Biosimilars in the U.S.: Current & Emerging Issues
Hospira
Amgen
Alliance for Health Reform
May 20, 2015

ED HOWARD: I want to take this opportunity to thank you for coming in out of that glorious spring day that we have outside to talk about a really complex and important aspect of health policy, that is to say biosimilars. On behalf of Senator Rockefeller in retirement, Senator Gordon, and Senator Blunt and our Board of Directors, I want to welcome you to this program and thank you for coming. We are here to take at least an initial look at one of the most interesting and complicated policy issues that the Alliance has tackled anyway, and that is the introduction of biosimilar pharmaceuticals in the United States. There's a statutory framework for bringing biosimilar pharmaceuticals to market. Now the Food and Drug Administration has actually approved one for use, but there's still a lot of open policy questions that remain for policy makers and those who communicate with them to understand and grapple with. And we've brought together I think some of the best authorities on this subject to share their expertise and to respond to your questions.

We are pleased to have, as partners, today Amgen and Hospira. They're jointly sponsoring this discussion and they constitute an unusual mixture of viewpoints because, on the one hand Hospira, whose name you may not be as familiar with as with some other names in the industry, is a leader in biosimilars, both here and around the world, particularly in Europe, but they are about to be acquired by Pfizer, which is a much broader and more conventional pharma company. I don't mean to use that term derogatorily. On the other hand, Amgen is best known as a conventional pharmaceutical company, again, not in a negative sense, but they have developed a particular interest and activity in biosimilars. So keep that in mind as the discussion goes forward.

Now, the logistics are similar, if you will, to some of the briefings that you may have attended in the past, that is to say, there are a lot of good pieces of information in your packets, including biographical information on all of our speakers, to whom I apologize for not being more fulsome in my description when I introduce them. There will be a webcast available next week, actually maybe Friday, on our website: allhealth.org; and a few days after that a transcript at that same location that you can take a look at. Some of you may know, because you're already watching it, that we are embarking on a new endeavor for the Alliance; that is, a live feed of this briefing that is available at – and I'm not sure whether there is a link on our website that you can tell the folks that you're in communication with to click on or not. Is that right? Right. So, you can go to our website if you are communicating with others who aren't here and there will be a link to the webcast. Presumably, you don't need to be watching the webcast on your laptop while you're sitting in the room eating your lunch.

You can see the hash tag that has been set up for this briefing: biosimilars. And you and the folks watching the live webcast could Tweet a question if you wanted by using that hash tag and we'll be monitoring the Twitter traffic.

I'm sorry? Well, you know, I'm new at this. I apologize for not being as audible as I could.

There are other ways to ask questions when the time arises. There are microphones that you could use to ask your question orally, there are green cards that you don't have to tweet, you just have to write on them and hold them up and the low tech version will be brought forward and we'll try to address those questions.

As I said, we have a terrific panel for you today. We're going to start with Amanda Bartelme, who is a Director at the consulting firm of Avalere. Next to her is Sally Howard. She says we're no relation and I can understand why she would say that. She is an Associate Commissioner at the Food and Drug Administration. Sumant Ramachandra is the Vice President and Chief Science Officer at the aforementioned Hospira, and next to him is Geoff Eich, who is the Director of External Affairs for Amgen's biosimilar operation.

So, we have, I think, a terrific opportunity to learn. We've asked our panelists to be monosyllabic and monoclonal in their description of the subject matter and we're looking forward to a good briefing on biosimilars and we're starting with Amanda.

AMANDA BARTELME: Excellent. Thanks, Ed. To get started I was given the daunting task of about 9 minutes to give a full overview of what we're going to talk about today so I will do my best. I'm going to defer a lot of the more technical issues to some of my colleagues here on the panel. But the first question is: what is a biologic product? What are we talking about here today? I think the important distinction here is that we're not talking about and to the right here the small molecule drug which is a very small molecule, obviously, a little bit more simple. A biologic product is a medicinal product that comes from living organisms and tissues and, for purposes of our discussion today, and when we're thinking about biosimilars, and sort of juxtaposing with small molecule generics, drugs that we're probably more familiar with, from my non-scientific self—I probably took chemistry for poets in college kind of thing, and for others in the room who might not be steeped in biochemistry and things, I think of the processes in a small molecule world it's more of a recipe. I can give you a recipe for chocolate chip cookies probably everyone in this room can make it. You get the right ingredients in there you come out with the right product. Producing a biologic product is more about the process. Think of yourself as more of a French pastry chef, that if you don't have the technique right your end product isn't going to be the right thing. So that's how I kind of distinguish these things in my own mind in remembering why, you know, to date we haven't had biosimilars or follow on biologic products because they're more complex, because it's more difficult to make, and there's a lot more that goes into it. So that is my very simple explanation that I think some folks on the panel will be able to expound on.

And what kinds of products are we talking about here? These are in-line products in the U.S., medicines that are being taken by millions of Americans and there's some examples here of things that are approaching or have gone off patent. So, in terms of what sort of biosimilar products can we see in the near future, this is what we're looking at. They treat a range of conditions—oncology, supportive care, inflammatory diseases—just a whole range of issues, but they're used across a lot of patients. Also represents quite a bit of money in the U.S. healthcare system right now, roughly about 70 billion dollars of product we think are going to be going off patent by 2017.

While biosimilars are new to the U.S. market they are not new globally. This is just an example of the products that have been approved and are already on the market in Europe and other places in the world, and Sumant can speak more to this later since his company is well into this space. But just to give you some background and to know that these products are being used around the world in other countries we just don't have any on the market in the U.S. to date. We have had the first approved and should be coming to market soon, but this while it's relatively new in the U.S. there's been much experience in patient lives around the world.

So the reason we have this pathway is because of the ACA and the BPCIA, which established the authority for FDA to approve biosimilar products which did not exist before. And so I just wanted to walk through quickly what we know from the language in the law and what are some of the remaining questions, and I think those are some of the things we'll be addressing today as a group, hopefully to the best that there are answers.

There's terminology in the ACA that a product can be biosimilar and then that a product could also be determined to be interchangeable. The one thing that's still unclear, and I'm not going to put Sally on the spot for this, but how interchangeability will be determined remains to be seen. So that's one issue that's sort of outstanding. And again, so the FDA has been given authority to approve the biosimilar and to determine if its interchangeability. And, again, we're learning more about what this process looks like. There's been more guidance coming out from the agency and, since we have had a first product approved, we know more about what that looks like and also Geoff and Sumant can talk about that as well since their companies are going through these processes now with the agency.

Coding and payment, which is really sort of my area of expertise—I work on the reimbursement and market access side of things—there is specific language in the law that talks about for biosimilars that are delivered by a healthcare professional, so Medicare Part B, something that's an infused product in a physician's office is going to be paid—and excuse me for getting technical—at its own ASP or average sales price, which is a reported metric, plus 6% of its reference product's ASP. I know that's a lot to process. We can get into that a little bit later, but what that does is say that there is a very specific payment rate that Medicare must pay for biosimilars under Medicare Part B, and

because of that you really do need a unique billing code to facilitate that. And that's one of the things we've expected. We've actually seen this with the first product. Some of the questions that still apply is the way the law is written. Those payment provisions only apply to drugs delivered in the physician office setting, it's not clear if that also applies to the hospital outpatient department. That's been given sort of to CMS to sort out. So, as products in the market we'll see if they decide to make a different policy there.

On code assignment, we do know that the first biosimilar to any reference product will be issued its own billing code. What is unclear right now, and what we're waiting to sort out, is whether or not that code will be shared among many biosimilars to the same reference product.

And, finally, this concept of interchangeability which is still getting sorted out, there isn't any clear direction in the law as to how CMS needs to deal with that from a payment and coding perspective, so they may have the authority to make coding and payment decisions for an interchangeable product in the future but we don't know what that will look like necessarily.

Some other pieces here around exclusivity for the innovator and the biosimilar which are fairly straightforward, but we'll move on.

