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The Biosimilars Landscape: Key Pieces of the Puzzle for Clinical and Commercial Success: 2017-2021, What All Developers Need to Know

Alicia Baker, John Carlsen, Mark Fletcher, March 27, 2017

AUDHALI: Good morning or good afternoon, everyone, depending on where you're joining us from, and welcome to today's webinar. My name is Tareq Audhali from Business Review, and I will be your host today. It is our pleasure to have Covance with us today, who will be presenting this webinar titled The Biosimilars Landscape: What All Developers Need to Know.

Today's guest speakers are Mark P. Fletcher, executive medical director, Inflammation, Infectious Diseases, and General Medicine. Alicia M. Baker, director, Global Regulatory Affairs Strategy, and John K. Carlsen, vice president, Covance Market Access Services. I'd like to welcome you to our webinar platform ON24. You'll notice this webinar is fully browser-based. If you disconnect for any reason, simply click on the link you received via email to rejoin the session.

In order to ask us questions, you can send them in via the questions widget. Just type them into the box at the top left-hand corner of your screen, and click submit. We're going to try to allocate some time towards the end of the session to address any questions or thoughts you may have. Please use the yellow help widget if you do require technical assistance. And you can move, resize, and maximize any of the windows in front of you to get a better view of the slides.

But now that having been said, please allow me to welcome today's first speaker. Mark, over to you.

FLETCHER: Thank you, Terry, and good morning, good afternoon, and good evening to all who are calling in. We greatly appreciate the opportunity in the next hour to give you a high-level view of our focus and our experience across Covance some of the clinical and commercial key features to move forward with biosimilar development and all aspects of that. And we think this may be useful to all developers who are at various stages of thought about the development of a biosimilar, whatever the stage. So with that, I'd like to turn it over to John.

CARLSEN: Great. Well, thank you. Biosimilars have certainly been a hot topic in the U.S. over the last few years, and the attention given to biosimilars has certainly not let up over the past several months. So what we wanted to do here was highlight some of the, what we think are the notable headlines related to various aspects of biosimilar development and commercialization.

If we start at the top of the timeline here, there have been several developments related to new product approvals and launches. So if we go back about a year to April of

2016, the second biosimilar was approved. That was Inflecha, Inflectra, I should say, a biosimilar version of Remicade. And then toward the end of the summer of 2016 the first biosimilar versions of the Enbrel and Humira were both approved, although those have not launched yet. Remicade did launch, or the biosimilar version, I should say, Inflectra did launch in October of last year.

And then in terms of some developments related to new biosimilar filings, the, an application or a filing for Herceptin was filed in November of last year. So that's pretty significant in that that would be the first anti-cancer biosimilar in the U.S., or at least it was the first filing for an anti-cancer drug. There's also been a lot of legal developments over the last several months.

Both in November of 2016 Amgen acknowledged that due to patent issues, its biosimilar version of Humira, although approved, will probably not launch until 2018. And then in January of this year, Sandoz said the same thing about its Enbrel, its biosimilar version of Enbrel, which also has been approved but won't launch until next year. And both of those delays are due to legal issues and patent disputes.

A very significant legal development relates to the Supreme Court. In January it announced that it is taking on the case of how quickly biosimilar drugs can be marketed, and that's a really important case because the outcome of that will determine whether biosimilar manufacturers have to continue to wait six months before launching a new biosimilar or if, or that will no longer apply. So everyone is kind of anxious to see how that will turn out.

And then, you know, not all of the legal developments have been as significant as the ones I've just described. In February, so just last month, Genentech filed a lawsuit to delay Amgen's biosimilar version of Avastin, but that lawsuit was thrown out just a couple of weeks later. So it really speaks to just how unpredictable the legal environment is surrounding these products.

And then the last thing I wanted to point out is that if we go back to January, there was a very significant development related to new FDA guidance on interchangeability, and we're going to be talking about that a little bit later in the presentation. So these are just some examples of how biosimilars have been making the news over the last year or so.

So the next thing I want to address is why are biosimilars making so much news in the United States. And there are really several reasons for that. One is that, relatively speaking, this is still a fairly new FDA approval pathway, especially when you compare it to, and when you compare the U.S. to other countries, like in Europe where biosimilars have been around for, in some cases, more than a decade. In the U.S., in contrast, the biosimilar approval pathway was only created in 2010, and the first biosimilar was not approved under that pathway until 2015, which was when Zarxio was approved. That's a biosimilar version of Neupogen.

Another reason why biosimilars have been getting so much attention in the U.S. is because there's a fairly controversial Medicare reimbursement policy related to biosimilars, and I'm going to be talking about in, I'm going to be talking about that in detail later on in the presentation. Also just in general, across the entire landscape of drugs and biologicals there is increasing scrutiny that's being given to high drug prices. And that's certainly not unique to biosimilars, but biosimilars could be an answer in

terms of one of the things that could help to mitigate rising drug prices. And so that's another reason why people are so interested in this topic.

