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Part 2: Are You Ready for Biosimilars? What the Oncology Team Should Know

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

Your host is Dr. Matt Birnholz.

Dr. Birnholz:
In the oncology field, offering patients a safe, effective, and potent alternative for approved biologic treatments has never been an option; that is, until recently, when the FDA approved a stringent regulatory pathway for biosimilar candidates. But while this approval makes it possible to offer more affordable treatment alternatives for patients, questions do remain on the scope of regulatory requirements needed to establish biosimilarity to an approved biologic. We'll be tackling some of those questions on today's program.

This is ReachMD, and I'm Dr. Matt Birnholz. Joining me to talk about regulatory pathways for biosimilars 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:
To start, Dr. Cohen, can you just walk us through this regulatory pathway for biosimilars development? What are the main steps we should be aware of?

Dr. Cohen:
It wasn't until 2010 that the FDA was permitted to begin considering copies of biologic medications, what we now call biosimilars, and that was done as part of the Accountable Care Act in 2010.

We can look at some differences here. With regard to the generics, the analytical characterization is required to demonstrate a quality profile and structural identity, which must be precisely the same. Preclinical studies are not generally required, although there is a requirement to show bioequivalence.

For originator biologics they also need to have a quality profile for the original analytical characterization of the molecule. Preclinical studies need to be done both in vivo and then in vitro studies, animal testing, and finally pharmacokinetic testing in phase one studies and phase two studies. And finally, clinical studies.

Biosimilars also require a quality profile, but in this case the analytical similarity must be demonstrated first. And then they must do potential toxicology studies for similarity, show pharmacokinetic equivalence, and then demonstrate no clinically meaningful differences between the originator or reference biologic, and the biosimilar which is proposed for introduction into the clinic.

Dr. Birnholz:
And pitting the regulatory pathway for biosimilars against the guidelines for originator biologics, how do they compare or contrast?

Dr. Cohen:

So the biosimilar regulatory pathway differs from guidelines for the originator biologics in important ways. When you look at the originator development, here the inverted triangle on the left, you can see that the analytical characterization is not really that important because it doesn't really matter what the characteristics are of that compound as long as it works.

So once you have an analytical characterization that is acceptable, you can go to your nonclinical studies, the preclinical trials and then finally test the clinical pharmacology. And then the important thing, the most important thing for the originator is to do the clinical trials, the phase three studies that ultimately show that the drug is safe and effective.

In contrast, in the development of a biosimilar, the really critical component is that analytical characterization. It has to be now highly similar, almost identical to the originator compound. The preclinical studies, the clinical pharmacology, the pharmacokinetics and the pharmacodynamics are of course important. And ultimately, the clinical trials that are done are very limited because all you want to do is show that these compounds actually do have similar efficacy, similar side effects, and no clinically meaningful differences.

When the clinical studies are done for a biosimilar, we are only testing the null hypothesis. That these drugs are not inferior and not superior. And that allows for testing in clinical studies with literally just a few hundred patients as opposed to the thousands of patients that would have been required by the clinical trials for the originator.

Dr. Birnholz:
So that sounds like there's some extrapolation built into meeting the clinical trial requirements for biosimilarity. What regulatory considerations come into play here?

Dr. Cohen:
Extrapolation is a very important process in the biosimilar regulatory pathway. The pyramid of biosimilar development is important because it includes both the analytic similarity of the biosimilar to the reference product, and also the limited clinical trial that are done to show that there is no clinically meaningful difference.

But in order to conserve the cost it's important to be able to extrapolate from a limited clinical trial to other indications. And here we use the example of HER2 targeting. We know that HER2 is a membrane receptor on some breast cancers, and that targeting that receptor improves the survival together with chemotherapy.

Dr. Birnholz:
Let's continue on the clinical trials track and focus on biosimilar immunogenicity testing. How does this, in particular, get considered within the clinical trials?

Dr. Cohen:
In assessing the immunogenicity of biosimilars in clinical trials the FDA requires that this be specifically looked at. So key considerations include, first of all, choosing a sufficiently sensitive patient population, and this means ones that are relatively healthy so that their underlying immunity is not impacted.

The duration of follow up needs to be considered because it's important to have a sufficiently long time course in order to identify any antidrug antibodies that might develop.

And in terms of assaying for the antidrug antibodies it's important to have a validated assay for the antidrug antibodies, one that is sufficiently sensitive, and should be able to assess binding and the presence of neutralizing antibodies.

Here we see a three-dimensional model of a typical antibody. And as you can see on the left there is binding to the FAB portion, the target. And then there is also a molecule, an anti-antibody which may be binding to the FAB portion. It can change the secondary and tertiary structure of that molecule in a way that may affect clearance, or even the binding of that target.

And you can see on the right-hand side a depiction of what might be a neutralizing antidrug antibody where it does impact the active site of the monoclonal antibody. So the monoclonal antibodies can be immunogenic, and when they are the variety of antibodies that might occur in the human body can affect the biosimilar in several different ways.