I did want to mention quickly that this concept of interchangeability, which was introduced really in the ACA and in the language of the law, is not necessarily a global concept and doesn't follow sort of a scientific pattern that we've seen established worldwide. So I think this has been an interesting challenge given to the FDA to determine what this looks like and what the standards are because there isn't a lot of, you know, as I mentioned before, there are products on the market already in Europe and other places around the world, so you can draw from that precedence. This concept of interchangeability is not something we have a lot of precedence to draw from, so it's a unique challenge.

ED HOWARD: Amanda, before you go on and I promise you won't get penalized on your time. Could you take a moment and just explain what you mean by interchangeability and why anyone would care about it. I mean, you don't have to do that?

AMANDA BARTELME: Can we table that question for a moment? Well—

ED HOWARD: Sure. Sure. We'll come back to that.

AMANDA BARTELME: I think the concept of interchangeability is that you could switch between the two products—the reference product and the biosimilar, the interchangeable biologic product—you could go back and forth with no discernible

difference in effect on the patient, and that you could basically swap these in one for the other.

ED HOWARD: So the pharmacist could decide to do it sort of at his or her own discretion as opposed to going back to the physician?

AMANDA BARTELME: Potentially. You get into some challenges there with how pharmacy dispensing laws change from state to state. I think it's also important, to follow up on that, to know that the vast majority of biologic products are not self administered so they're not things that you're picking up at the pharmacy necessarily and giving to yourself at home. They're medicines that are being delivered within the setting of care, so in a hospital, in a physician office, and so the prescribing decision and the decision on what's actually being dispensed and given to the patient is more in the hands of the hospital or the provider. So it's not so much you go to the pharmacy counter and the pharmacist can just switch out the product for you.

ED HOWARD: Thank you.

AMANDA BARTELME: So CMS has recently put out some guidances on how they're going to treat biosimilar products in various programs, and this gives an overview, and we sort of benchmark to either how they treat a branded or an innovative product versus a generic product, or if it's a system that they've developed that seems to be unique to biosimilars.

Starting with the Part D benefit, so even though I just said most of these products are not going to be self administered, there are a number that will be self administered and fall into the prescription drug benefit under Part D. And so they put up guidance for of these products, how will they treat something. So for a transition fill. If you're new to a plan and you're on one product and maybe you join a new Part D plan and the product you've been on is not covered on formulary, how they treat the transition fill requirements is similar to how they do it with innovator products. So they can't switch you from one brand to another without giving a transition fill. For generics, the plan can just have you switch immediately. So it's an important distinction.

The review process for the formulary and therapeutics review is the same as we would see with a branded product. They're expecting the same standards and the same review timelines.

As the USP coverage requirements are interesting because they're saying that for a biosimilar and the innovator product, they will not count those as two separate products to meet the number requirement for how many products you have to have on formulary, so in that case, they're treating it much like a generic. On the low-income subsidy cost sharing, this is falling more to the innovator, how they're treating innovator products, the

coverage gap discount program—so for Medicare beneficiaries that fall into the donut hole, they do not—this was actually in the statute, this was not up to CMS's discretion—they are not on the hook for the 50% discount that branded manufacturers are. They're treated the way a generic product is. And we can talk some more about that later if folks have questions.

In terms of meeting your formulary changes, also being treated much like a branded product. And protecting classes they were silent on at this point. If and when a biosimilar is approved, that'll be covered under Part D and could fall into the [Unintelligible] classes. I think we can expect to see some guidance out of CMS, but at this point they've not issued anything.

Medicare Part B, I mentioned this earlier, there are specific coding and coverage we think will fall in line with what we see for new branded biologic products on the market, but the payment, there's a separate distinct metric setup for biosimilars. And for Medicaid rebates, which also sets the 340B ceiling price, CMS put out guidance to say that this would be the same rebate amount required of biosimilars as what branded products are being charged.

I do have another slide that gives a lot of detail on this but I'm going to go ahead and skip that. Folks have it in their packet if they want to really get in the weeds but I will give it to Sally to take over.

SALLY HOWARD: Thanks.

ED HOWARD: Go ahead, Sally.

SALLY HOWARD: Well, good afternoon. I'm Sally Howard. I'm Deputy Commissioner for Policy Planning and Legislation for the Food and Drug Administration. I, too, am not a scientist but I work with a ton of them and they've spent a lot of time on the many different complex issues that come up with biosimilars and interchangeables and I thought, for purposes of this talk, I would just help provide an overview of really the regulatory framework that the FDA applies and talk through some of the guidances and some of the difficult issues that we're struggling with.

So I started out with what are therapeutics biologics but Amanda has covered that nicely and I think that Sumant and Geoff will also pick up on that, so I think I can skip over that. Understanding that the biologics are just far more complicated, as Amanda said, than the small molecule products, they are very dependent on process and so as we look at biosimilars and interchangeables and the standalone biological products, we're very much focused on not just the ingredients, as Amanda said, but the process that's followed.

So, just a quick overview of the product framework. So, what we call originator or reference product comes through the FDA through what's called a 351A pathway, and what this basically means is just like other new molecular entities, new drugs, they come through and they have to provide the FDA with sufficient data to support that they are safe and effective. And so, we are looking at—I mean, they have to do the classic phase 1, phase 2, phase 3 trials. They're providing the FDA with all the data that we need to make the finding of safety and efficacy. And so contrast this to the biosimilar and interchangeable products, again, similar to Hatch Waxman and the generic program, the biologic biosimilar products are not going through the phase 1, phase 2. They're not demonstrating safety and efficacy on their own but they're rather relating back to the reference product. And so what they need to be able to demonstrate is that they are bio-similar to the reference product.

And so what does that mean? So, biosimilar and biosimilarity, again, it reflects the concept that biological products aren't like small molecule products. They are very different and so with the generics they must be bio-equivalent to their reference product. For biosimilars they must be highly similar to the reference product because we, again, know that there may be some differences but so long as they're highly similar and there's no clinically meaningful difference the department would be able to approve this as a biosimilar.

Again, as we look at biosimilarity, what we're looking at is do they utilize the same mechanism of action? They'll be used for the same conditions of use will be proposed in their labeling as have been previously approved for the reference product. They need to have the same route of administration, dosage form, and strength, and then, again, because of the process issue, we have good manufacturing practices that must be complied with by the biosimilar product, and we will inspect for that just as we do for the reference product because every time, with even the standalone biological product, if they were changing out their process in any way they need to come back to the FDA so we have a quality check to make sure that there's no inadvertent impact to the safety, purity, and potency of the end product.

So then how does interchangeability relate to all of this? As Amanda said, it's a new concept. We will be issuing guidance on this concept of interchangeability. We have it slated for 2015 but I will tell you it is very complicated. So, for interchangeability, they initially have to demonstrate that they are biosimilar, so that they're highly similar and there's no clinically meaningful difference. But unlike biosimilars, they have to provide the FDA with data that supports that there's no diminishment in the safety or efficacy of the product if it is alternated or switched between the interchangeable product and its reference biological product. And so what that means is, it is not just that it can be like a one-time switch, but that you could, in theory, move patients back and forth from the interchangeable product back to the reference product and that there wouldn't be any safety issues related to that. And so, it's not surprising that the first products are going to

start as biosimilar and we fully expect that part of that patient experience that is developed will help inform the interchangeability but again it's that automatic switching, that ability to do automatic switching that makes interchangeability a very different issue.

So, as Ed and Amanda said, we approved our first biosimilar, Zarxio, March 6, 2015, and this was a biosimilar to Neupogen. We went through an advisory committee and that will likely be part of our approval process for the filgrastim product there was a unanimous decision by our advisory committee, which makes it easy, recommending that the biosimilar be approved. So the name that we gave to Zarxio, the INN that we provided is a placeholder name, is filgrastim-sndz, which is, as you might guess, sndz. It is not intended to be a policy, a naming policy, and again, you'll see that we're going to be issuing a naming policy later in 2015.

