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### ReachMD

www.reachmd.com  
info@reachmd.com  
(866) 423-7849

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## Assessing Biosimilar Medications for Inflammatory Bowel Diseases

### Narrator:

Welcome to Crohn's & Colitis Perspectives on ReachMD. This series is produced in collaboration with the Crohn's & Colitis Foundation, providing updates and driving innovation in IBD research, education, and clinical support.

### Dr. Ullman:

Biosimilar medications have entered the clinical landscape of treatment protocols for several disciplines, but some specialties have been slow to adopt them into practice. Gastroenterology and, in particular, the care of inflammatory bowel diseases is no exception, but there are, in fact, biosimilars available for Crohn's disease and ulcerative colitis, which raises the question: What do we need to know about these treatment options before applying them to patient care?

This is the Crohn's and Colitis Perspectives on ReachMD. I'm Dr. Thomas Ullman, and joining me are 2 experts from the FDA, Dr. Sarah Yim, who's Acting Director of the Office of Therapeutic Biologics & Biosimilars, and Dr. Juli Tomaino, a pediatric gastroenterologist and Lead Medical Officer at the FDA.

Sarah and Juli, thanks for joining me today.

### Dr. Yim:

It's nice to be here. Thanks for having us.

### Dr. Tomaino:

Thank you for having us.

### Dr. Ullman:

Sarah, if you will, can you start us off and define biologics and biosimilars respectively?

### Dr. Yim:

Sure. A biologic is a molecule or a mixture of molecules that's produced in a living system like a cell. A common example is monoclonal antibodies. So, the gene for the desired monoclonal antibody is introduced into a cell for production in a cell culture and then later purification into the medication. And a biosimilar is a biologic that's analogously produced in the same way and has a legal definition of being highly similar and having no clinically meaningful differences from an existing, original FDA-approved biologic product.

So, monoclonal antibodies are actually a great example of why you need different follow-on pathway for biologics. It's relatively easy to make an exact copy of a gene and put it in a cell and make a protein with identical amino acids, but when a cell produces a protein from a gene, it doesn't stop there. and because cells and cell cultures have this inherent variability, this means that the proportions or even the types of variants may differ between batches or over time with manufacturing changes. For example, the Remicade in 1999 would likely have a different variant profile than the Remicade of today, so this kind of complexity and variability is why we need to use a word like biosimilar rather than biocopy or bioidentical. If the original product is not identical to itself dose to dose, there's no way a follow-on product could be identical to it. But FDA reviewers are very careful to ensure that follow-on products meet the high legal standards set for biosimilarity, and prescribers and patients can be confident that there are no clinically meaningful differences between biosimilars and their reference products.

### Dr. Ullman:

That's very helpful, Sarah, and I think that that last point that you made is really the one I think most worthy of stressing, is that there is

really no meaningful clinical or pharmacologic difference between the biosimilar and the originator and that it's been rigorously evaluated before FDA will give biosimilar approval. Am I getting you right on that?

Dr. Yim:

That's absolutely very important. I think the other thing is that I think people have this perception that my brand name product is a single molecule, and really what it is, is it's kind of a mix of slightly different versions of the molecule, so I want people to start kind of envisioning their molecule as not being quite this monolithic thing.

Dr. Ullman:

Very helpful. So, turning to you now, Juli, which biosimilar medications are currently approved in the US for Crohn's disease and for ulcerative colitis?

Dr. Tomaino:

The FDA has biosimilars to Humira (adalimumab) and Remicade (infliximab) both to treat Crohn's disease and ulcerative colitis. There are currently 3 approved biosimilars to Remicade—Inflectra, Renflexis and Ixifi—and both Inflectra and Renflexis are currently marketed. FDA also has approved 4 biosimilars to Humira, but unfortunately, these are not currently marketed in the US due to patent settlements and agreements.

Dr. Ullman:

Got it. And it's important to note that the Crohn's and Colitis Foundation does have this on their webpage.

So, now that we know a little bit more about the medications that are currently available as well as some background information that Sarah so nicely reviewed in terms of what a biosimilar is in terms of definition and what similarity really means—Sarah, if you can talk to us, what's the safety profile of the available biosimilars, and does it differ in any way from the safety profile that we have available to us for the originator molecules?

Dr. Yim:

Well, Tom, as I mentioned, the legal standard requires that there be no clinically meaningful differences between the biosimilar and its reference product, so when FDA approves a biosimilar, it means we've concluded that the safety and efficacy profile of the biosimilar has no clinically meaningful differences compared to the reference product. So, what do FDA reviewers use to determine that? Well, every application for a biosimilar contains a comprehensive analytical data package, so that's carefully reviewed to make sure that the biosimilar has the same package of analytical characteristics, the same primary, secondary, tertiary structure, similar functional activity, potency and binding; it has an equivalent pharmacokinetic and exposure profile; and then typically, the application also contains clinical data in a sensitive population that shows that immunogenicity is similar and that also the efficacy and safety of the product in that population is similar.

