

FTC Follow-on Biologics Workshop
February 4, 2014
Segment 3
Transcript

SUSAN DESANTI: Appreciation to our presenters this morning for keeping us on schedule and to all of you in the audience for keeping us on schedule. We're going to discuss state substitution laws now. And before we begin, I'd like to reiterate the perspective that the FTC has on these issues. We believe that competition should take place as vigorously as possible, consistent with patient safety. So if some regulations or restrictions are necessary, they should be no broader than necessary to protect legitimate concerns-- whoa. No broader than necessary-- are they? Yeah, they're on. OK.

All right. Is this better? All right. OK. A working mic always helps. OK.

So, basically, competition should be legislatively restricted only if it's necessary to prevent significant consumer harm. And if some kind of restriction is necessary, then it should be crafted as narrowly as possible, consistent with the legitimate patient safety concern or other legitimate concern. So that's how we look at these things.

We are often asked to comment on proposed state legislation, to assess the likely competitive effects associated with it. And in that context, we will typically take a look at the justifications for the restrictions, if we find that there are likely anti-competitive effects associated with the legislation. And, obviously, if there are no likely anti-competitive effects, then there's nothing to balance on the other side. You're going to go with whatever the justifications are. And we don't have any expertise there. But we do have expertise on likely competitive effects, and that's what we typically comment on.

So I'd like to start this panel by focusing on the first question-- we need to get our questions up. OK. So the first question is, how would particular provisions in new state substitution laws or similar legislative proposals likely affect competition between biosimilars and reference biologics, competition between interchangeables and reference biologics, and investment in biosimilars and interchangeables? And in that context, of course, costs associated with implementing particular provisions can also have an effect on competition.

I'm going to start with three people who did not have the opportunity to present this morning. It would've been great if we could have had a two-day conference, but considering that just finding one day with no snow was really a challenge, we were probably wise to stick with one day. But I want to get the perspective of Marissa Schlaifer, Krystalyn Weaver, and Bruce Lott, and then move to everybody else. So Marissa could you give us your perspective on this question?

MARISSA SCHLAIFER: Sure.

SUSAN DESANTI: Little closer in.

MARISSA SCHLAIFER: So I think, obviously, this is a three part question. And when we talk about competition between biosimilars that have not yet been identified as interchangeable and reference drugs, in that area, today, as the drugs would become available, pharmacies, specialty pharmacies, other pharmacies need to notify physicians anyway before those medications can be changed. So the legislation is unnecessary. The need for physician notification or prescriber notification is already there.

When we look at the competition--

SUSAN DESANTI: Excuse me, Marissa? Where? Where are the requirements for physician notification?

MARISSA SCHLAIFER: Well, today, if a pharmacy dispenses a medication that is not a generic equivalent or, in the future, an interchangeable medication you cannot make a change without physician notification or prescriber notification.

SUSAN DESANTI: And that applies to biosimilars? That will apply to biosimilars?

MARISSA SCHLAIFER: That applies to any drug that is not a generic-- is either not a generic equivalent or an interchangeable biosimilar. So that would apply to-- if the substitution was being made for a therapeutic interchange between generic Lipitor and generic Zocor today. Or between biosimilars that have not yet been identified as interchangeable, pharmacies call physicians. That has to be done. Physician not just notification but consent is required.

When we look at interchangeables, when the FDA has identified a medication as interchangeable, we're creating unnecessary communication between the pharmacy and the physician's office. And I think it's very important to a pharmacist and to a pharmacy-- information exchange between the pharmacy and the physician's office is very important. There's lots of things that pharmacies do need to communicate with physician's office about.

When we're readjusting a dose, questioning a medication where there might need to be something tweaked because of a patient allergy, we want to make sure we're not introducing unnecessary noise into that interaction between pharmacies and physician's offices, because we want to make sure that the physicians have time to pay attention to those very important questions that may come from pharmacies.

And I think on the last question, the investment in biosimilars and interchangeables-- probably someone from a manufacturer that is making the biosimilars and interchangeables is better prepared to speak to that than I am. But, as someone said earlier, it will require additional investment in sales and marketing to combat the false notion that would be out there that these drugs are not equivalent.

SUSAN DESANTI: So you're saying that you believe that physician notice and perhaps other requirements and state laws could convey a false notion that interchangeables are not equivalent with the reference biologic.

MARISSA SCHLAIFER: Correct.

