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Inflammation Biosimilars: Examining the Totality of Evidence for Approval

Announcer:
You're listening to ReachMD. This medical industry feature, titled "Inflammation Biosimilars: Examining the Totality of Evidence for Approval," is sponsored by Amgen.

Here's your host, Dr. Charles Turck.

Dr. Turck:
This is ReachMD, and I'm Dr. Charles Turck. Joining me to discuss the development and approval process for biosimilars is Dr. Gil Melmed, who's the Director of Inflammatory Bowel Disease Clinical Research at Cedars Sinai, and Professor of Medicine at Cedars Sinai and at the David Geffen School of Medicine at University of California, Los Angeles. Dr. Melmed was compensated for his participation in this program by Amgen.

Dr. Melmed, it's a pleasure to have you here today.

Dr. Melmed:
It's a pleasure to be here.

Dr. Turck:
So Dr. Melmed, would you start us off with a bit of background on the concept of biosimilars as therapeutic options?

Dr. Melmed:
Of course. But first, I think it's important that we take a step back for a moment and consider biologic products or medicines. Biologics are therapeutic proteins made from natural living sources like plants or animal cells, even microorganisms.[1,2] Now, *biosimilars*, on the other hand, are biological products that are highly similar to an already approved biologic on the market—known as the reference product. Biosimilars have no clinically meaningful differences to the reference product in terms of safety, potency, and purity.[2]

Sometimes, people confuse biosimilars for generic medications, which can also be developed after a patent expires and are usually more affordable than the branded drug.[3] But unlike generic medications, which are often small molecules and synthetically produced with an identical structure to the branded drug, biosimilars are generally much larger, complex molecules that are structurally highly similar to the reference product.[2,4] And if we look at the development and approval process, the primary goal for a biologic is to evaluate an established clinical effectiveness. But for a biosimilar, the goal is to demonstrate its similarity to the reference product, culminating in a totality of evidence.[1,2]

Dr. Turck:
Now, you just mentioned totality of evidence, and I'd like to take a closer look at that. What's required from biosimilar studies to demonstrate similarity?

Dr. Melmed:
So biosimilar development uses a stepwise approach with increasing certainty to generate the totality of evidence, which demonstrates the safety, purity, and potency in one or more appropriate conditions of use, for which the reference product is licensed.[1,2] Starting off, the *in vitro* studies for analytical characterization established structural and purity attributes, as well as functional activity evaluation.[1,2] Then, if there's a relevant animal model, *in vivo* or nonclinical studies are performed to determine the toxicology profile

and nonclinical pharmacology.[1,2] The next step is clinical pharmacology testing, which includes pharmacokinetic and pharmacodynamic studies to demonstrate human pharmacokinetics similarity between the proposed biosimilar and the approved reference product.[1,2]

And finally, phase 3 comparative clinical equivalent studies are performed to determine safety, efficacy, and immunogenicity in sensitive disease states to demonstrate that there are no clinically meaningful differences from the reference product.[2]

Dr. Turck:
Thanks for breaking all that down for us, Dr. Melmed, and it seems that the stepwise process can establish the totality of evidence to a license approval for a single indication. But what if the reference product has multiple approved clinical indications?

Dr. Melmed:
That is a great question. So once the proposed biosimilar is licensed by regulatory bodies, based on the totality of evidence, the sponsor can then seek appropriate use of the biosimilar in one or more additional indications that are approved for the reference product based on extrapolation. In this setting, extrapolation is the approval of a biosimilar for a clinical indication that was held by the reference product, but which wasn't directly studied in comparative clinical trials with the biosimilar.[5,6] Regulatory guidance explains that extrapolation may be supported by knowledge of the reference product, the totality of evidence from the biosimilar development program, and scientific justification.[2] Sufficient scientific justification is required for extrapolating the available data to support biosimilarity for each clinical indication use that is sought.[2] So for example, scientific justification should address whether the mechanism of action is expected to differ across indications, if the pharmacokinetics, pharmacodynamics, and biodistribution vary across patient populations, whether the immunogenicity is expected to vary in different patient populations, or if there are variations in expected toxicities among different indications and patient populations.[2]

Dr. Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Gil Melmed about the development and approval process for inflammation biosimilars.

Dr. Melmed, we've been talking about the requirements to bring a new biosimilar to market and you've introduced the need to generate the totality of evidence. So, let's dig deeper into the steps involved, starting with the first two stages, which are analytical characterization followed by nonclinical studies. What can you tell us about these studies?