And then finally, in the U.S. we have a lot of big blockbuster biologicals that have either recently gone off of patent or are expected to go off patent in the next few years. And so there, that makes those products very attractive from a biosimilar development standpoint, in that those are very high-profile targets for companies that are developing biosimilars.

So that just gives you kind of the, an overview of why people are so interested in the topic of biosimilars. Before we go any further in the presentation, we are going to go to our first polling question.

AUDHALI: Thank you very much. Yes, that's absolutely right. So now it's time for the first poll question we're running in today's session. So, audience members, if you could, please select the answer that's most relevant to you and hit submit. So all you need to do is select the answer that's most relevant to you and hit submit. Now the question is, what's your involvement in biosimilars? We've got a few options there for you to choose from. That's CMC, clinical, preclinical, regulatory, market access, or not currently working biosimilars. So you've got a few choices there, CMC, clinical, preclinical, regulatory, market access, or not currently working on biosimilars.

While you make your selection, I'm just going to hand you back to our speaker briefly to provide some context.

CARLSEN: Sure. Well, we know we have a lot of people from the various aspects of pharmaceutical and biological companies on the line today, so we're just looking to get a better picture of kind of where you're coming from and where your interests might lie. And as we'll talk about throughout the presentation, all of the areas listed on this slide here are areas in which Covance can work with drug developers.

AUDHALI: Okay, lovely. Thank you to everybody who took part. Now let's go ahead and see what those results are. Okay. We've got quite a mix there, don't we? We've got a few people not currently working on biosimilars there and also in clinical as well.

CARLSEN: Great. Well, yes. So I think this, again, just underscores the fact that we have kind of a broad mix of stakeholders on the line today. So hopefully there will be a little something for everyone in today's presentation.

BAKER: Okay, great. So this is Alicia, and I'm going to pick it up from here. What are biosimilars? Today's discussion will focus around the regulatory environment including an overview for development pathways and an update on key issues from 2016 through what we project to be happening through 2021. We'll cover a discussion of CMC bioanalytics and pharmacodynamics, discuss a cost-effective (fit for purpose) preclinical tox program. We'll identify key clinical issues for both PK equivalence and planning and execution of Phase III equivalence studies, followed by a discussion of early initiation of market access and commercialization messages. And then we'll wrap it up with a summary, and we invite your questions.

So what are biosimilars? In the U.S. they're defined by the Biologics Price Competition and Innovation Act of 2009, also referred to as BPIC Act. And the EU defines biosimilars according to EU Directive 2004/27/EC. The spirit of the definition is the same between the U.S. and the EU, although they word them slightly differently. The biggest difference between the two is that the FDA will determine interchangeability in their regulatory review, and the EMA will not comment on interchangeability and leaves it up to the individual member states.

So this line shows the products that are being targeted for biosimilar development. So many of these products, many are in the rheumatology space, but there are also multiple biosimilars in development, so as we see with oncology as well. There is a lot in this space, and it can be daunting but it should not be discouraging. Because there are so many companies going after this, there's definitely a market for it. So as you can see, there are a number of companies going after each target. It gets to be a little competitive, but, clearly, there's the market out there for these biosimilars.

So this is a stepwise assessment of the totality of evidence. This is the drug development pathway for the biosimilar, your first being your quality, structure, and function. You have to generate the totality to prove your biosimilarity, and you have to have the same protein sequence and demonstrated potency showing minor differences in post-translation modification, such as glycosylation. And you should have the same effector functions regardless of potential contribution of mechanism of action. So this would be your first step in development, your quality and your structural and functional data. And then you would approach the agency and start talking about the similarity of your compound.

The next step would be your pharmacology. Your PK in healthy volunteers or most sensitive population, equivalent PK establishes same dose as the reference product, assuming equivalent potency and functions. Generally, a 90% confidence interval to be within 80% to 125% is standard. And your pharmacodynamics with dose-response equivalence can infer clinical efficacy. So again, you would generate this next step of data, and then approach the agency again.

And then your last step in development would be your Phase III clinical study. Your clinical efficacy confirmed in a randomized, blinded, head-to-head study in a sensitive population with sensitive endpoints. Your clinical safety is confirmed in at least one sensitive patient population with enough exposure and time, and then immunogenicity assessed with drug tolerant assays in sense, in a sensitive population.

So as stated, it's a stepwise assessment, and currently all of these steps are necessary to show biosimilarity. The regulations are written such that, in theory, if you show strong analytical and functional data, additional clinical data may not be needed. But currently, agencies are not comfortable with this so, therefore, each step provides a critical contribution to the totality of evidence. Each step should rely on the most sensitive state-of-the-art capabilities, and no step can overcome or refute significant differences in the other development steps.