So there's been a lot of interest on the Hill asking FDA what guidances have you issued, what guidances will you issue, why haven't you issued more guidances? So, I thought that it might just be helpful for this group to understand the final guidances that have been issued to date. The three final guidances were just issued end of April, and then some of the draft guidances that have been issued to date are listed on this slide. I'm not going to read them, with the latest one being issued just on May 12th, and they were the biosimilar additional QA document.

Of note, guidances to come, you'll see some of the trickier issues here. We've had a lot of interest in the nonproprietary naming for biological products. In fact, I think that Sumant will talk briefly about that issue. The labeling, as well, and then technical guidance, the statistical approaches to evaluation of analytical similarity data to support biosimilarity. And then, the last one is likely to be the latest one, and that is interchangeability; a lot of technical scientific issues that will come into play with interchangeability. And then, on the non proprietary naming, you know, there are just a lot of comments that we've gotten with very strongly held views on multiple sides of the table about what the right name should be, and I would just summarize some of the competing concerns on naming seem to be ease of use; that we not somehow adopt a naming system that confuses people; that puts the biosimilar at some sort of disadvantage; that allows for safe use and pharmacovigilance, and these are all incredibly important issues for us to consider and we have been thinking through what that right convention would be to properly balance all of the concerns that we have heard to date.

So just sort of summing up some of the things that I hope you can take away from this. Again, one of the key concepts is just the difference between biosimilar development and the standalone or reference product development being safety and efficacy for the reference product, which is a standalone, and then the biosimilar development being a comparative approach that it is highly similar to the reference product.

And the second concept is that as we've been working with the drug development programs, and that is our highest priority I would say, right now, is we have been working with a number of companies and their drug development programs with biosimilar products in the pipeline. We've developed a stepwise approach. Basically the most important thing for us is that they be able to establish the structural and functional characterization of the biosimilar product and the way they go about doing it is really a totality of the evidence approach. We work with the scientists in the drug development program from the beginning to try to walk them through what makes the most sense for them. There isn't a one size fits all. Sometimes, some of the studies that we've listed here may or may not be appropriate, may or may not be needed. And so we have a lot of conversation with them to make sure that the package they put together for us can help demonstrate biosimilarity.

Another concept to just introduce you to, and then I think, again, Sumant is also going to touch on this, is extrapolation. Again, we've issued some guidance on extrapolation and basically what this means is you've established biosimilarity for a certain condition of use and you shouldn't have to demonstrate biosimilarity independently for each other condition of use, so long as there is a scientific justification that lets us extrapolate. We want to be able to do that. It's going to be case specific, of course, because of the science involved.

We are strongly supportive of a biosimilar and interchangeable market. We think, for a whole host of reasons, that they will be good therapeutic tools for providers to use. They will allow competition to happen, which drives down price and makes these products more accessible to everyone that needs them, and so we've just outlined some of the external levers that aren't within our control. And then, I just highlighted for you the education and outreach that we're doing, just terms to become aware of. You know, right now we have what's called an orange book, for the biosimilars product you'll see a purple book and it basically lists all the products that are biosimilar, the biological products, and the interchangeable products. We hope that this quickly becomes as exciting and well used as the orange book.

And again, we think the key role for the FDA is to have a very strong program and to be able to give the public, including providers, the confidence that's needed in these products; that they are as safe and effective as their reference products; that people can be confident, that they can rely on them; and we think that in establishing that very strong FDA approach that we will be able to develop the confidence that will be the foundation for a very successful biosimilars market.

Thank you.

ED HOWARD: Thank you, Sally. Very good. We turn now to Sumant Ramachandra. Go ahead.

SUMANT RAMACHANDRA: So, my name again, is Sumant Ramachandra. I'm the Chief Scientific Officer of Hospira. Just as a way of introduction, Hospira actually has been in the biosimilar space since, from a development perspective, since around 2006. We launched our first product in Europe in 2008 with a biosimilar, epoetin, and we've, since then, launched actually two further products, a biosimilar version of filgrastim and a biosimilar version of infliximab, all in Europe. We've also launched drugs in Canada and Australia and recently got approval in Brazil.

So, we actually deal with both the generic space, the biosimilar space, as well as infusion device space and have employees all over the world that actually work on this particular area. As mentioned before, Pfizer is in the process of acquiring Hospira, and that was announced in February of 2015.

Now, biosimilars, from my perspective—I'm a physician, and a scientist by training—really, biologic drugs, as a whole, have made a tremendous impact in patients' lives all over the world. It's just this new technology that came out decades ago that is clearly continuing to make inroads in many diseases that were very hard to treat. But, as drugs get into the marketplace and exclusivity in the market expires, there has to be an appropriate competition within that market. And competition does really multiple things. And today, our focus on sustainability and what is sustainable for the healthcare system but competition does is it drives innovation but it also drives affordability, and that is what the biosimilars area does for the healthcare system. There are very few large levers in the healthcare system to pull to help drive sustainability. But it turns out that the high cost of drugs, once exclusivity has expired, is a large lever to pull and can result in cost savings to the patient, individual patient, to the healthcare system, and help improve outcomes for those patients. The costs that we're talking about are not in the tens of dollars or the hundreds of dollars. They're in the tens of thousands of dollars to over a hundred thousand dollars. So when we keep this in mind, when we talk about that 70 billion dollars that Amanda talked about, or clearly we're pursuing a subset of that in primary oncology and inflammatory diseases, the significant savings that could occur are very large.

So, this is our history. Since 2007, the first batch approved to where we are today, which include a simple biosimilar, let's call it Simple in the simple terms of Nivestim. It's as simple as it gets, from a biosimilar perspective, to a bit more complicated one which is a biosimilar version of epoetin alfa, to a monoclone antibody which is a biosimilar version of the drug Remicade out there. And what we have seen is that providing high quality drugs in the marketplace, even in markets in, like we're talking about Europe, where they're nationally funded systems, has actually increased patient access and improved outcomes for these particular patients. So you may see a lot of passion from me because I actually have seen the positive benefits of what we have done in Europe and in other markets.

Now, these are the markets that we have typically operated in. We're in mostly in the highly developed markets such as U.S., Canada, Australia, Europe and a few other of the emerging markets, but we are pursuing generally around 70 billion dollars of local market value that will expire by 2020. And, by the way, I'm quoting to you a number that's from 2012. This market of original biologics are still increasing at about a compounded annual growth rate around 9%. So if you take a base that big and you keep compounding to 9% you're talking of even larger numbers at the time that the market actually expires than we are pursuing to introduce high quality drugs in a competitive manner.

So, I want to talk to you about three topics. Very quickly: naming, appropriate coding and reimbursement, and extrapolation and education. These three topics together create a sustainable marketplace for the long term. So we believe that naming must be simple and intuitive to be effective. In general, the same INN should be applied to the original product as well as the biosimilar product.

ED HOWARD: And then INN is?

SUMANT RAMACHANDRA: Is the International Nonproprietary Name. It's the WHO, the World Health Organization, terminology. Some people in the U.S. call it USN. If you do change and have distinguishable names it's not a nonproprietary name anymore, it's individual to the particular product. But, you know, that's an ongoing process that the FDA is working through.

Appropriate coding and reimbursement. We support very thoughtful and science-based approach to setting unique reimbursement codes for biosimilars. Biosimilars are not generics and that's a key point that you'll hear all across the board. And you have to treat this category different than you treat generics for a variety of reasons, not just the cost of development but the uniqueness of how biosimilars are developed as compared to the original products, allows you the space to say that these are different than generics, as has been mentioned before.

And extrapolation. The FDA has taken a very positive step in the first approval for giving this extrapolation to the first biosimilar, it's a case by case basis, but extrapolation is a single most important tenet for sustainability or development for biosimilars. Why is that? If you have to repeat every single test that the original molecule had to repeat it costs you more and more and more to develop. The market becomes unsustainable and, frankly, people won't go and develop competition into this marketplace. So we also then need to drive from that awareness of the patient and provider level because extrapolation is a concept that has been around for a long time. It's used by the original companies when they make manufacturing changes, but in the field of biosimilars there's a lot of confusion. What does extrapolation mean?