Dr. Ullman:

Very helpful. Can you go on to discuss a little bit what the term interchangeable means and whether any of the approved biosimilar products in the Crohn's and colitis space have interchangeable designation?

Dr. Yim:

Sure. So, I'll start off by saying that no currently approved biosimilars are approved as interchangeables. Let me then step back and go over what that means. A determination of interchangeability has specific legally defined requirements which, in addition to the requirements for biosimilarity, requires information to show that, "The risk in terms of safety or diminished efficacy of alternating or switching between the use of the product and the reference product is not greater than the risk of using the reference product without such alternation or switch." And that's from the regulation. So, that information is intended to support a determination that the product can be used according to the legal definition of interchangeable or interchangeability, which means that the biological product can be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.

So, a couple things about that. The additional information on alternating or switching often requires clinical data on patients alternating or switching, often called a switching study, so that's not an insignificant expense because then sponsors have to go and conduct a clinical study. Therefore, it may not make sense from a business perspective for a company to seek interchangeability because, for example, the particular biologic is given in the hospital or an infusion center setting where the healthcare provider would be likely to order the infusion and have knowledge of what is infused because it's right there. Substitution at the pharmacy level may be more relevant for outpatient self-administered types of medication.

The last point I want to make about that is interchangeability is not a higher standard. So, although additional information on alternating or switching is required by law, this does not mean that there would be a concern about a biosimilar that did not provide that information. In fact, depending on business or other considerations, a product may be approved as a biosimilar first and then become an

interchangeable later once the additional information has been submitted, or a biosimilar may pose no additional concern regarding alternating or switching but may not be designated as an interchangeable because the sponsor did not seek the designation.

Dr. Ullman:

Very helpful. I think you straightened out in my head at least some things that I hadn't quite had straight before and that whole notion that approval for one doesn't necessarily exclude approval for the next biosimilarity to interchangeability. Some products it's possible, I guess, might never seek an interchangeable designation after they have achieved biosimilar designation. Am I mistaken in that? And I know maybe it hasn't happened yet as I'm asking you in effect to read the minds of marketing departments and scientific advisors for pharmaceutical companies, but is that something that FDA is anticipating happening?

Dr. Yim:

You know you're absolutely right. So, as I said, I think interchangeability sort of makes more business sense for the medications where patients are likely to pick them up from the pharmacy, for example, because really, for interchangeability, we're talking about pharmacy-level substitution, or as routinely administered by infusion where healthcare providers are all around, interchangeability doesn't have quite the same meaning.

Dr. Ullman:

For those just tuning in, you're listening to Crohn's and Colitis Perspectives on ReachMD. I'm Dr. Thomas Ullman, and here with me today to talk about priority considerations when using biosimilars to treat patients with Crohn's disease and ulcerative colitis are Dr. Sarah Yim and Dr. Juli Tomaino from the FDA.

So, earlier, we covered the biosimilars that are currently available, but I'd also like to look back at the history of these medications to better ground us on where we are today. Sarah, can you explain how and why the biosimilar pathway was created?

Dr. Yim:

Sure, Tom. There are a number of factors that came together. First, as you all know, the existence of the generics pathway for chemical drugs has been in existence since 1984. Then there was the growth of recombinant therapeutic biologics, which started in the 1990s, and then there was concern that differences in biologic and drug regulations would lead to inconsistency; that is, if you were a chemical, you would submit a new drug application and then be subject to having follow-on generics after a certain period of time, whereas if you were a biologic, you submitted a biologic license application and no follow-on pathway existed but you might never have a follow-on product. And in Europe there is really not a different treatment for drugs versus biologics in the regulatory aspect, so when recombinant therapeutic proteins began to blossom, they were better positioned to harmonize the approval system for biologics and drugs, including with an abbreviated pathway, so they were already several years ahead of the US in creating an abbreviated pathway and approving biosimilars. So, all these factors were putting mounting pressure on Congress to come up with an abbreviated pathway for biologics, and that resulted in the Biologics Price Competition and Innovation Act of 2009.

Dr. Ullman:

Excellent. Staying with you for a moment, Sarah, what were the access and cost issues that brought about this pathway's creation?

Dr. Yim:

Well, I think access and cost of medicines has been a long-time issue, but the stakes are getting higher with the increasing cost of biotechnology and the murky financial aspects of the US healthcare system. I was looking at an article from Avik Roy of Forbes earlier this year with data from the IQVIA Institute which quoted, "In 2017, biologic drugs represented 2% of the US prescriptions but 37% of net drug spending," and, "Since 2014, biologic drugs account for nearly all," approximately 93%, "of the growth in net drug spending," so that's more recent data, but certainly, at the time of BPCIA, I'm sure something similar was going on.