So overall, keys to success. The biosimilars have to be systematically engineered to match the reference product. You have your biosimilarity assessments to be conducted against the innovator reference product at all levels of product development, which includes your physiochemical attributes, primary, secondary, tertiary, and quaternary structural assessment, biological activity, preclinical in vivo

biosimilarity, Phase I PK and safety, Phase III efficacy and safety, and impact on shelf life on all of the above is critical.

The inherent variability of biosimilars exist in the innovator reference product as well. So it's important for you to decipher how these differences have a clinical impact. The characterization of the biosimilar will always be much higher than that of a new biological entity. And the characterization, of course, will always include reference product versus biosimilar.

So next we're going to talk about some key issues in clinical practice. So, of course, sourcing of the reference product is critical. The agencies have in recent years relaxed their position on the reference products such that they're not, you're not step-running separate studies with each country reference product. You typically see a three-way bridging study in Phase I PK and/or PD study to compare the U.S. reference product, EU reference product, and the biosimilar product.

Extrapolation of indications beyond those studies we, studied we know is possible as we've seen with recent approval which is supported by regulatory guidance, provided that efficacy and safety of the biosimilar is justified, based on the overall totality of evidence. So as we've seen, for example, with Inflectra, they were able to extrapolate all of the indications for the Remicade product, reference product.

Substitution of biosimilars either with a reference product or between biosimilars has regulatory measures to define automatic substitution policy. And switching or interchangeability, which is a very hot topic now, it's determined by FDA but not the EMA. And this is still yet to be seen in the U.S., but the FDA has come out with a recent guidance document called Considerations in Demonstrating Interchangeability with a Reference Product just this year. It's a draft guidance, and it provides the following considerations. So switching studies should be designed to determine whether alternating between a biosimilar and its reference product two or more times impacts the safety or efficacy of the treatment course.

Sponsors should carefully consider the product presentation, which is interesting, including the delivery device and container closure system as differences in presentation may affect determination of interchangeability. Given the unique delivery devices and presentations associated with biologics, this could potentially be a challenge and something to be addressed early on. And requirements for interchangeability will vary based on the product submitted, obviously. So there's no single data package for all proposed interchangeable products. So, obviously, early agency engagement is encouraged to discuss this issue.

The post-marketing pharmacovigilance, there's confusion in naming of the biosimilars for AE drug reports. The post-marketing solutions are to apply appropriate measures to identify the product and batch number used in patients as well as agency-driven risk-management plans to include specifically focused post-marketing studies. And for real-world acceptance and reimbursement, we have a limited understanding of biosimilars, and some solutions for this are physician education of the biosimilars and also providing a reimbursement process analysis and value proposition. And John will touch more on this later.

So while we're mostly focused on discussing the U.S. and the EU, which are usually primary targets for initial development, we also want to discuss some of the other key players in this market, and let you know that we keep our finger on the pulse

of what is going on throughout the world. Both India and China are significant producers in the biosimilars market. So India recently provided a revised guidance document made available in 2016, and they're poised for big growth in the next three years or so, projected to increase from $186 million in 2016 to $1.1 billion by 2020, according to industry estimates. India is preparing for this, and even investing in biosimilar development by establishing manufacturing facilities in other countries.

China is also another big player in the market. Analysts see substantial growth opportunities for monoclonal antibodies in the next five years. Approximately 5.5 million RA patients in China cannot afford using drugs from global companies, such as the reference products. However, China is still slightly behind in its regulatory pathway. A technical guidance was released in 2015, but it wasn't derived from any overarching law. So to date, there is not an abbreviated pathway for biosimilars in China. They're still approved according to the same pathway as innovative biologics.

So in summary, the key messages are major markets are harmonizing but they're not completely there yet. Other countries' regulatory sophistication is highly variable. For example, Australia, essentially the same as the EMA, versus India, which has no comparative exercise needed versus China moving towards EU. Early engagement with regulatory strategists can help you design an efficient program to meet needs of as many markets as possible. And early and frequent engagement with regulatory agencies help to confirm your development plan and the appropriateness of the data you're generating.

FLETCHER: Thank you, Alicia. This is Mark coming on again. Now you see kind of the high overview that the development of biosimilars is really putting the usual biologic development paradigm kind of on its head. So typically, the biggest part of a development program for innovative biologic is the critical data package. But by design, we're comparing a known and well-understood biologic product to a new biosimilar. So this is really a comparative type of assessment.

So the CMC, the structural and functional characterization, is really the base of the pyramid, and then the idea is that with that being extremely strong and show highly comparable biosimilarities between the reference and your particular biosimilar, makes you require much less in the way of non-clinical studies, as well as the overall clinical information going toward both Phase I and Phase III. So I'd like to talk a few minutes about each of these, starting with a little more detail about CMC analytics, which is a comparability exercise as Alicia has pointed out.

