antenna up about that with intravitreal injections, and any other unexpected adverse events.

Dr. Turck:
And what were the results?

Dr. Awh:
So, we identified 5,085 eyes of 3,964 patients with at least 28 days of follow-up.

The first of these injections was given back in September of 2021. The majority of these eyes, not surprisingly, had been previously treated with a different anti-VEGF agent, with a mean number of prior injections of 5.6. So that's important, because these are patients who have been treated and had already established sort of an equilibrium with their vision.

The mean number of additional biosimilar injections following the first in our group was 1.65, so we did have a number of patients who had more than two injections. We found examples of 13,459 injections of biosimilar. We saw no statistically significant difference in visual acuity at 1, 2, and 3 months, and again, that's what you'd expect, because they should have already had whatever initial improvement in visual acuity they may have gotten with their first injections, because they had been pre-treated, so this stability, I think, is what we should expect.

We had 9 cases of minimal anterior chamber or vitreous cells, none of these had vision loss, none led to any changes in treatment. There were no cases of retinal vasculitis, no cases of inflammation that were presumed secondary to a drug reaction.

We did have three cases of presumed bacterial endophthalmitis, with an incidence of 1 in 4,486. That's not surprising with interventional injection of any agent, even though this is a pretty large number, 13,000, it's still a small number when you're talking about rare events, so there's something called the law of small numbers, and that these three cases of endophthalmitis all appeared during the first 900 injections that we gave, so that could actually make you think, wow, this stuff is really dangerous, but then there were no cases of endophthalmitis in the next 12,500, so the incidence is not 0, and the incidence is not 1 in 300. It's blended, and probably, we need hundreds of thousands of injections to really know the incidence, just as we've learned with other agents we inject in the eye.

Dr. Turck:
Before we close, Dr. Awh, can you share some key takeaways we can learn from your research?

Dr. Awh:
So, our conclusion from this analysis is that we saw no unexpected adverse outcomes, so that was really very reassuring to us to see this fairly large number of eyes treated, the clinical efficacy of the biosimilars appears equivalent to the reference product, and we are continuing to evaluate and report, and we already have, are starting to analyze data on almost an order of magnitude more injections

with these biosimilars.

Dr. Turck:
That's a great way to round out our discussion today focusing on biosimilars, and I want to thank Drs. Carl Awh and Leah Christl for sharing their insights. For ReachMD, I'm Dr. Charles Turck. Thanks for joining us!

Announcer:
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