SUSAN DESANTI: Krystalyn Weaver. Could we hear from you?

KRYSTALYN WEAVER: Sure. I think it is on. And I would echo the thoughts that were just shared. I actually want to bring up a specific example from Tennessee of a similar type of situation where there were specific laws that carved out a specific class of drugs and changed the requirements of how those drugs can be substituted. And those are the epilepsy drugs in this case.

And in that case I think there's pretty clear evidence that it affected the competition and changed behaviors. There was a 29% increase in the brand usage in that instance where those barriers that were put up, including physician notification, really inhibited the substitution of those generic products and resulted in increases in costs to the state and millions of dollars just in the Medicaid program. And so I think that's probably a pretty concrete example of how that can inhibit that competition through these types of state laws.

SUSAN DESANTI: OK. Aaron Kesselheim, that sounds somewhat similar to what you reported in your presentation.

AARON KESSELHEIM: Right. I mean, I think that the interchangeability of small molecule drugs is dependent in large part on the interchangeability at the level of the pharmacy because, as I said, a lot of physicians have been conditioned over the years of the brand name exclusivity period to write the brand name product, even when they don't have-- they don't care either way whether or not the brand or generic is substituted because they are interchangeable as bioequivalent small molecule drugs.

So in the case that Krystalyn was just talking about where the state put up this additional barrier in the interchangeability of these small molecule products, I think that it's a very predictable outcome that prescribing of the brand name would increase and substitution of the generic would decrease.

SUSAN DESANTI: Thank you.

GEOFFREY EICH: If I could just ask a question in terms of how this is structured. We actually have the Tennessee bill, and there's a distinguishing feature that it's prior notification. Do you want to talk about that now or--

SUSAN DESANTI: Sure. No, let's go into it now. Thank you for bringing it up.

GEOFFREY EICH: Sure. So the Tennessee legislation-- I have it in front of me. There's two things. The first point is that it should be identified by the patient before interchanging and then later it says, "the prescriber of said medication must be also notified prior to the interchange." These are fundamentally different constructs than a post-substitution post-dispensing and we would argue it can be a substantial number of days after the fact for this communication to take place.

The point isn't for the prescriber to have the information in front of them. The point is that if the patient has an issue, that the record exists, so that when the patient meets with the physician, that record can be brought to bear. There's no need for sort of, this needs to be sent to the physician for their approval. It's not an intervention at all.

AARON KESSELHEIM: I agree with you that this is a different construct. But I think that in reality a situation where a biologic manufacturers, all this notification is required after the fact. And I think many pharmacies will implement that in ways that will provide notification before the fact because, otherwise, two or three days down the line, you're going to be calling the physician. The physician is going to say, well, I don't know what went on. Then the pharmacy is going to call the patient, and then you've got this very expensive drug that may have to recall.

And the patient hasn't gotten their dose. And I think that the response to that confusion and the embarrassment that the pharmacy itself might have is that they would probably implement that as a pre-dispensing notification. So practically speaking it's probably more similar.

GEOFFREY EICH: I think it's a really good point. Just another quick point on that. I think what we need to remember, though, is that patients and physicians are generally groups that are advocating for a fewer number of days before the communication takes place. From a perspective of insuring a complete and accurate medical record, from our perspective, the hypersensitivity issues, if you will, between any of these biologic products, regardless of how they're approved, is likely to be highly similar, right? The concern is just being able to understand down the road, if there is a change in efficacy, which products the patient has received in their history.

And so I think that it goes to the point that patients and physicians, if we're going to see successful biosimilar implementation, have to have confidence. And we need to listen to the people who are going to use, and most importantly, ultimately the patients who are going to rely on these medicines.

RONNY GAL: So Geoff, the following question is for you. I completely understand why a physician would want to have access, would want to make sure, if something happens down the road, he can tell what drug exactly this patient was prescribed.

But from experience with physicians, the last thing they want is the accountability that exists with them having to maintain the electronic medical records themselves. Because they don't trust the guy in their back office or the 10-physician room. And you're hearing here that the guys who actually provide the drug actually have a system to do that. How do you answer that concern those physicians would have?

GEOFFREY EICH: That's exactly right. And I think that, if the most desirable solution is the use of an electronic health record where the patient's medical history exists in a database, it's not push, it's pull. If there's an issue, the patient's medical history can be brought up. I think Steve mentioned the use of Surescripts. So we've exchanged an abstract that Thomas actually wrote with Express Scripts to say, look, this is where we see this implementation is. These are the opportunities. These are the challenges.