So some of the key issues are that we understand, particularly from doing a very large number of CMC bioanalytic characterizations of biosimilars at Covance over a number of years, that there are key factors in the analytics of a biosimilar in the comparative exercise that could impact the efficacy, the safety, particularly the immunogenicity and certainly the PK of a biosimilar product. And the way forward first is to understand as much as possible where and if any differences, and there will always be some differences, are because we know that certain differences in the potency, perhaps the effector function, particularly also glycosylation, oxidation, and deamidation, aggregation characteristics can affect efficacy.

And many of these factors could also affect safety through development of immunogenicity or other side effects, and also through changes in the PK half-life

through aggregation or glycosylation affecting immunogenicity, the PK of the drug, all of which has to be well characterized in your overall package.

But assuming in this stepwise approach that you do this, so I just wanted to understate a particular case study that might be illustrative of some of the key factors and how we've helped at least one client here to move forward with their development program. This is an Asia-based company who has been developing adalimumab biosimilar for Humira. They came to Covance with a number of potential clones, cell clones, expressing their adalimumab molecule, and they were tasked, we were tasked to help them select the best clone to minimize the development risk based on our analytic experience and translation of key quality attributes. That are, that is the attributes that, when different, might have the greatest risk for demonstrating differences between the reference product and their product.

So we designed an analytical program based on their target product profile, and we worked through a lot of the preliminary clinical quality attributes, as I've mentioned. Of particular interest was the glycosylation profile across the different clones relative to the reference adalimumab. And as an example, the glycosylation profile of adalimumab is seen in the graphic on the right.

So through our analytics, although we did discover some small differences being observed between the various selected clones, there was confidence in the selection that we chose for them or recommended because we understand from a lot of prior experience some of the CQA qualities and a way to minimize the risk of impact on a particular mechanism of action.

So overall, Covance really has extensive experience in constructing these type of CMC strategies for clients as their cells around linking the structure of the biosimilar and its function to what would be potential effects on PK and PD and through that efficacy. So we added value, I think, to this client by helping them select the best clone to carry forward to minimize this kind of risk.

So the next step, assuming that you have a highly characterized and highly similar CMC bioanalytic characterization, the next question is, how do you design a fit-for-purpose and very cost-effective nonclinical testing program, and do you need to do one even? So in general, testing in the preclinical space of like monoclonal antibodies or even other non-monoclonal antibody biologics. It involves, you know, characterization of this relative to the market innovator product.

Now it turns out there aren't any specific regulatory guidances that are unique for a biosimilar, though there are many for general biologics and development, you know, including the EU, the FDA, the World Health Organization. And typically, companies use that, those guidances for biosimilars just as they would with an innovator biologic. The key here again is, as we've talked about before, a stepwise approach to the testing. So the first step is really relevant in vitro work, looking, for example, at binding, functional assays. If it's a monoclonal antibody with an Fc function, you have to characterize both the target binding and the effective function Fc components to see how similar they are. This is very important.

The next step is really determined based on that level of similarity or dissimilarity, what in vivo work might be needed in the preclinical model. And if you do need to do that, then what's needed is really done on a case-by-case basis with regard to a PK or PD study or what additional toxicology studies might be.

So a general strategy that we have worked with many companies on is, really, is there a need for toxicology testing at all? And at this time, there's really no global agreement about this. For example, at one end of the spectrum, the EU indicates that toxicity testing is usually not recommended unless there is some particular signal in the comparative assessment of your CMC bioanalytical or PD that would suggest there might be some issues. On the other hand of that spectrum, the FDA at this point is saying testing can be discussed, and including justifications for not doing some degree of toxicity studies.

The WHO has some general regional guidelines that I will get to, but currently they do request testing at least one repeat dose toxicity. Note, but they are in the process, if you will, of modifying their guidelines, which would appear to be more in line with the EU, that is a more minimalistic approach. So it's really the toxicology work . . . demonstrating the biosimilarity to the reference is still occurring, you know, for antibodies, but you need to satisfy certain requirements if you're going for a global or more potential broad market. You may, for at least some of the markets, require toxicology studies for now.

The overall goal is, really, in the future going forward is to assess whether you need to do any toxicology studies. The stronger your comparability data is in the CMC to support the biosimilarity of your product via this characterization, then the more minimalistic need for the preclinical program is required.

Now assuming that you have moved through this and you're moving now into Phase I for showing bioequivalence of yours with the reference product, there are, from our experience in doing these type of studies, a number of key success factors that we think are useful to be, you know, cost-effective and done well in terms of expertise and time. One is that you need a highly experienced bioanalytical lab that can do the PK and have a good assay development for the anti-drug antibodies, both a presence screening assay and a neutralization assay.