So, I'll guide you through this very quickly. Okay. Here are two products. One is our Nivestim in Europe and on the bottom is Amgen, my colleague sitting next to me, Neupogen in Europe. They're both filgrastims in Europe. They're both actually called filgrastims. They have unique brand names. They actually have different batch numbers because Amgen has batch numbers for its particular product, we have our batch numbers. They have different artwork, they have different elements that you could actually recognize the particular product, and the pharmacies in Europe as well as the U.S. keep track of actually what has been dispensed to the patient, whether it goes through an outpatient pharmacy for self administration or through infusion centers or hospitals. So, in general, what we have seen is that you can actually track the product with the same INN, and you don't compromise pharmacovigilance. And so this is a concept that actually is important to recognize that INN can stay the same for the biosimilar as well as the reference product.

Now, the next topic is coding and reimbursement. We have to make sure that we don't just work hard on getting to approval but we actually get approval and then make it sustainable in the marketplace. So the market dynamics are very important. We believe that grouping all of the biosimilars under a single J code or a blended reimbursement will actually create a disincentive to invest in this crucial area of medicine.

I think we will see that as a unique theme across folks is that here on the table is that they should have different J codes to ensure that each of these biosimilar products, because they are launching ours, continue to actually operate into the marketplace and in a sustainable manner.

And then the third topic is extrapolation. In the fields of extrapolation and naming I've put two policy papers out there on behalf of Hospira. They are available publicly. But I want to make note that extrapolation is a concept that has existed for a long time. We extrapolate day to day in medicine. As a physician, I don't have all the data of the particular patient. In fact, that patient may not even be reflected in the clinical trial fully that was done. So extrapolate from scientific and clinical knowledge to treat a patient. Now, in the field of drug development we actually take data and extrapolate it on a day to day basis. If it's scientifically rigorous and justified you should be able to approve a biosimilar drug for all the indications as compared to the reference product if the right rigorous testing was done on the biosimilar product. And I have to say, applaud for the FDA. We have a track with the FDA for a long time in this field, very high quality discussion, guidance documents at a very high level. It comes down to the individual case by case basis discussion between a sponsor and the FDA to drive a program forward and to drive that. And then the pyramid was shown, so I'm not going to belabor it, but this totality of evidence concept is very important to recognize. By the nature of biologic drugs there are going to be subtle differences between a biosimilar and a reference product. The key thing is to show that these differences do not manifest in clinically meaningful differences. And so, you have to take the evidence in total to determine

whether it's a biosimilar and that lays with the FDA, but a sponsor, such as us, have to provide them their needed data to get them there.

So, extrapolation is a key concept. Been around for a long time. It's utilized by original drugs. It will continue to be utilized by both biosimilars and original drugs but a lot of education is needed to actually drive people's understanding of this concept. Again, biosimilar is not generics. They're far more complex. They take longer to develop. We are a generic company as well as a biosimilar company and have developed proprietary drugs. It takes about 3 to 5 years to develop a generic drug, around 5 million dollars maximum. It takes up to 8 plus years to develop a biosimilar drug with up to 100 to 200 plus million dollars and, on top of that, you have to have capital investments. So you have to actually create a marketplace that actually sustains that level of competition so that you can reinvest in the R&D pipeline to bring more and more biosimilar versions of drugs out there.

I will also probably say, compared to 5 years ago to now, companies, such as Amgen and Hospira, work together to really sustain this field and moving it forward even though we have come from very different ways. A long standing biotechnology company in Amgen, a generic company in Hospira that's been in the biosimilar's field for a long time, we're actually working together and we've formed a forum called the Biosimilars Forum to help advance some of these concepts that we will have some differences of opinion on, but if you can get to a better ground and drive to a sustainable market that's the end goal of what all of us are going to hope for.

Lastly, biosimilars give great promise to American patients and providers and payers but we have to actually settle these three topics: naming, appropriate coding and reimbursement, and then extrapolation and education associated with this emerging field of biosimilars, which will make an impact for American patients for many years to come. Thank you.

ED HOWARD: Thank you, Sumant. And turn to Geoff.

GEOFF EICH: Great. Thank you. So, I'm Geoff Eich. I work for Amgen, which is one of the biotech pioneers. We helped found the biotechnology, medical biotechnology industry in California, which, as you guys know, this is a uniquely American creation, the biotechnology industry, and it's now expanding worldwide and that's actually a very exciting space.

Just a couple of things to start with. The two words Amgen and biosimilar is in close proximity to each other probably has some people asking questions. Why would a company like Amgen enter the biosimilar space? And I think what we realize is that biosimilars do have a role to play in healthcare; that it is important to have a high quality, sustainable, patient-focused biotechnology and biosimilars program in a country, and it's

also vital to be able to have innovation and new medicines. You have to be able to create head space for those new medicines. And so, this is actually a very positive development in the evolution of biotechnology. You're seeing the technology spread around the world and, ultimately, we're doing this with a focus on expanding our ability to help patients, help patients in different countries, help patients have access to the medicines they need earlier, and have them be able to access the medicine completely through their course of therapy. So, done right, this is actually a material opportunity.

I'm also going to preempt one question, which is people frequently ask. We are not making biosimilars of our own brand biologic medicines. We are making biosimilars of a portfolio of nine medicines that are other people's brand medicines in addition to developing innovative therapies.

So let me just start here, and with apologies to the folks on the webcast, who in the room can think of three applications, confident you can think of three applications for biologic medicines in healthcare, and I promise I won't call on anybody. Let me see just a show of hands. How many people are thinking they have a good sense of at least three applications?

Okay, good. That's a good place to start. So you think about medicines that we use frequently—Ibuprofen, aspirin, etcetera—and then you can also then think about some of the biologic medicines that you've probably heard a lot about. Growth hormone became a biologic medicine. Many of these were originally purified and then became recombinant DNA medicines, and the beginning of this process was figuring out that you could take a living cell and you could program that cell's genetic composition to make a product of interest. And the early biotech medicines replaced what should have already been in a healthy patient's body.

If you move to the right, you see where Amgen is focused in its biosimilar program, and this magnificent creation is actually the natural weapon of a human immune system. It's how the immune system goes after problems in a body. And what we've recognized as a collective community of academia, of industry, regulators, etcetera, is that these medicines can be genetically engineered to replace what's in the body, but also to do very specific targeted jobs in a patient's body when their immune system is not doing what it should do. And so examples of where biologic medicines are used are insulins for diabetics, growth hormones for children who are not growing at the appropriate rate, monoclonal antibodies, like Humira, that can treat rheumatoid arthritis, psoriasis, and also diseases of the gut. You've got medicines now used in oncology that can help interfere with the process of breast cancer, of colorectal cancer, lung cancer, and others. So this is the world that we're entering. And we're going to focus on the most complex medicines and we want to ensure that we can bring high quality, reliably supplied biosimilars of those medicines to U.S. patients.

So where I'm going to go for the next maybe five minutes is give you a snapshot, not into where we've been, because I think everybody knows where we've been. We've passed a law. The FDA has implemented the law. We've put together the large portion of the framework around that law, and the first biosimilar product has been approved in the U.S.

And now the question is, okay, so how does society actually get the benefit of biosimilar medicines? How is this actually going to work in U.S. healthcare? And you have to start that question with an understanding that each biologic is its own medicine. It's its own medicine. Our version of a particular brand product is going to be ours, Sumant's will be theirs. There's going to be a number of ways that you can tell the difference between any biologic medicine.