Today, though, most do not have access to be able to pull up the patient's medical history using the script technology. If that were the case, it would be fantastic. But the reason it's important-- very, very quickly-- is just to make sure that the first adverse event report, the spontaneous report, goes to the right place. If it goes to the wrong place or if it goes to a series of places that are somewhat ambiguous-- you can think about this in terms of a fraction.

You're looking to see five or more of event x. If each of those five are spread across four different manufacturers, none of which are having a problem-- there's an issue on a loading dock or the temperature excursion-- we fail to meet statistical significance that says, hey, there's a signal. And that's why-- I mean, I appreciate Bruce's comments. But they're fundamentally misguided. Right? All biologic manufacturers are going to have to follow their products in the post-market setting, and the agencies made this very clear in their need-them article in 2011.

SUSAN DESANTI: OK. I just want to go back for a moment to the issue that was raised about whether, in fact, pharmacists would be likely to treat post-notification the same as pre-notification because, as a practical matter, they would want to make sure that the physician didn't have anything negative to say about the substitution of an interchangeable. So I'd like to ask our two pharmacists, Marissa and Krystalyn, what their views are on that.

MARISSA SCHLAIFER: That's an interesting suggestion. I mean, with the new proposed legislation-- obviously, once legislation is passed, we would be figuring out how to implement. From just a practical point of view and for any of you that have spent or haven't spent but have looked from the outside at what goes on in a pharmacy, more likely than not, any notification would take place during the down times in the pharmacy, which tend to be in the evening or during the lunch hour.

Not necessarily if a prescription's being filled, it's crunch time in a pharmacy. If it's not required for notification to be done in advance, I would think it highly unlikely that it would happen at that time. If it happens to be a slow day, Saturday or Sunday, calling and leaving a message for a physician's office. There's nothing the physician could do about it at that time, could happen. But during crunch time in a pharmacy, I find it highly unlikely, if not required, that that would happen.

SUSAN DESANTI: Krystalyn?

KRYSTALYN WEAVER: I agree about the hectic nature of the pharmacy but, I do think that, speaking to the liability of the cost of the product, pharmacies aren't allowed to take products back I think in every state law. And so for a large chain pharmacy, I would imagine that they would institute policies to make sure that that wouldn't happen, that the physician wouldn't change their mind once they receive that notification.

And I also think that there's a level of creating anxiety of the safety of the product if you have to do that notification even if it's after the fact. And I would say that pharmacists really look to the FDA as the experts of determining that this product is safe and effective to be interchanged. And the profession has come out with a letter from our professional associations at the national level in support of that argument that we trust the FDA and their scientific knowledge in determining

the safety and don't really feel that that needs to be questioned once interchangeability has been determined.

SUSAN DESANTI: OK. I'm going to have to ask all our speakers, including myself, to speak more closely to the microphone because people are having terrible trouble hearing and, in particular, in the center section, some of you wouldn't know this but there's a blower going.

We've tried to turn it down, and there's just not anything else we can do about it. So I'm very sorry. So the only thing we can do is ask our speakers to speak more loudly into your mikes. OK. So thank you very much for both those observations. I'd like to move on--

AARON KESSELHEIM: I think we have a comment over here.

MARK MCCAMISH: Before you move on, just one quick question.

SUSAN DESANTI: Sure.

MARK MCCAMISH: And that is you saw Ronny's presentation talking about Europe and the variability of responses within different countries, something we face all the time in terms of moving things forward. In the states, there is the issue in terms of state legislature that's being addressed at every state. And you saw also in presentations where there is no concern about biosimilar interchangeability and then major concern about biosimilar interchangeability from a scientific perspective depending upon how you present the data.

And I can tell you it's very easy to scare the bejesus out of someone because it's not identical. You can go down this pathway. It's not identical. It's not a generic. It is a biosimilar. It's not identical to it so you should be afraid of it. And we have plenty of experience with this. And look at California as well. California was broadly passed by the legislature, but then vetoed by the governor.

And my comment here is we try to take a little bit of a pragmatic approach because we're passionate about getting biosimilars out and patients getting the advantage of access, lower cost driving the access that is there. But with various states, you have the possibility that you'll have such divergent approaches in every state that a manufacturer will really be driven nuts in terms of addressing these various issues.