Significant medical and scientific biosimilar expertise about the unique aspects of developing and running clinical studies with, you know, a biosimilar development program. And then, certainly, how to assess bioequivalence, and a strong track record of transitions. Particularly, how do you overlap or transition from Phase I to Phase III, can you be more aggressive and do interim analyses in Phase I to start Phase III, or are they always serial and so forth?

And then, certainly, time is of a great factor. Rapid startup times are critical and having operational capabilities globally, particularly U.S. and EU, and I'm, certainly more and more Asia-Pac area is very important, and that you have a highly collaborative interaction between your clinical research unit that might be doing this Phase I study in normal volunteers and the bioanalytical lab so that you get the data out that you need quickly, all of which Covance has. And a dedicated early clinical service biometrics team that can analyze and present the data for rapid decision-making.

Now assuming that we go through all of these steps, then as you move forward, at the top of the pyramid now you're still at the present time, for the most part, need to do a Phase III pivotal study to demonstrate that your biosimilar is highly comparable, highly similar to the reference products. So some of the unique considerations I'd like to talk about just for a few minutes before we move on.

And usually you do need to demonstrate biosimilarity of the two products is a comparative exercise. It's not really that you're trying to show this is efficacious, because it's already been proven that this product and its records is efficacious, it's really about showing no clinically important differences in terms of efficacy and safety. So some of the key design issues that we have helped walk through clients who are looking at this is what therapeutic indication would you use that would be considered the most sensitive to show any potential differences. This is what regulators are looking for, a sensitive measure. To see if you do have any differences between your biosimilar and the reference product, you have to have a sensitive population.

And this could depend on also the background therapy that these patients would have, if they're blinding and stratification required. And in terms of whether you had incurred any switching from the originator to the biosimilar product as part of the later stages of this study. And also the primary endpoint variable that you would use, and then particularly from that endpoint. So for example, an ACR20 response if you were doing a rheumatoid arthritis development program or other inflammatory arthritides.

What's the choice of an equivalence or a non-inferiority design and what the equivalence margin would need to be, which is really a clinical and regulatory kind of selection that you have to justify and get acceptance by regulators about the margin. And this drives what the sample size would be. While there have been some recent considerations of alternative statistical approaches that might be more efficient, at this time the regulators are mostly interested in classical inferential type of designs.

Just I wanted to mention that we do have considerable experience in all these aspects of biosimilars, just to indicate that we had this broad experience across the full spectrum of drug development, working on many different, unique biosimilars, close to 100, and more than 150 different projects. And many of them are involved in the rheumatologic space, but certainly a number of them, if not more, in the non-inflammatory biologics, including antibodies as well.

So in terms of clinical expertise and regulatory autoimmune inflammatory disease for a minute, Covance can help you, and we're helping clients with this area in terms of rheumatology drug development, Phase 1b to IV experience in RA for the biosimilars being developed for rheumatoid arthritis, for example. But a strong track record of smooth program transitions from this Phase I to Phase III.

And we also have a very large proprietary database and a number of databases that can help identify particular sites that are motivated and have interest in biosimilar studies, which may be the non-classical type of site for a new, innovative product because this biosimilar, by its nature and definition, is highly similar to an approved product. So it's not a new mechanism action, and identifying sites that have interest to do these relatively large Phase III studies is going to be important to you as well. Thank you.

AUDHALI: Thank you. Now it's time for the second interactive poll we'll be running in today's session. So, audience members, if you could please select the answer or answers that are most relevant to you and click submit. And the question is, are you developing biosimilars inside or outside the U.S.? That's, are you developing biosimilars inside or outside the U.S.? The options you have are in the U.S. only, in Europe, in India, in China, or other. So select any that apply to you, and then hit submit.

While you make your selection, I'm just going to hand this back to our speaker very briefly. Could you maybe comment on the question just to give the audience a bit more time to vote?

FLETCHER: Yes, thank you. Thank you, Tareq. So this just helps us understand our audience today and where your interests might be relative to the focus for development of your products. We have a broad audience that's signing in, and we just wanted to understand where you're at. We have, though we didn't mention, a strong presence in Europe and the U.S. but also in the Asia-Pacific area, and are doing a lot of work with partners there in the biosimilar space or with their partners that are also in the U.S. or Europe.

AUDHALI: Lovely. Thank you very much for that. And just before I move on to show the results, I'd like to remind everyone that we will hosting a live Q&A session at the end of this webinar. So, please, if you do have a question for any of today's speakers, type it into the box at the top left-hand corner of your screen and hit submit. We're going to try to get to as many of those as we can at the end.

Okay, thank you to everybody who took part in today's poll, and let's go ahead and have a look at those results. Okay. So the majority are going for other than. Does that surprise you?

FLETCHER: No. I think that depending on the stage of development, we saw commercialization and early analytics the most prominent. I think, certainly, the markets in the U.S. and Europe are the most advanced, and so I can understand that. But the other could be really individual countries and so forth, which we have worked on and are working on as well for individual biosimilar development in a particular country. So that's not surprising to me at all. Thanks.