Dr. Melmed:
Well, the analytical characterization establishes a high degree of structural and functional similarity, as the testing is extensive. For example, a biosimilar manufacturer may measure about 100 attributes across 40 or more assays.[7] These can include the primary structure, the products impurities and excipients, its stability, the biological function, in addition to the receptor binding and immunochemical properties.[1,2] Next, nonclinical assessments *in vivo* compare biosimilars to the approved reference product if there's a relevant animal model available. These can include comparing the toxicology profiles, pharmacokinetics, and pharmacodynamics, just to list a few examples.[2]

Dr. Turck:
Now, if we move on to the clinical studies, what factors of the study design are important to consider for biosimilar testing?

Dr. Melmed:
So first up is the clinical pharmacology study, which is the phase 1 study in human subjects to establish pharmacokinetics similarity. Let's design a study for a biosimilar in the inflammation therapeutic space, comparing dose selections of the biosimilar to two reference products such as an EU, or European Union, and a U.S. product. Here, you could design a randomized, three-arm, parallel group study in healthy adults that's single-blinded using a single dose.[8]

In this example, we can see that the biosimilar produced a dose response very similar to those of the reference products.[8] And in my opinion, it would move forward to clinical equivalent studies to see whether it's a viable alternative to these biologics.

And so finally, we get to the clinical equivalent studies. As a study design example, a comparative clinical equivalent study of a biosimilar for inflammation versus a reference product could be performed in a randomized double-blind active comparator-controlled study in patients with active disease. Assessments would include safety, efficacy, and immunogenicity.[2,9]

And it's important to remember that biosimilar clinical studies are equivalence studies designed to identify any clinically meaningful differences from the reference product. So they're intended to demonstrate that the tested biosimilar is neither inferior nor superior to the reference product within a specified margin.[2,10]

With that being said, some key considerations in the study design include the indication, as extrapolation is possible if the data is informative across populations, study duration to detect safety signals, study endpoints, which should be clinically meaningful, and patient population, which should provide a meaningful assessment of endpoints.[2,10-13]

Dr. Turck:
Is there anything else we should consider regarding comparative clinical equivalent study designs?

Dr. Melmed:
Yes. We also have clinical equivalent study designs, incorporating a *switch* between a biosimilar and a reference product.[4,14,15] So for example, a single-switch, three-patient-arm, comparative follow-up study would assess the efficacy, safety, and immunogenicity of biosimilars and reference products to make sure that they are indeed equivalent. In other words, we're looking for no clinically meaningful difference between biosimilars and reference products.[4,14,15] Although not required, incorporating a single switch is pretty crucial to show the FDA that the risk in terms of safety or diminished efficacy when switching between a biosimilar and a reference product isn't greater than the risk of no such switch.[4,14,15]

Dr. Turck:
Now, when we have an approved biosimilar, how can we differentiate it from the reference product biologic? What's the naming convention they're following?

Dr. Melmed:
You bring up an interesting point. So biologic products, including reference products and biosimilars, are all subject to FDA's naming convention.[5] And so the name includes two parts, a nonproprietary core name, plus a unique four-letter suffix which is used to distinguish among products. For example, a biosimilar will share the same core name as the reference product, but it'll have a different four-letter suffix.[5] The FDA adopted this naming policy for clearer product identification and pharmacovigilance. So it is important for clinicians to use the four-letter suffix when prescribing or documenting these products.[5]

Dr. Turck:
Now we're almost out of time for today, but before we close, Dr. Melmed, any final thoughts you'd like to leave with our audience today?

Dr. Melmed:
Yes. It's important to keep in mind that biosimilars undergo a rigorous development and evaluation process to ensure high quality.[1,2] They are FDA approved and regulated. Regulatory requirements are designed to establish similarity to an approved reference product based on the totality of evidence from nonclinical and clinical studies.[1,2] The same benefits and risks as approved reference product, and to ensure safety, purity, and potency.

Dr. Turck:
Thank you. Those are all great points to consider as we end today's program. And I want to thank my guest, Dr. Gil Melmed, for breaking down the biosimilar development and approval process. Dr. Melmed, it was great speaking with you today.

Dr. Melmed:
Thank you so much for having me.

Announcer:
This medical industry feature was sponsored by Amgen. If you missed any part of this discussion, visit ReachMD.com/IndustryFeature.

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