And so what we've tried to do is come up with a pragmatic approach. And not that we have a concern about the safety issue, not the documentation issue, but is there a way that you can say, OK, only for those interchangeable biologics-- and this is what we've kind of suggested-- that only for those interchangeable biologics, which is just a subset, you can communicate to the physician-- it's not a notification, communicate-- which of those drugs was used. Was it the originator? Was it the biosimilar?

So it's not pejorative to the biosimilar. That's what we want to avoid is any suggestion that the biosimilar's of a lower class, a lower quality than the originator. And so what we have thought through is, can you have it so that it's agreed upon where you would then communicate with the

physician whatever the drug was, whether it's the biosimilar, whether it's the originator. So they're getting this communication within, I don't know, 10 days or something of what it was, so they can document it for their records. And if it's a safety concern they document it. That's there.

Now, I don't think that's magic. What I'm trying to instill in here is, without some kind of a pragmatic approach, there is a risk that you'll have North Dakota all over the place, some Floridians some places, some Californians some places, et cetera. So I think the issue is it's pretty easy to influence legislatures about the potential of a safety risk if you want to suggest it, even though they're isn't. And the data around that-- so I'm just interjecting, is there a pragmatic approach?

And that's why we've tried to come up with some kind of a language-- not that it's perfect or great or whatever-- but if it's standard and everybody can apply for it and understand it, would that be better for an access? Would that be better for patients? Would that be better for competition?

SUSAN DESANTI: We're going to take a comment from Sumant. And then I want to ask Steve Miller a question.

SUMANT RAMACHANDRA: So we're a third company in this, actually, Amgen and Novartis and Hospira, and it's actually not a compromise. It's a consensus. It's very important to understand that we want to move a topic forward. There are a lot of issues on biosimilars. This is a market forming event. It doesn't happen very often in the history of medicine to have a market forming event.

There's going to be follow-on biologics in the next few years in this market. And the first thing you need to ensure is that all stakeholders have confidence in the products that are going to be out there. What that means is that the loop on communication has to be closed. That's all we're asking for. We're not asking for some burdensome process. This is a post-dispensation communication between the pharmacist and the physician. So if anything does happen-- and Geoff is right-- a patient may go on a original biologic and then on a biosimilar and eventually may go back on original biologic at some point, depending on the pharmacy and the pharmacy benefit manager. And what we want to ensure is that when a market forming event happens there's going to be a period of uncertainty in that market forming event.

That confidence is there in the products that are in that market and that communication fosters that particular confidence. We're asking for transparency in the system, and if it's very difficult for me as a prescribing physician to understand why there is such opposition to that, especially since we are generic based company by heart that has been in the biosimilar business for over eight years. And has had a tremendous amount of experience in Europe.

We're the only US-based company, with Sandoz being the European-based company, that has had this experience. And we have seen that communication does foster confidence. And that's all we're asking.

SUSAN DESANTI: OK. And do you have a sales and marketing force in Europe for your biosimilars?

SUMANT RAMACHANDRA: We do have a small sales and marketing force along with medical science liaisons with this. And I will tell you that the physicians, the medical societies, and even pharmacy groups do appreciate that because there are a lot of things that are virtually unknown about biosimilars. Again, this is a market forming event. Maybe 10 years from now, 15 years from now, we'll be talking a different language.

But I think what we have to understand is that we have to first be led by the science and clinical data of these biosimilar products. And the health authorities are the adjudicators of that with the sponsoring companies. If we can get that data into the hands of the prescriber to give them the confidence to actually write the prescription in the right manner and know that the patient is getting a drug that is safe and effective, that's what really matters at the end of the day. This is a pro-patient approach by closing the loop between a dispensing pharmacy, a prescribing physician, and a patient getting a drug. Because all three parties are involved in this, and it doesn't make sense to have a one-way communication.

SUSAN DESANTI: Bruce Leicher. Bruce Leicher, you've been waiting for a while. Then I would like to ask a question of Steve Miller. And then we will come back.

BRUCE LEICHER: Just to clarify-- excuse me. Just to clarify one point. We're in complete favor of transparency of information. We're just in favor of transparency in a manner that doesn't create competitive restriction. With the availability of e-prescription networks to every physician in the United States for free and the prevalence of the systems in all the pharmacies and the ability to, today, call a pharmacy to find out an NDC number, there's no need for special notice that will cause the barriers to adoption of interchangeable biologics.