CARLSEN: All right. Well, this is John Carlsen again, and I'm going to be talking about market access for biosimilars. And I should note that I'm going to be focusing on market access issues for biosimilars in the U.S., which is my area of focus. I work for a division of Covance called Covance Market Access Services, and we do have global market access capabilities. But for just in the interest of time, we're, I'm just going to be focusing strictly on the U.S. today.

And market access is something that we've been working with clients on for several decades, both drug companies as well as biologic companies. And I would say for any company that's developing a biologic, market access is a very important part of the product planning and development process, and that's equally true for biosimilars. So we strongly encourage biosimilar manufacturers and developers to really make sure that they engage in the full spectrum and market access planning activities. So doing things like landscape assessments and primary research with stakeholders, looking at the policy and insurance environment.

Those are all very important, especially for this first wave of biosimilars that's going to be coming to the market over the next few years. So on the remaining slides I'm going to be talking in more detail about market access issues.

In the U.S. whenever you're talking about market access, particularly for these types of products where areas like oncology and rheumatoid arthritis are so important, a big piece of the market access landscape is coverage under Medicare Part B. Particularly if you look at the first two biosimilars that are on the market in the U.S., there's a biosimilar version of Neupogen and a biosimilar version of Remicade. Both of those products are provider administered, and that means they're both going to be covered under Medicare Part B and they're both going to have, because of the nature of the diseases, there Medicare is going to be predominant payer for those products.

Now what I'm going to be focusing on when I talk about Medicare and commercial payer issues, I'm going to be focused on biosimilars that are approved under the new abbreviated biosimilar pathway. So there are other ways that a biosimilar can come to market but, by and large, most of the attention right now in the U.S. is focused on the abbreviated pathway, and that's going to be my focus as well.

And at the very beginning of the presentation I mentioned that Medicare Part B has a fairly controversial reimbursement policy for biosimilars under the new pathway, and that's what I'm going to be talking about now. Basically, what this, what the nature of this policy is is that if you have multiple biosimilar versions of the same innovator product, which we don't have currently on the market but, you know, we expect to see that in the future, then all of the biosimilar versions of an innovator product will be paid under the same Medicare Part B payment rate, which is based on average sales price.

So every product will share the same payment rate, and that is every, you know, every version of the innovator product will share the same ASP payment rate, and it will be a weighted average ASP payment rate. And so, and the way that the weighting works is going to be based on market share, essentially. So ASP stands for average sales price. And as the name would suggest, ASP is based on actual sales data that's submitted by manufacturers to CMS, or the Centers for Medicare and Medicaid Services.

So if you have a scenario like we've depicted here, which I should note is purely hypothetical where you have, let's say, three biosimilar versions of the same innovator product, each of those manufacturers will report sales data for their biosimilar to CMS. And CMS then will use that data to calculate a weighted average or a blended ASP payment rate that will be shared by all three products, and whichever product has the most market share is going to have the most influence on the ASP for the product. And so this is, it's very important to understand this dynamic in the U.S. reimbursement landscape, because essentially what it does is it removes a lot of the pricing flexibility for biosimilar manufacturers.

Now in reality, each biosimilar manufacturer can technically price their product at whatever level they wish to, but in practice it's very, you know, what the reality is is that each, you know, especially for biosimilar manufacturers that are not the first to market, you need to take into account what the ASP payment rate is that has already been established. So again, in theory you can price your product however you want, but in reality, really, if you want your product to be viable in the market, you're going to need to take into account the pricing that's already been established and try to stay pretty close to that if you want providers to have an incentive to purchase your product.

Now that's one piece of the U.S. market access landscape is reimbursement under Medicare Part B. Another important piece of U.S. reimbursement or market

access is coverage by commercial insurers. And with commercial insurers, it's much harder to generalize about their payment policies because, for one, there's so many commercial payers across the country in the United States, and each one has different policies. And they also, in contrast to Medicare, they tend to make their, their reimbursement policies tend to be not as publicly available. So with Medicare, everything is published on the CMS website. With private payers, there's not always, there often, I should say, is not that level of visibility and transparency.

So to get around this, one of the things that Covance has done over the last few years is we've conducted several surveys with commercial payer decision makers. So we've done our own primary research where we've looked at commercial payers' attitudes towards biosimilars and how these payers expect to cover and reimburse for biosimilars. And what we found is that for the most part commercial payers in the U.S. are very willing to steer utilization toward lower-cost biosimilars as long as there is a meaningful difference between the price of the biosimilar and the price of the innovator.

So, you know, if it's just a nominal difference, that's not going to be enough to move the needle. But if there is a significant difference, then that could prompt commercial payers to take action. And when we did our surveys with payers, one of the things we looked at was differences across therapeutic areas, and we particularly focused on RA versus oncology because, as I mentioned earlier, these are the areas where we have the first biosimilar products in the U.S. They, we have one in oncology and one in RA.

