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Part 1: Are You Ready for Biosimilars? What the Oncology Team Should Know

Announcer:
Welcome to ReachMD. This medical industry feature, Exploring the Development of Biosimilars in Oncology Practice, is sponsored by Amgen Oncology. Amgen Oncology: advancing oncology at the speed of life.

Your host is Dr. Matt Birnholz.

Dr. Birnholz:
The introduction of biosimilars into oncology practice is proving to be a much-needed treatment option for patients and healthcare systems alike. But how are biosimilars developed and manufactured, and are they as safe and effective as generics or original biologics? These questions, along with an in-depth review of the procedures used to maintain quality and safety for biosimilars, will be the subjects in focus today.

This is ReachMD, and I'm Dr. Matt Birnholz. Joining me to talk about the evolving roles for biosimilars in oncology practice is Dr. Gary Cohen, Associate Professor of Oncology at the Johns Hopkins School of Medicine and Emeritus Director of the Sandra and Malcolm Berman Cancer Institute at Greater Baltimore Medical Center.

Dr. Cohen, welcome to the program.

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

Dr. Birnholz:
Before we dive into the specifics, Dr. Cohen, can you give us a general overview of how biosimilars are being introduced into the marketplace?

Dr. Cohen:
When we think about the biosimilars, clearly the expiration of patents for the biologic medications is what allows for the introduction of the biosimilars into the marketplace. There is a rigorous but abbreviated program for the FDA to review these medications in order to provide cost savings without compromising quality, and that is the critical part of this. Competition may increase access to biologic products for appropriate patients.

Dr. Birnholz:
So with that background understanding on the competitive environment in tow, can you help us distinguish biosimilars from generic drugs and original biologics, respectively?

Dr. Cohen:
A generic drug, by definition, is an exact chemical copy of the reference small molecule medication. Unlike generic medications, biosimilars will not, and probably cannot be, absolutely identical to the reference biologics.

In the bottom left corner, you see an illustration of a typical generic medication and the biosimilar, or the biologic medication, and you see a vast difference in size.

Biologics are made in cell systems, and these cell systems have an impact on chemical synthesis, which causes a great complexity and variation in the biologic medications so that the biosimilars end up being far more structurally complex, although they are highly similar

to the reference compound.

So to further explore the difference between the generics and the biosimilars and the original biologics, we can look at the left hand column here. You can see that with generics the scientific difficulty in making them is low. The time it takes to produce generics is a few years, three to four years. And the cost of making a generic is also low.

In the case of the originator biologics on the right-hand column here, the scientific difficulty is quite high, and there's an extended length of time that's required to get those drugs to market. The cost is high.

The biosimilars fall in the middle but are far closer to the cost of the original biologics so that the biosimilarity difficulty is quite substantial, and the time it takes is seven to eight years. The cost of those medications is in the neighborhood of 200 million dollars, so less than the cost for the originator, but certainly quite substantial compared to generics.

Dr. Birnholz:
So now looking specifically at biosimilars, how does the FDA define this type of treatment?

Dr. Cohen:
They call that a biologic product that is highly similar to the referenced biologic product, notwithstanding minor differences in clinically inactive components which would then not have an effect on the overall safety and efficacy. And that there is no clinically meaningful difference between the biosimilar and the referenced product in terms of safety, purity and potency.

Dr. Birnholz:
And since most of the biologics that oncologists deal with are in the form of monoclonal antibodies, can you give us an overview of their makeup and development?

Dr. Cohen:
Monoclonal antibodies, as you know, are complex proteins, and are sensitive to manufacturing conditions. One of the important components of the final product is post translational modifications, and that can quite cause quite substantial changes from a reference product.

Purification may introduce some modifications as well. The raw materials that are used can do that. The post translational modifications can affect the mechanism of action, can affect the bioavailability, and with that, the clearance of the molecule over time, what we call the pharmacokinetics. The immunogenicity of the molecule is also a factor and can be changed by these post translational modifications. The effector functions and the binding to the target can also be affected. So these are all changes that can occur, which ultimately must be shown to be highly similar to the reference product in the analytical aspects.

Dr. Birnholz:
Let's stay on that manufacturing theme and turn back to biosimilars. Can you elaborate on the steps needed to take biosimilars through development and manufacturing?

Dr. Cohen:
The biosimilar manufacturers begin with limited knowledge of the reference product. It is possible to identify the amino acid backbone. Once that amino acid chain is known, it is possible to make a molecule that has precisely the same amino acid sequence.

However, there are lots of things that are unknown beyond that amino acid backbone. The cell line that it's grown in is likely proprietary to the originator manufacturer. The growth media is something that is not known to the biosimilar manufacturer. All these things can cause slight differences.

And once these unknowns are put together in order to attempt to make a biosimilar, they need to be analyzed and then compared back to the reference product. And in so doing, there are going to be changes and ultimately further modifications, which are then analyzed again so that ultimately a biosimilar molecule can be obtained which has the same analytical characterization as the reference product. This won't be exactly the same, but it should be highly similar.