And so, you can think of biologic medicines as each having slight differences in the structure of the medicine, the active, or drug substance. They'll have variation in the formulation, the fluid in which the medicine is injected into the patient's body. They can have differences in container closure, devices. There are many different ways for biosimilars to have distinguishing features from each other And, as a great example, in Europe there are a number of biosimilars of one of the early medicines, EPO. And, Sumant's company, as an example, invested in their biosimilar and actually has different additional indications of use and roots of administration compared with another biosimilar medicine. And so, when you think about this diversity and you understand the space that these medicines are used, as we've said, primarily in hospitals and in clinics; they're administered by healthcare providers; there are some that are used in a patient's own home—what you can see is that this diversity among biologics, it does have actual implications in terms of policy. How are these medicines to be coded? How do we actually ensure that the coding of the medicines gets to an individual product-specific level and not only a group level. We want data to be able to be aggregated and pooled when it's appropriate and disaggregated when it's appropriate down to an individual product. How should the medicines determine whether there's an interchange, whether there's an ability to have two biologic medicines alternated or switched? One important question is where does that matter most? Is it important for an infused breast cancer medicine to be interchangeable and have patients going back and forth, or actually, is the societal benefit achieved when hospitals have multiple sponsors and manufacturers making multiple versions of that product competing, and is that the societal objective?

You can think about naming. How will the name actually reflect the diversity of the biologic medicines at the actual structural level? And then, for states, where the practice of healthcare is regulated, how should those medicines be used? What is the importance of a patient's medication history to be able to have accurate adverse of that reporting and ensure that each manufacturer can be accountable for their own product.

So, we've talked a little bit about the differences between generics and biologics, and I agree with Sumant, and I'll just echo that this is likely to look, in the U.S., over the next

five years certainly like a branded space. And the reason is that each of these medicines has their own set of features and attributes and datasets and development decisions that were made by the sponsor and ultimately our objective is to compete with each other for the best value for the healthcare community. That patients will receive a benefit, that physicians receive benefit, that their patients are receiving their medicines at the right time and with the right period of use, and that the healthcare system is also benefiting from increased competition. This is a well designed pathway. It's a well designed program, and done the right way it will be very, very successful.

So, I want to close out with really just four points that we think, as we observe the biosimilar program in the U.S. where it's going and hopefully our contribution to its success, four points that are absolutely vital. The first is the goal. The patient and physician confidence in biosimilar medicines is vital and the reason for that is, is that patients and physicians ultimately have many, many choices. For the biosimilar program in the U.S. to be successful physicians will have to opt in and patients will have to have a positive experience. And I want to start there, because it's vital that we get: physicians the data they need; that we're fully transparent about the data; that they have high confidence in the quality of the medicines; and, that they know that they'll be reliably supplied.

The regulatory standards are vital. And the reason for that is, shortly after FDA approves any biosimilar medicine, academic treatment centers, like MD Anderson, Memorial Sloan Kettering, Geisinger Health System and others, will begin to do side by side assessments. We've heard this from any number of consumers that they will actually want to evaluate the biosimilar medicine and the brand medicine head to head in the post market setting. Our biosimilars have to withstand that level of scrutiny and so that really is the true test, is that the healthcare community builds and maintains confidence in these medicines.

It's vital that we find ways to have all of the relevant information that a physician needs to make a treatment choice for her patient conveniently and accurately and in its entirety provided to her. There is a wealth of information on biosimilar development of medicines, the datasets, whether they be analytics, pharmacology, or clinical data that is available to the physician and we need to ensure that they're able to have the data to make an informed choice. We have choices in terms of how we drive single point accountability and, by single point accountability for medicine's quality, I mean that a company like Amgen, a company like Hospira and others, can make the choice to invest in quality for their individual manufacturing plants, facilities, and others. That begins with knowing that you can be accountable all the way through patient use for your individual medicine. We have the opportunity in the choices that we make around naming, around coding, and others to ensure that each manufacturer can be accountable for the quality of their medicine and can stand accountable to the patients we serve. We need to make every effort to ensure that that persists as biosimilars enter the U.S. market.

And finally, it's vital that we work together, and this is where the Biosimilar Forum that Sumant mentioned, has taken 11 companies from very diverse backgrounds and begun to focus, along with academia, regulators, others to say how do we work, not just in the U.S. but even potentially worldwide, to ensure accurate non-biased participatory education so that healthcare providers have a baseline understanding of biosimilars before considering individual products.

If we do these four things right we will achieve the goal of patient and physician confidence and that is exactly where Amgen's biosimilar program is focused for the success of the U.S. program most certainly. Thank you.

ED HOWARD: Great. Thanks very much, Geoff. Okay. This is a lot to cope with and you should feel free to ask questions at any level. As again, I mentioned to you, there are microphones, there are green cards, and if you're Tweeting to hash tag biosimilars, we'll be monitoring it to bring a question you submit in that manner forward as well.

And let me just start, if I can, while the machinery is starting to crank, to just make explicit why this discussion is happening, if you will, why it's important. And a couple of you have alluded to it. What we're talking about here is the potential for substantial savings over the projected drug costs that are now in the pipeline and I wonder if that's what's really driving the development of biosimilars and the extent to which we're able to foresee the magnitude of that impact.

SUMANT RAMACHANDRA: So, I can start and then I'm sure the others can also—so, savings is one part of the equation. I think that the companies you're talking about here—Amgen, Hospira, the people you're talking about at the table, the FDA, Avalere—we really care about patient and patient outcomes. I think it's very important to not forget that. Savings is one aspect to help increase access. Access helps improve outcomes, and that's where the equation lies. So while there's a lot of interest in the U.S. it's because exclusivities are starting to expire this year all the way through 2020-something, and that is worth billions of dollars so, of course, naturally competition will go after that. But at the end of the day, if we don't forget that these medicines we're creating do go into people we'll lose sight of why we did this. And at the end of the day we want outcomes to be better and we want high quality medicines to exist in our marketplace to drive those better outcomes.

ED HOWARD: Okay. And I was actually struck with something on one of Sally's slides that she didn't make a direct reference to, which is that 40% of total drug spending is on biologics or thereabouts?

SALLY HOWARD: And this certainly doesn't come from the FDA, this comes from Express Scripts who, in a number of their slides and presentations quoted the 40%

number. It is, I believe, but would turn it over to Amanda because I am not an expert on reimbursement or the costs or the expense, but I think, as others have alluded to, it's one of the highest growing areas.

AMANDA BARTELME: That's definitely right, and I think to Ed's points earlier, I think the cost savings is a major driver and one of the things that payers are really looking forward to as they're struggling with their budgets and they're paying for biologic products now because, to points made, these are really important tools to help patients manage a variety of diseases. So they're looking forward to, and I think from a consumer standpoint too, competition is good, it will bring prices down, it will bring out of pocket cost for consumers down, it'll help health plans expand their budgets further to serve more people and I think there's another piece of this, as we were talking about the difficulty or the complexity of manufacturing some of these things. Getting more participants in this space actually can expand the market as well and make sure that there aren't shortages or that you can keep up with the demand for these products. So I think that's another point that we don't want to miss, that it's not just about the savings but it's about meeting overall demand and having more players is a good thing.

ED HOWARD: Yes. Let's go to Mike. I would appreciate it, and I know our panel and the rest of your colleagues in the audience would appreciate it, if you would keep your questions as brief as you can so that we can get to as many of the questions as we can. We have already a pile of green cards and please identify yourself with your affiliation if you have one. Yes, sir.

MIKE MILLER: I'm Mike Miller. I'm came to Health Policy years ago when I had hair, out of a clinical research lab, and I'm a physician for original training, and I guess picking up on what Amanda just said, I wondered if the panelists could talk more about the complexity of manufacturing or producing or growing biologics versus small molecule drugs specifically how sensitive the process is to getting what you want versus something that isn't what you intended.