And what we found is that, through our survey, is that payers are more willing to steer utilization toward biosimilars in RA as compared to oncology. And that makes sense when you think about RA historically, because for many years now RA has been a crowded space. And even before biosimilars, there's been a lot of aggressive payer management in that space. Whereas with oncology, the payers have been somewhat hands off historically. So it stands to reason that payers expect to be more aggressive with, in terms of steering utilization toward RA biosimilars.

But that said, I think one of the notable takeaways from this part of the survey is that payers are still willing to get involved in oncology management and steer biosimilars, and steer utilization towards biosimilar therapies in oncology. So they're still willing to take action, it's just their willingness is a little bit less as compared to RA.

Another thing that we found notable about our research with commercial payers, which I should note is synonymous with private payers. People use those terms in the U.S. interchangeably. One of the things we looked at was interchangeability. And by all accounts, it could be a while before we see a product with an official FDA designation of interchangeability. But one of the things that we found interesting from our survey was that private payers, most private payers are willing to make their own determinations of interchangeability, even in the absence of a formal designation by the FDA.

And the survey participants indicated to us that they may use resources like Compendia listings, the results of clinical trials, peer-reviewed studies, clinical guidelines like NCCN, input from key opinion leaders. So these are all sources of information that commercial payers are willing to go to, you know, even in the absence of an FDA interchangeability designation. So payers are ready to, you know, they're not necessarily going to wait for the FDA to take action in that area.

Now for more than three decades, Covance has been a pioneer in providing, in working with manufacturers to provide robust customer support programs. And by these I mean things like reimbursement hotlines, patient assistance programs, provider-facing field teams to help with reimbursement and market access issues. And we feel that these resources are especially important for new biosimilar manufacturers. Because by definition if a product is biosimilar, there's not too many ways that you can differentiate that product from the innovator product, because, you know, that's what biosimilar similarity is all about is that there's no clinical, clinically meaningful differences.

So you have to look for any opportunities for differentiation if you're marketing these products. And we think that by providing robust customer support programs, that's a great way to do that. I think, number one, you have to offer these types of programs to at least be competitive with the established innovator products. But if you can go above and beyond and offer resources that are even more robust, that might be a great way to differentiate your biosimilar.

And so with that, I think we'll wrap it up. I'll turn it over to you, Mark. Okay. Well, I'm going to keep talking. So we just have this one last slide. We want to leave plenty of time for questions, but we really just wanted to end on our summary of Covance's capabilities. You know, I mentioned early on that all of the areas that we've talked about in today's presentation are things that we can work with manufacturers to support them on, whether it's CMC or market access or, you know, other aspects of the drug development process. We really feel that Covance as an organization has the full spectrum of capabilities to help manufacturers in all these areas. Okay, Mark, I see that you're off mute, if there's anything that you want to add to that.

FLETCHER: No, you did it very well. And again, having only an hour to give you a high-level view, we are glad to speak to any of you, and you'll see connections to Covance about questions that you may have through the links. We appreciate and happy to try to respond to questions that you may have. Thank you very much.

AUDHALI: Thank you. And just a reminder for the audience, in order to ask questions, you can send them in via the questions widget. Just type them into the box at the top left-hand corner of your screen and click submit. So we're going to move into our Q&A session now, and we're going to get to some of these questions that have been coming in throughout the session, but, please, do keep them coming in. We're going to try to get to as many as we can.

This first question is, what biosimilars are expected to be approved in the near future?

CARLSEN: I can take that question. This is John again. There are several biosimilars that appear to be on the horizon in terms of awaiting FDA approval over the remainder of 2017. For example, we're expecting another version of Remicade to be approved fairly soon. We also expect to see later this year the first biosimilar version of a epoetin alfa, which is marketed under the brand, currently marketed under the brand names of Epogen and Procrit. In terms of that, that's what the, the brands for the innovator products.

We expect multiple versions of Neulasta to be approved, which is kind of a second-generation Neupogen, more or less. And we also expect another biosimilar version of Humira, and we also expect approvals of the first versions of Herceptin and Avastin. As I mentioned in the beginning, those are notable because those would be the first anti-cancer biosimilars approved in the U.S.

And I should note too that all of that, everything I just said is based on what information that's publicly available. So that's by no means an exhaustive list of what's on the horizon, because companies are not obligated to disclose publicly if they file with the FDA. So there could be others that are in the works that we just don't know about. But that's a snapshot of what we can expect based on publicly available information.

AUDHALI: Lovely. Thank you very much. Moving straight into the next question here. This one is, when is the Supreme Court expected to make a decision on biosimilars?