I think you should also pay attention to the language that's very carefully used by people forming a coalition. They talk in terms of biosimilars when we're talking about laws that are for interchangeable biologics and there's a big difference between the two products in terms of the approval of the FDA. Interchangeable biologics are intended to be substituted.

In terms of the question that you asked, I just want to make one point. One of the fundamental problems with the compromise is it doesn't define what an interoperable health record system. Is it a full health record of every patient? And when is that going to be implemented across the country? What is being implemented and is in place today and can be accessed by doctors is an interoperable prescription record. And that's what we really are talking about that the notice would provide. So all they have to do is drop from the proposal this special notice that doctors don't want, that labels interchangeable biologics as somehow different. And allow the laws to go into place that allow for the e-prescribing.

GEOFFREY EICH: The laws affect the brand and interchangeable equally.

BRUCE LEICHER: No, they don't because the brands are already selling with a sales force.

GEOFFREY EICH: No, no. The communication-- the communication is for either the brand or the interchangeable and in either circumstance, the communication exists. So in what way is that not the case?

BRUCE LEICHER: It doesn't provide for notice when a biosimilar is prescribed, for example. So let me just--

GEOFFREY EICH: We already agreed the pharmacy doesn't have discretion. We had that conversation.

BRUCE LEICHER: I understand that. And that's one of the competitive problems is it creates a scenario where a doctor--

SUSAN DESANTI: OK. Guys. All right. Excuse me. Geoff, Bruce, we've got a lot of material to cover, so Steve, you mentioned Surescripts, and that's been referred to here. So could you please describe how that works and to whom it's available?

STEVEN MILLER: Thanks. I'll just make one comment before I start and that is-- you already heard from the two pharmacists. I represent a pharmacy. A system already exists. You don't need a compromise. You have an existing system that's already safe and effective. And so the idea that you need to have this notification is truly unnecessary in the current environment.

Now, what Surescripts does is-- Surescripts is an organization that was set up by the PPMs and the pharmacies about a decade ago. And it is just pipes that communicate between doctors, pharmacies, PPMs. So we currently have over 500,000 doctors that are enrolled in Surescripts. We have 65,000 pharmacies. We have all 5,500 hospitals. So the pipes already exist. And we actually have products that already exist in which physicians can actually pull down the medication history for patients.

The biggest problem out there is this. There are 300 different systems that are at the point of care. So we thought, over time, there would be consolidation of these systems and that you'd have winners and losers and the marketplace would consolidate. With the stimulus, what happened is more and more systems actually came into the marketplace. So we currently have 300 systems that are used by different doctors, hospitals, clinics et cetera.

Those systems have varying capabilities to accept message. Some of those systems are so immature they can't express even the formulary that a patient's on. So the idea that these systems have this great interoperability is a fantasy. Will we eventually get there? The answer is yes. But will we have it in the near future? The answer is no. So this new argument that we need the perfect medical record is actually somewhat bogus because we're not going to have the perfect medical record for a long, long time.

Even capable of organizations have trouble consolidating their medical records. Am I Steve Miller? Am I Steven Miller? Am I Steven B Miller? I have records spread out throughout the United States where I have lived over my life. And the idea that you're going to have a comprehensive pull of all those records is very unlikely. And so if this whole biosimilar

argument is dependent on having the perfect medical record, we'll be having this debate many years in the future.

SUSAN DESANTI: Bruce Lott, I want to make sure that I get you in since you didn't have an opportunity to present this morning.

GEOFFREY EICH: Bruce, do you want the Tennessee bill?

BRUCE LOTT: I have it memorized.

GEOFFREY EICH: I'll get the prior notification right this time then.

BRUCE LOTT: I worked on that legislation when it passed down there. And I believe that, whether it's prior or post dispensing, notification is a barrier to substitution. We've seen this type of legislation with small molecules in numerous states. And in almost every single state it has been rejected. As legislators looked at this type of legislation, they realized that it did have an impact, whether pre or post, it did have an impact on substitution. And as a result, it did create costs for states.

It has been one of the most common types of processes used as an effort to create an obstacle to substitution in the states, and it's one of the reasons that we are somewhat suspicious of its use in this particular place. So, obviously, we would oppose notification as a generic manufacturer and as a manufacturer that's working to develop biosimilars as well.