GEOFF EICH: I can start. I guess we have an interesting perspective having started early on in the development of biologic medicines. One of the questions we had as we were looking at entering the biosimilar space was would this be sufficiently complicated and challenging such that our scientists who were used to working on cutting edge medicines that no one's ever seen before would find biosimilar development stimulating. And I think what we found is that we've been rewarded. We thought it would be very complex. It has been incredibly complex. The processes are very, very similar and there's a number of aspects of biosimilar development that, frankly, require a lot of work in the design of the medicine. You know, once you find the clone and you can express the medicine with a series of characteristics that you think are close to what you've observed then that's a great place to be because the development is a bit more straightforward. Now, in practice, the more complex the medicine the more likely we are to see something that's outside

maybe what we've observed with the reference product. And, in fairness, the reference product sponsors have a lot of history in their medicines that a biosimilar developer doesn't. We sit on both sides, so we know exactly what that difference is. And then, now you're in the space where your development program, you have to answer the question what's the meaning of the observed difference? I think from our perspective it's vitally important that sponsors use the most sensitive assays to assess whether a difference exists and then design their programs, both in pharmacology and their clinical testing, to actually highlight the difference if it exists. It's possible, certainly, to create a clinical trial that sort of doesn't necessarily have the capability to show a difference, but that's kind of a pursuit in futility. You have to design the right clinical study to answer the question, or you can answer it in pharmacology. But, in either circumstance, it's got to be the most sensitive test. We should never pass on to the healthcare community, or flip over the fence to the FDA, you know, sort of an unsolved problem. That's the job of the sponsor is to put the very best science into it so that we go into that, if you will, road test at M.D. Anderson or another center with a real sense of confidence in our hypothesis that we're going to have patient's experience no difference using the biosimilar than they would have if they had used the reference product.

SUMANT RAMACHANDRA: So, as someone who actually has a company that makes biosimilar products as well as small molecules, there are distinct differences. So your point is well taken. You have to develop the science around this from the research and development laboratories, but very importantly, you have to actually have solid high quality manufacturing put in place to actually supply the market and sustain the market. And Hospira, from its history, grew by partnership with people like GlaxoSmithKline through the human genome science acquisition that they bought and our EPO is going through there. So where we actually didn't have the internal initial capability we actually partnered and got that knowledge and capability in through partnership.

It's also important to remember that the original drug, and this is well published, there are three seminal papers in this area if anyone actually cares to take a look, one is by Martin Schiestle from Novartis Sandoz. The other one is by Christian Schneider, who is a member of the CHMPF of the European Medicines Agency, and the third is a recent paper that was published by Martina Weise out of the European experience called *The Science of Extrapolation*. If you take those three papers in combination you'll kind of understand that the field of biosimilars did not evolve out of nowhere. The field of biosimilars is based on decades of history of the original drug and the experience that regulators have from the original drug. Little known facts are, for example, extrapolation is used on a routine basis when an original drug makes a change to its manufacturing process. A drug like Remicade, which we have a biosimilar for called Inflectra, that particular drug, at least for Europe, has 30 plus changes—manufacturing changes—over its history. And Martina Weise and her colleagues that wrote this paper said don't imagine, for a second, that the drug that's being used today is exactly the same as the drug that was approved like 10, 15, 20 years ago. That's not a bad thing. It shows that the

life cycle of a biologic drug has to exist in the marketplace, and biosimilar drugs, as well as the original drug, will continue with this life cycle and that's an important concept that this field is based out of years of experience that regulators and scientists and companies have had with the original drug.

ED HOWARD: Okay. Yes, go ahead.

DR. CAROLINE POPLIN: I'm Dr. Caroline Poplin. I'm a primary care physician. I want to get back to the question of price. It seems that in this country, as drugs come out, they're more expensive than the previous drugs and then all the prior drugs move their prices up so that everyone is getting the same high price. It's not just a problem for biosimilars. Tom Brokaw is out with a book about his multiple myeloma. He's taking REVLIMID, lenalidomide, which is a simple molecule I think, and he's paying $500 a pill and he takes them twice a day. And that's a simple molecule. To the man from Amgen, and the man from Hospira, soon to be Pfizer, another maker of very expensive products, how can we get—we have competition on quality. How do we get price competition going and, in Europe where apparently they're ahead of us on biosimilars, is there any price competition or—Americans just can't afford it and insurance companies just put all these medications in high tiers and say, well, if you have cancer and you need medicine you have a 50% co-insurance.

AMANDA BARTELME: I think we can spend a whole day talking about just your question so we'll try and hit some of the high points. But you've raised some real important concerns. I think one thing that is a brilliant piece of the way the law was written for the physician administered drugs is that it actually sets, without explicitly doing it, by the way the payment methodology works for Medicare, it sets a ceiling price for what you could charge for a biosimilar and there's no business case to charge at the same price. You have to come in below of what the innovator is to even gain a market advantage or even be on par because your payment rate is tied to the rate of the innovator product. So I think that's a brilliant part of the law which will ensure, on the Part B side, on the physician administered side, that biosimilar products will have to come in at or below what the innovator price is. So that's locked in. The degree to which we see a discount, whether that's 15%, 20%, 50% remains to be seen and I think that's the difficult—that's sort of the million dollar question that nobody really has a good answer to. But we are expecting to see discounts there and I think when we're talking about things that are this expensive—to your point, $500 out of pocket per pill—a 20% discount on that is a significant amount of money. So even though we're not going to see the huge percent falloff that we see on the generic side, there is going to be savings in here. But, to your point, these are still going to be high cost medications and that's still going to be a challenge for payers and for consumers who are going to bear the brunt of some of this. But hopefully, in aggregate, it starts to pull things down.

SUMANT RAMACHANDRA: So, Hospira, as a company, has existed in a non-monopolistic world almost our entire life. So we compete. That's just the nature of what we do. We do follow on products. That's what generics are and that's what biosimilars are.

So what we have seen in Europe is that there is a clear cost reduction. It's clear, okay. What it depends on is per market. Europe is not one country it's market dependent on the countries. We have seen anywhere from, if you aggregate things for 20%-30% cost reduction. If you compare prior to a biosimilar entry and if you mature things out in a two- to three-year cycle you'll start seeing that reduction. That reduction actually benefits the entire system because that same cost can be applied to increased access or to new therapies. At the end of the day, we do need also new drugs. Not just biosimilars, but we need new drugs against new targets that will make further inroads into people's health. And the most important thing that one can do is, first of all, health authorities can assure high quality sponsors, are getting approval, but then, sound policies have to be in place to ensure that the market is sustainable with competition. And those two things, hand in hand, will result in a market that actually has sustainability for the long term.

ED HOWARD: And I should say, and we were talking earlier about the extent to which there are biosimilar entrants expressing an interest in exploiting that availability of drugs coming off patent, and I wonder if that is, in your collective experience or expertise, likely to develop in the course of the next few years? Geoff?

GEOFF EICH: I can take that one. I mean, I think what's fascinating and a completely optimistic indicator for biosimilars in the U.S. is the level of interest. I think the FTC estimated one to three competitors per molecule and in the vast majority of cases we're looking at well in excess of 5 and, in many cases, in excess of 10 competitors per molecule—per brand biologic medicine. So there's a lot of interest. There's a tremendous amount of capital investment for Amgen. That investment is well north of a billion dollars in investment in a portfolio of nine biosimilars and also in a successful U.S. biosimilar program for the reasons that Sumant described. We have to create sustainability in healthcare. Drugs represent somewhere between 15% and 18% of the total cost of healthcare and that is not an elastic number and so we're going to have to find ways to be efficient with healthcare and ensure that we serve patients. And there's a lot of ways that biosimilars can play a role, but I think the early indicator is that this law, the implementation of the law, has actually been well crafted and we just need to give this a little bit of time and I think we're going to see a very successful program in the U.S.

SALLY HOWARD: And I would agree. We currently have, are working with 51 biosimilar development programs and I mean we see a very robust pipeline. I mean, they're clearly at different points along the way, but we're engaging with a number of companies, with a number of programs.

ED HOWARD: Yes, sir.