And biologic drugs have revolutionized the way many serious debilitating and life-threatening diseases are treated, but if they are too expensive and patients can't afford them, then they can't take them and benefit from them, and that's why having biosimilar options makes sense. The abbreviated development program allows them to be developed and marketed at a lower cost, but they are required to have the same high standards as the original reference biologic product, so having more and lower-cost options hopefully will increase access and lower healthcare costs through competition.

Dr. Tomaino:

Tom, as a fellow gastroenterologist, I'd be interested to hear about some of the clinical experiences with biosimilars that you and your peers have had.

Dr. Ullman:

Sure. So, it was at first a bit of a daunting issue on a certain level because we didn't know how this was going to roll out in practice, and

I think FDA and all sorts of regulatory bodies have been very helpful and our colleagues in medical education have been very helpful in addressing our concerns up front, but when the medications finally hit the market, it was bizarrely seamless, in part because certain insurers just carte blanche went into contract with a number of different drug manufacturers; then all the sudden 15% of our market a particular biologic became the new preferred agent, whether it was biosimilar or the originator molecule or reference molecule. And all the sudden many of our patients ended up on so-called biosimilars without our barely knowing about it, and sometimes these were one-time forced switches, and sometimes these—depending on the insurer, sometimes these were forced new starts, so all new starts with a certain insurer in New York State where I practice a certain biosimilar, and so all of our patients who we were starting with that particular insurance would go on to the biosimilar, and it's been seamless.

What FDA required in those packets that we were discussing earlier that demonstrate biosimilarity has really come to be. I have not appreciated any difference in my patients, now about 2+ years into the process. On even transition I've seen no differences among my patients. This is something that's certainly been very, very encouraging in practice, makes me wonder whether this whole issue of interchangeability may have already happened under our own eyes without our knowing. People who move from other states based on the state-oriented insurance approval that we have in the US and the system that we live in has people changing their insurance somewhat frequently and as a result might have had their infliximab changed from one product to another and back or from one product to another and then to a third. It's all been terrifically seamless, and I've been very encouraged in terms of what I've seen in my personal clinical experience with biosimilars, and this has been echoed by that which I've heard from my peers around the US.

Dr. Tomaino:

That's a great rundown of experiences from a US perspective. What about in terms of the global vantage point on biosimilars?

Dr. Ullman:

So, as was mentioned before, Europe and some parts of Asia as well got a big head start on us in terms of biosimilars, and we've seen publication from Hungary, we've seen publication from South Korea, from Italy as well, and it's all been very encouraging, and it's really pointed to the notion that there is nothing to worry about. There's no great cause for concern, no small cause for concern even with at least one-time switches with biosimilars, at least in the Crohn's and colitis space. There was a larger study that was performed in Norway called the NOR-SWITCH study where they combined a number of different clinical conditions using infliximab for therapy to see if there was any difference with one-time switches, and there wasn't. And I think that, while we didn't speak about that in terms of the regulatory pathway, what we have in the US is probably not too different from the European model as well, which is if you can demonstrate it just in one clinical-disease setting, all indications or all FDA-approved indications for that use are effectively approved for a biosimilar. And so the European and South Korean and other experience outside the US I believe has been really terrifically encouraging, and we're now seeing it mirrored in the US.

So now to bring our discussion home, can you add or reiterate where listeners should go if they want to learn more about this?

Dr. Tomaino:

Sure, Tom. For more information, please review the Crohn's and Colitis Foundation and FDA Office of Therapeutic Biologics & Biosimilars websites on biosimilars. They are available at [www.FDA.gov/biosimilars](http://www.FDA.gov/biosimilars) and [www.FDA.gov/purplebook](http://www.FDA.gov/purplebook).

Dr. Ullman:

I would add to that notion that scarcely a large gastrointestinal meeting goes by—a large society meeting or the Crohn's and Colitis Congress or any of the public meeting offerings go by without a really nice CME-oriented talk on biosimilars, and just about any practitioner can very safely Google CME and biosimilars with Crohn's and colitis as tag words and find all sorts of CME offerings that are out there. This is really an interesting space that we're in, and it's moving I think pretty rapidly, but there's lots of information and education for many folks to go out and grab.

Dr. Ullman:

Well, with those thoughts and resources in mind, I want to thank both you, Sarah and Juli, for running through the latest on biosimilar therapies for inflammatory bowel diseases. It's been great having you both on this program, and I'm very grateful for the wisdom you have set forward.

Dr. Tomaino:

Thank you for having us.

Dr. Yim:

Thank you for having us.

Narrator:

The preceding episode was brought to you in collaboration with the Crohn's & Colitis Foundation. If you have missed any part of this

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