Now in the biosimilar development the product is what defines the process. So the first thing is to choose the right cell line that has the correct attributes that you want. And then there has to be the development of the drug. This has to be optimized to achieve the similarity. It's a constant process of testing and looking back to the reference compound. And then there are nonclinical features that have to be tested. This could be in vitro or in vivo studies in animals. And finally the clinical production which can then lead to the use of these drugs in a clinical trial. And every step along the way has to be tested again to make sure that things are moving along properly.

Dr. Birnholz:
And digging a little deeper into those iterative quality assessments for biosimilarity, what goes into that determination process?

Dr. Cohen:
There's an extensive analytical characterization that is required to determine the similarity in quality of the biosimilar. And the process, of course, begins with the primary structure, again, the amino acid sequence, which can be copied precisely.

Nevertheless, the biologic function must be reproduced accurately. And then there is the receptor binding, the quality of the binding, and the immunochemical properties that are engendered by the molecule. The biosimilar molecule must have a stability and the same pharmacokinetics as the reference molecule. And then there will certainly be general properties about the molecule including impurities, what's called the excipients, the inactive substances.

So there are a lot of tests that go into demonstrating that the quality and the function of these biosimilar molecules is highly similar to the reference compound even before we get to clinical testing.

Now when the reference product is made each lot can have slight differences because, after all, this is made in cell systems, and the cells go through changes over time. And so the manufacturer must determine a standard range which would include an upper and lower margin of acceptability. And it's well known that among all biologic medications there is some variation from lot to lot. But as long as various characteristics are tested and they are within acceptable limits these drugs are considered to be acceptable.

When a biosimilar is produced, the biosimilar might have different moieties, especially in the post translational modifications, compared to the reference product, but the only question is whether those really affect the clinical nature, and that's determined by looking at different analytical characteristics of the molecule.

And as you can see in the graphs in the bottom, looking at glycosylation for instance, or at compliment dependent cytotoxicity, uh you can look at the biosimilar, compare it to the reference product and show that it either is or is not within the allowable range. And if it's not, of course, that's when you need to go back and make the proper changes to be sure that this remains within an acceptable range.

Dr. Birnholz:
So how does this characterization of biologic function play out within the biosimilar development process, then?

Dr. Cohen:
Schematically we can think of the biologic function of the biosimilar molecule. There is a neonatal FC receptor binding, which primarily determines the clearance of these drugs, what we call the pharmacokinetics. But of course what we're more interested in as physicians is the target binding and the effectiveness. And we know that when there's binding to the target there is inhibition of that target, and neutralization of the target, and finally the induction of apoptosis.

But another aspect is the binding of the immunologic functions. And so there is an FC gamma receptor which relates to the antibody dependent cell mediated cytotoxicity, what we call ADCC, and also compliment-dependent cytotoxicity, the CDC, which occurs at a different site on the FC portion.

And this example is with the anti-HER2 compound where, again, the FC receptor, the neonatal FC receptor binding determines some of the pharmacokinetics.

And the binding to HER2 can be evaluated. We know that the HER2 signaling, and cell growth is thereby inhibited by proper binding with the anti-HER2 molecule. In the case of the FC receptor, the gamma receptor binding for ADCC, that is also important and needs to be considered. But with the anti- HER2 molecule the compliment binding does not appear to be important and needs not be considered in the total testing.

Another example is the anti-VEGF molecule where, again, the anti-VEGF binding causes inhibition of the VEGF alpha signaling and causes regression of the cells. In that case the FC receptor binding is unimportant, so the ADCC is not a factor. And also as with anti-HER2 the compliment binding is not a factor, so those aspects do not need to be considered in developing an anti-VEGF biosimilar.

Dr. Birnholz:
Those are great examples, Dr. Cohen, thank you. But before we close out our discussion today, let me just open up the floor to you for any takeaway thoughts on the biosimilarity protocols you've talked about in relation to more commonly understood comparability protocols. What do we need to know there?

Dr. Cohen:
The manufacturing process generally changes over time even for the company that is making the originator compound, and that's because things improve over the two decades or so of the patent life. But this modified process that occurs is done in the setting of the company knowing what processes are used, and what analytical tests are important.

In the case of a biosimilar production there's a knowledge gap in the product history, and the process of evaluation and testing, and so

all of that makes it a little more difficult, which requires that there absolutely must be these extensive analytical studies, as well as preclinical and clinical trials as well to show that the biosimilar is indeed not clinically meaningfully different from the reference compound.

Dr. Birnholz:
Well that's a great way to close out our program today, and I want to thank my guest, Dr. Gary Cohen, for helping us better understand the biosimilar development pathway and highlighting aspects that are most relevant to oncologists.

For ReachMD, I'm Dr. Matt Birnholz. Thanks for joining us.

Announcer:
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