JOE ZORZOLI: Good afternoon. My name is Joe Zorzoli. I'm with UCB, Head of Public Policy for the group. My question is around labeling. Zarxio was our first biosimilar approved by the FDA and it adopted Neupogen's prescriber information. So my question is, as Sandoz begins to collect post marketing survey data will they have the ability to update that label?

SALLY HOWARD: So we have a labeling guidance that we have slated for 2015. I'm afraid I'm not going to be able to answer that. That's really a CDER-specific question and I'm more of a policy person so I think it's going to be very dependent on what our folks at CDER see in that marketing situation.

ED HOWARD: If I can just try to play with your question a little bit. The importance of the question has to do with the allowable uses of the drug, is that right, and the labeling is where that list of uses is available?

JOE ZORZOLI: I think indications, that's partly right. But the other part of the question would be around adverse events and things like that if they differ from the originator product. And so, how would the maker of the biosimilar update those type of differences?

SALLY HOWARD: And I would have to kick that back to our folks at CDER. I'm sorry.

GEOFF EICH: I think one of the things that's going to be really important to early adoption of biosimilars is going to be credible transparent data. And, you know, different than generic drugs, there is a lot more information created in the development of a biosimilar. That's what takes that $250 million and 8 years. And to the extent that that information can be made available to providers is going to be determined in terms of how willing they are to use these medicines. You can think about some of these medicines being used in curative cancer settings. There is data available. We have to find some way to appropriately put the data out in a way that people have access to to make an informed choice. You also can't anticipate a world in which a biosimilar study that's head to head with a reference product gives you very accurate information that will answer some providers' questions and there's got to be a way for that information to be made available.

SUMANT RAMACHANDRA: So, from our perspective, we're actually being quite vocal about this. Even if the overall label ends up being the same there has to be a mechanism for the basis of approval, i.e., the data that you generated in each step of the comparison pathway for biosimilarity is made available, whether it's through publications or the ability to promote it. So those are things that obviously the FDA is

working through. We have shared our opinion, but the reality is there is the original drug with the original label. There's a biosimilar that comes onto the marketplace that has a basis of approval of what it was based on. So that has to also be out there in one form or another and there are mechanisms to make sure that they are available, appropriately good mechanism that the FDA does allow.

ED HOWARD: And the gentleman's question actually suggests a couple of the questions that have come up on cards that I wanted to surface for you folks. And that has to do with the continued monitoring, post FDA approval of the efficacy and safety of biosimilars or, for that matter, biologicals in general given what has been pointed out several times that these entities tend to change subtly over time. So maybe it's not exactly the same product, how are you going to assure that the efficacy and safety remain, and the other question had to do with the same subject in asking whether there is an answer out of the European experience that's different from what you expect here.

SALLY HOWARD: I'll start with this. I'm sure others will have views, too, but pharmacovigilance, which is the monitoring of safety of the products, FDA does this in two ways. We have a Sentinel system which is actively surveilling and we look at claims data and we're very actively looking at how products are working and whether there are adverse events. And then there is what we call passive surveillance which is when there are adverse events people report to us. And I'll start with the passive, some of the flaws with passive surveillance is, especially in the generic's world which we would kind of look to, many times the report is made actually to the reference product. It's not reliably made to the actual generic product. So it's sometimes difficult for us to tell the precise product that was used that caused the adverse event. And in active surveillance, some of the complexities that we have with our Sentinel system, which is a terrific system that is constantly mining millions of health systems or records, the complexity there is that there's not a standard format used necessarily, and so when we're trying to do pharmacovigilance and, from our perspective, it's if there's a problem—I mean, we're looking to see how fast can we find which product caused the problem so we can address it very quickly, so we can minimize the scope of the recall, and so that's the one thing is, let's say there is a problem. And the second thing is we want to be able to understand over time the safety profile of the biosimilar versus the reference product versus an interchangeable product. And so, as we look at a number of the policies that are being discussed now, that's foremost in our mind is are we going to be able to track back? Are we going to be able to really understand the safety profile of each of these products? And some of the challenges we have are, unlike where the NDC code is used all the time in the pharmacy benefit side, it's not used in the physician and hospital setting, so that's where you get to J codes, and so how are we going to be able to track through the J code versus the NDC code and what settings these products are used in, all make for a very complex policy problem to be solved.

SUMANT RAMACHANDRA: From a European perspective, we have launched these three products where you could only take a look at two of our products where they've been long enough in the marketplace: Epoetin and Filgrastim, and then our data was actually confirmed, let's say in numbers by what Novartis did when they looked at their experience and then European database for safety, the database actually collects this information. In general, it's around 90 plus percent of cases can be identified in Europe. For us it was 95% and 99% on the two products. I think Sandoz had, or Novartis Sandoz had it also in the 90's, and the European database, which is run by the European Commission Health Authority, their EMA actually was 90%. So it's a very high number, but the uniqueness in Europe in general is that there is brand name prescribing in most of the markets so, in general, you do know what's going to happen. In the U.S. there's not an absolute requirement for brand name prescribing so it may be slightly different from a dynamic perspective, but in terms of European data, 90% and north.

GEOFF EICH: So I would just add a couple of things. One of the things we want for Amgen biosimilars is to absolutely be distinguishable in code, in name. We want to ensure that we can actually get the report on our medicine. And the other side of the numbers, and we know this, having also been a brand biologic sponsor, is that a large proportion of reports that do come in from patients, physicians, pharmacists, they don't have accurate identifying information of the manufacturer. So they are investigated and they're filed and they become, if you will, sort of "class" adverse events. They're somehow related to the class but not to a product. We will never do that to another sponsor and, more importantly, we will never do that to a patient. We want to ensure that every single concern with our product results in a phone call to us so that we can do the investigation, do the due diligence, understand why that problem has occurred. We also don't want our problems, if we were to have an issue, to be seen as a broader class problem because you could actually hurt patients that way in the sense that, as Sally said, if the recall is larger than it needs to be then that's actually hurting patient care. And so, from our perspective, this is very simple. Just do the right thing, have single point accountability for your medicines—brand or biosimilar—and let's focus on the patient and let's focus on ensuring that clinicians have confidence to use these medicines, patients have a good response, and we can get to the part which everyone's waiting for, which is the societal benefit.

ED HOWARD: I've got a question here that requires me to ask a threshold question, and it involves J codes. And my question, before I ask this one, is what the heck is a J code?

AMANDA BARTELME: I can take that one. I'm the resident coding geek. So, J codes are a form of hick picks code, or the Healthcare Common Procedure Coding System codes. If anyone has ever—you know some of those ads that say you can become a medical billing coding specialist? People need to learn about six different sets of codes that describe services, products—all different things that we put on claims for medical care, and J codes are used for drugs and biologics delivered in a physician office or

hospital outpatient department. So, infused drugs and intramuscular injections and other things, so not oral drugs, not things you're taking yourself, with a few exceptions I should caveat that. It's the billing code used in those settings of care and the code identifies the project so then the product can be paid.

ED HOWARD: Okay. As Bill Cosby once said, "I asked you that question so I could ask you this question." You mentioned biosimilars should have separate J codes. But what about interchangeables? Shouldn't interchangeables have the same J code as the reference biologic? And I guess I should clarify that it's my understanding that this is a theoretical question because there are no such things as interchangeables as defined in the statute at this point in time.

SALLY HOWARD: There's no approved interchangeables.

ED HOWARD: Right. Okay. Anybody want to take a crack at that? Should they have the same J code, if we ever have one?

GEOFF EICH: I'm happy to start. I think that, you know, Sally pointed out that the hick picks code or the J code, which simply means the product identifier, persists into claims databases. So it means that a patient goes in, sees their physician, they're administered a medication, and it is this code that persists into the claims database that provides the source. It's the big data for FDA to direct its technology, which is called Sentinel, to connect a patient, a product, and an outcome—hopefully a good outcome. Any time any biologic medicine does not have a product-specific code you're going to see a patient, an outcome, and an amalgamation of products. There's great value and need to be able to aggregate data but we cannot exist in a place where we can't disaggregate data to a specific product.