Dr. Birnholz:
So Dr. Cohen, earlier you mentioned the consideration for sensitive patient populations in these biosimilar trials. Can you elaborate on that a little more?

Dr. Cohen:
We know that biosimilar trials must have the clinical testing, and it's important to have sensitive endpoints that can distinguish between the biosimilar and the reference product if any differences occur. So we need sensitive populations that may provide greater support for extrapolation, and we know that the endpoints may differ from those of the pivotal studies that were done by the reference product to get

initial FDA approval.

Now when we're thinking about pharmacodynamic endpoints to establish a biosimilarity, we think of a lot of clinical endpoints. We certainly need to demonstrate the clinical benefit. And in doing that studies have to have ethical considerations, there have to be time considerations, when are various endpoints looked at. Cost considerations are certainly included there, and the sensitivity of the endpoints is important.

In the case of biosimilars we want to make sure that the endpoints are sensitive, and that may differ from the originator because what we're interested here is in measuring activity. It's not that important to look at overall survival, which of course can be confounded by lots of different factors. And the relationship between changes in the pharmacodynamic marker and the clinical outcomes is really important.

Now once we understand that the pharmacodynamics is acceptable, the biosimilars need to be studied clinically. And we know that in breast cancer there are many potential endpoints that can be looked at in studies.

So all of these things can be studied. And the studies that were done on the originator anti-HER2 clinical trials, overall survival and progression free survival were looked at as statistical endpoints. But, in fact, those things are difficult to show with fewer patients and in a short timeframe. So the biosimilar studies concentrated on response rate and the pathologic complete response.

Dr. Birnholz:
And staying with the anti-HER2 clinical trials for a moment, what were some main considerations going into the development of a phase 3 biosimilar trial?

Dr. Cohen:
So considerations when developing that phase three clinical trial for a biosimilar, in the case of HER2 positive metastatic breast cancer, we know that those populations are more heterogeneous, and metastases can occur in various organs. If you do have hepatic metastasis you may have some degree of hepatic compromise, and that might relate to whether patients do better or worse, have more or less toxicity, so there are these confounding factors of performance status and the site of disease.

And then of course the response rate may be difficult because we know when patients have multiple metastases, they sometimes have mixed responses. One area may get better when another area gets worse, so what does that mean? So in developing a phase three clinical trial for a biosimilar, you would want to focus on the early breast cancer population where those patients are healthier, much more favorable performance status, a homogenous population.

Dr. Birnholz:
What about biosimilar trials across other cancer types? Have any unique considerations needed to be taken into account from one trial to another?

Dr. Cohen:
We know that in lung cancer uh several potential endpoints were used. In the case of the originator studies, overall survival and progression free survival was studied, but again we know that these parameters to find a statistical significance takes thousands of patients and a long time.

So that instead, it's possible in the biosimilar study to just look at the overall response rate if you're dealing with a stage three or stage four disease. And so in the case of anti-VEGF clinical trials in lung cancer, the endpoint was overall response rate rather than survival or progression free survival.

It's also important to recognize the patient population that you're dealing with. So when you're looking at angiogenesis and the antiangiogenic drug, bevacizumab, we know that in metastatic colorectal cancer bevacizumab has been used, but it's not because of response rate because in fact there is no difference in response rate when bevacizumab is added to chemotherapy. There is a difference in overall survival, but to show that requires thousands of patients. And so overall response rate is not an option as a reasonable and sensitive pharmacodynamic endpoint in metastatic colorectal cancer.

In contrast, adding bevacizumab to chemotherapy in non-small cell lung cancer does substantially improve response rate, and there's a strong association between the tumor response and survival. So overall response rate in trials of bevacizumab, or a bevacizumab biosimilar, are sufficient for looking at the pharmacodynamic marker in lung cancer, but not in colorectal cancer.

Dr. Birnholz:
Dr. Cohen, before we wrap up today, I want to consider one more critical factor to the successful adoption of biosimilars, and that's whether these regulatory pathways are actually meeting physician expectations. What can you tell us about that?

Dr. Cohen:

Studies were done in 2016 with a variety of physicians. Many of them were oncologists. And that 2016 survey showed that only 12 percent of US physicians were comfortable with the idea of extrapolation. Physicians wanted a thorough understanding of biosimilars before they felt comfortable prescribing them to their patients. And in a 2016 survey, 87 percent of physicians felt that data from the biosimilar trials would be important in their decision making.

In order to meet those expectations, we know that generating robust and rigorous data is important, and there must be a totality of evidence that physicians will appreciate. Matching the critical quality attributes, the CQA is something that is also measured in this testing. Clinically appropriate trial designs, we need to choose the right populations and choose the right endpoints. And finally, we need to be sure that the data is published in peer reviewed journals so that physicians can review it personally and have the ability to make their own critical judgments.

Dr. Birnholz:
Well those are great comments for us to think on as we come to the end of today's program, and I want to thank my guest, Dr. Gary Cohen, for helping us better understand the current lines of thinking around regulatory pathways for biosimilars.

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

Announcer:
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