CARLSEN: I can answer that one as well. My understanding is that they are expected to begin hearing arguments in late April of this year, and that a decision is expected by late June. Now, you know, I think all of those timelines are subject to change, but that's my understanding of where things stand. And as I mentioned earlier, that will be a big decision because that will determine whether or not biosimilar manufacturers have to keep waiting six months before they can actually launch their product once it's FDA approved, which is what we're dealing with with the current legal environment.

AUDHALI: Okay, thank you very much. Audience members, do keep these great questions coming in. Next one is, can the Phase III pivotal equivalence trial be designed to include switch data that will be sufficient to support a regulatory designation of interchangeable?

BAKER: Well, I can take one, Tareq. Thanks. FDA has been pretty vocal about indicating that, more than likely, interchangeability will not be granted with initial approval. However, there is flexibility in the regulations. And as FDA becomes more comfortable with the biosimilars, it may be possible. So that's why continuous dialogue with FDA is important as to continue these discussions to see if a switching design can be incorporated into a Phase III study.

As previously discussed in the presentation, switching studies should be designed to determine whether alternating between a biosimilar and its reference product two or more times impacts the safety or efficacy of the treatment course, and this we know is based on the recent guidance document. So it's important to keep that dialogue because, you know, pushing the envelope, somebody will get there. Eventually, interchangeability could be a possibility at initial approval.

AUDHALI: Okay, thank you for that answer. And the next question here is, has an innovator company ever produced a biosimilar to its product or, by definition, would that be a follow-up biologic?

CARLSEN: Yeah, I can speak to that. In my knowledge the answer to that is no. I don't know of a company that has developed a true biosimilar version of one of its own

products. I know a lot of companies that are known as innovator companies, so say Amgen, for example, I think it stated that they do not plan to cannibalize their own products, so they will only be developing biosimilars for, you know, products that they are not the innovator for.

I think, you know, and I can't say this definitively, but I would think most innovator manufacturers would be in the same boat, that they would have an incentive not to develop biosimilar versions of their own products. Technically they could. You know, if they got approved under the abbreviated pathway, that would be a true biosimilar and not necessarily a follow-on biologic or, you know, or a, I can't remember the term that the person used in their question, but it is possible for an innovator company to do that. I just don't think, I just think that there are a lot of disincentives for them to actually go down that road.

AUDHALI: Okay, lovely. This next question is, which are the companies in biosimilar space one should, sorry. Which are the companies in biosimilar space that one should keep track of?

CARLSEN: Yeah, I can take that one as well. And as with my previous answer about biosimilar products on the horizon, this is by no means an exhaustive list. But I think the categories fall, or the companies, I should say, fall under a few different categories. One category is the big generic companies that you would expect to see in this space. A lot of those companies are players here, so companies like Dr. Reddy's or Teva or Sandoz. Those are all kind of known for being big generic companies. Prospera is another one, which is now part of Pfizer.

And then there's also companies that are more known as being innovator companies like Amgen or Baxter or Boehringer Ingelheim, Biogen, Merck. Those are a few examples of those. And then there's companies that are much smaller companies that appear to be solely or mainly focused on biosimilars, so companies like Celltrion and Coherus and Biocon and Samsung Bioepis. All of these companies are in this space. In many cases, some of the smaller companies are partnering with some of the larger companies, and those partnerships appear to be somewhat fluid in that, you know, the smaller companies may be partnering with more than one larger company, depending on what kind of, depending on which specific product they're developing.

So again, not an exhaustive list, but that gives you some examples of some of the companies to watch for in this space.

AUDHALI: Okay, lovely. Thank you so much for that answer. And I'm afraid that does bring us to the end of our Q&A session. I'm sorry we couldn't get to all of the questions, just had way too many. Okay. So before I conclude the session, I'm just going to go back over to our speakers, see if there's anything that they'd like to add before we end.

FLETCHER: Thank you, Tareq. This is Mark. I do want to comment that I realize that there were a few comments from the audience about the focus being on rheumatologic biosimilar development. But in fact, we develop biosimilars and support the companies developing biosimilars across the spectrum. And if you have more interest, we would be very happy to have a one-on-one, you know, connection to discuss other therapeutic

areas of biosimilar development that, you know, we have had or have experience in. So this was focused on rheumatology, but certainly we have broad therapeutic experience in biosimilars. Thank you.

AUDHALI: Thank you very much. And that does lead me to thank today's speakers, Mark, Alicia, and John, for what was a great presentation, and to thank Covance for sponsoring this session. For the attendees, you will receive an email shortly telling you how you can access the on-demand version of this webinar, or you can access it directly through our website which is www.business-review-webinars.com.

As the webinar ends, a survey will appear in its place. We would appreciate it if you could stay behind and answer those questions for feedback. We do look forward to sharing further webinars with you, so please keep an eye out on our website, follow us on Twitter at BRWebinars for daily updates, and join our LinkedIn group as well, Business Review Webinars. Thank you all once again, and I hope you all have a great day.