You know, one of the things we're going to learn about biosimilars or that biosimilars will teach us about biotechnology is a vastly greater understanding of what these small differences that we see between products actually mean. And Sentinel is probably one of the most sensitive assays to understand what those potential differences can be. We will do ourselves scientifically a disservice but, most importantly, we do ourselves a disservice by not being accountable to patients if we allow for anything other than the ability for Sentinel to get to an individual product, an individual patient, and the outcome.

SUMANT RAMACHANDRA: And, from our perspective, a J code is a good way to distinguish between each biosimilar and the original drug. So I think having that ability to distinguish within a J code is a good way and good policy sense across the board, regardless of interchangeability or not.

ED HOWARD: Okay. Yes, ma'am.

ANGELA MAAS: Angela Maas with Specialty Pharmacy News. My question is on the naming issue. So, with about 70 biologics right now in the U.S. market that have different brand names with the same INNs, if the FDA gives biosimilars different INNs would that mean, then, to be consistent, that it would need to go back to those existing products and have them have distinguishable INNs as well?

SALLY HOWARD: Very good question. And I will tell you it's not the first time we've been asked that question. Again, I think, as we're continuing to sort out what the right policy would be, one of the concerns that has been raised to us a number of times is, if you were to have something that wasn't the same name how should you apply something different, and should it apply just prospectively? Should it apply prospectively and retrospectively, should it apply just to biosimilars, should it apply to all types of biological products? And, again, this has, in some of the other questions that are posed are things that we're struggling with and why you don't see a naming guidance out yet.

AMANDA BARTELME: I think one of the challenges here, too, with this question and the last question, is we're dealing with unknowns a bit here and we're trying to predict the future and we're thinking about things that are used for very different purposes. We're talking about tracking for pharmacovigilance. We're talking about billing and coding and payment and reimbursement and claims processing and naming has a role in all of those things, coding has a role in all of those things. But I think the question that everyone's grappling with is does a code have to be able to successfully do all of those things? Does a name have to successfully navigate all of the potential pitfalls with reimbursement, with pharmacovigilance? And I think that's the struggle because it's finding the right balance of how do we have a sustainable market that encourages competition, that encourages high quality products, and has patients having access without getting into this morass of technicalities that are bogging it down. So I think both of those questions kind of speak to that, and it's about how do you sort that out and come up with the right framework that everyone can operate under?

GEOFF EICH: I can also answer it from a biosimilar perspective. I don't need the reference product to have a change in their name. It's not a fairness issue or an equality issue it's just simply an accountability issue. If the reference product is Adalimumab and ours is Adalimumab Amgen or AMGN or whatever else, that's perfectly fine. It just means that one goes directly to the reference product sponsor and one phone call goes directly to us if it's our product. I don't think we need to overcomplicate it. What we need is just to be able to say, look, we are standing accountable. We've got MedLine ready, MedInfoline ready to answer questions, concerns, issues. If we've got an issue we're going to solve it. And therefore, and in there doing, we're getting to the next level which is, hey, and we really think that this is a compelling choice for you to think about.

SUMANT RAMACHANDRA: But if you are going to the one distinction is that if you are going to prescribe something you've known for 10-15 years and you see something

else as different you wonder if it's different. So if there is going to be a change of policy, our perspective is that it should encompass the field, so if there is a drug X that is going to have this additional qualifier as a biosimilar then you need to look at the original drug and ask the question is that also needed for that original drug? Because if someone does call in a report and just uses the word Adalimumab and they don't know what else was associated with it, at least if it has that qualifier you can tell which Adalimumab it was, frankly. So if you want to keep it even and pro competitive you should do it for both the original drug as well as the biosimilar. And we're not opposed to that. Actually we welcome that if that's going to be the path.

ED HOWARD: I have what I think is a related question, I'm not quite sure, that someone has submitted from Twitter and it has to do with awareness, which was one of Sumant's points, and the familiarity and comfort level that providers who might be prescribing these would have with biosimilars. And the question is: Why is there, if there is, such a low level of awareness about biosimilars among physicians and patients?

SUMANT RAMACHANDRA: So people can speak from different perspectives, so there is awareness, there's probably misinformation awareness that has to first be cleaned up. That's number one. There's a lot of myths out there about what a biosimilar is that has been propagated over a long time. Then there's actually awareness, what we're talking about, which is that biologic drugs have been critical in treating patients for a long time and there'll be a lot more biologic drugs that'll be out in the marketplace. So when we talk about awareness we want to move to the positive side and start talking about the benefits of a biosimilar as well as the original biologic and how a very competent health authority looked at the data and gave approval for that and what the post approval commitments are, what was the basis of that approval. So I think we want to move the conversation in a positive direction and, while there may be awareness, some of the awareness has been in the negative direction.

SALLY HOWARD: And FDA's aware. I mean, we fill a vital role in that as well, that education. We want to be able to help with the educational process as the regulator to be able to stand behind the biosimilars as a valid choice for the patient, for the provider community, and we feel that we really are a vital part of that education.

GEOFF EICH: I would just add a very simple answer: they're brand new. I mean, I think that's the very easy answer, is it's new, it's something different than what we've had with brand and generic drugs in the U.S. Education is going to be vital and that's one of the reasons the Biosimilar Forum was created.

ED HOWARD: We're going to try to cram in one last question because there are several that have to do with states that we're not going to be able to get to, but I did want to try to squeeze in one. And that actually proceeds from a premise that I would ask the panel to judge the correctness of and that is that states have been passing automatic substitution

laws that require most biologics to be changed if there is a biosimilar. And actually, we have some material in your packet that would point in the other direction; that there are states considering laws to require notification.

GEOFF EICH: Let me just clarify. First of all, the practice of healthcare is regulated at the state level and so how biosimilars are used is something that is a matter of each state's jurisdiction. What is being changed and updated are the state pharmacy acts in each state to enable when the FDA determines a product to be interchangeable that the pharmacy may be allowed to substitute. And today, under current law, there would not any substitution of biologic medicines. And so, all it does is, it takes the existing statute for generic drugs and it now includes a circumstance in which the FDA has determined a biologic medicine to be interchangeable with another. And it also makes clear that the physician retains the ability to have a medically necessary product dispensed, that the record keeping should be the same, as is the case for any other medicine in that state, and the one difference is around the communication between the patient's healthcare team. And this is something that the 11 large companies developing biosimilar medicines, patient groups, physician groups, PBMs, others, have really coalesced around since 2013. And it's an understanding that, for these medicines, which persist in a patient's body for weeks, if not months, it's vitally important to have an accurate medication history and not just an accurate medication history that's at the pharmacy. Today, in the U.S., pharmacists report, on average, 5 or less percent of the adverse event reports that are submitted to manufacturers and submitted to the FDA. The disproportionate majority are either the patients themselves or physicians or other healthcare providers. And so, the entire intent of the state pharmacy act and the only difference between the generic statute that's existing is this concept of an interchangeable product is suitable for automatic substitution and that we want to ensure that the patient's healthcare team—the patient, the physician, and the pharmacist—have equal shared accurate patient medication history.

SUMANT RAMACHANDRA: And also just to add, the communication we're talking about is after dispensation not prior to. And that's an important thing because if the interchangeable is designated by the FDA and a substitution occurs at the pharmacy level no one is blocking that substitution to occur, but the communication to close the loop with the healthcare provider, the physician who prescribed it, is absolutely important to just put all three people in the same loop: pharmacist, patient, physician.

ED HOWARD: Okay. Well, I don't know about you folks, but I have learned a lot in the last hour and a half and I want to congratulate you on staying with an admittedly complex but potentially very important area of development in the healthcare system. And I want to thank our colleagues at Hospira and Amgen for their participation and their support for this briefing and ask you to help me thank our panel for taking on a tough subject in a very plausible way.

[Applause]