If I could very quickly, since there's been so much talk with regard to the notification piece, if I could address a couple of the other--

SUSAN DESANTI: Please do.

BRUCE LOTT: --parts of your question, I'd be more than happy to just very quickly do that. We believe, also, that imposing barriers to substitution, whether it's through notification or other means, creates a disincentive for at least some manufacturers to seek the interchangeability status. Interchangeability will be a high bar, and it will be an expensive and a difficult effort, we suspect, for companies to meet.

Some companies may decide that they will seek biosimilarity and utilize sales forces. Others may go the path of the so-called biobetters as well. And, as a result, this type of notification requirement is not really relevant in those types of scenarios. So it does bring the question, who is attempting to do which pieces with regard to this?

And I would also point out that, as several of the presenters said this morning, the existence of these barriers to FDA approved interchangeable generics could undermine a competitive market that generates a savings. If you try to apply those types of barriers in the biosimilar world, you can undermine the competitive marketplace that was intended by Congress when they passed this legislation.

SUSAN DESANTI: Thank you. Emily, you have a question?

EMILY SHACTER: Is this working? Yeah. I'm a little bit confused by Sumant's comment that we know less about biosimilars than we do about another protein products. Of course we know less now because we don't have any yet and won't have any very soon. But biosimilars are going to be FDA approved to meet their intended clinical purpose. So I'm a little bit confused by why they should actually be treated differently. We need pharmacovigilance for all products and especially for-- well, and as well for protein products, not especially, as well.

So I'm really confused as to why they should be treated differently when they're going to be rigorously approved by the FDA to meet their clinical intended purposes with the same safety and efficacy profile. I don't get it.

SUSAN DESANTI: This is exactly the question that I thought we should move on to now, which is, OK. If these prior or post notification requirements might have anti-competitive effects or somehow undermine competition, what are the justifications for them? And I believe I heard from Geoff that it's very important that the precise biosimilar or interchangeable that's prescribed be reported on the patient's medical record so that we can keep track of what biologic or biosimilar is actually causing any problem that might arise.

So then the question becomes, is it best to put that on the patient's medical record? Or, Steve, you raised some questions about whether that is a practical solution. And also I think I'm hearing that pharmacists and pharmacies keep extensive records of what is prescribed. So I would like comments on this. Yes?

MARISSA SCHLAIFER: So I think the reference that's been made several times to the need for an accurate-- that without physician notification, we'll have an inaccurate or incomplete medical record is somewhat, speaking representing CVS pharmacies and CVS specialty pharmacy, but I think, more importantly, as a pharmacist, it's discredits and is somewhat demeaning to the role that pharmacists have in the role of keeping a complete medical record or part of that complete medical record.

Pharmacists are relied on today to be where physicians go when they want to know about what drugs have been prescribed by other physicians. Are there drug interactions with prescriptions from other physicians? Anything about whether or not a patient takes their medication or not. None of that information is in the portion of the medical record that resides in the physician's office. There's another half of the medical record and that's what resides in pharmacies today.

So I think it's the pharmacists right now that are making sure that the patient gets the right drug at the right time. And I think it's very important that we recognize that there's two halves to a medical record. And anyone that thinks that all information is in a medical record that resides in the physician's office today is just not looking at the big picture.

SUSAN DESANTI: I wanted to go back. Steve Miller, is there any fee for a physician to join Surescripts and obtain access to--

STEVEN MILLER: Nope.

RONNY GAL: So comment about this issue of adopting earlier, and this is referring to what Sumant was saying and the question that was asked here. Doctors, in principle, have no incentive to use a biosimilar drug. As somebody mentioned to me, why would I ever use anything except the gold standard? I've been using it for 20 years. You are offering the same drug for less money for someone, not for me, not for my patient. Why should I use it?

And, further, why should I use a drug from a generic company when there's this innovative company which keeps on investing R&D dollars in my therapeutic area and inventing new drugs. So why should I ever use biosimilars? So doctors don't really have a lot of incentive or, at least, historically did have incentives to like low cost options. It's just an unnecessary staff to bear.

So they're getting more concerned about the overall cost of health care that is beginning to impact their own personal income, but once you begin to add paperwork, once you begin to add things they have to worry about when they are to use biosimilars, they have less and less incentive. You need to add disincentive to participate in this market. Obviously, that has to be balanced with, true safety issues, if one exists. I'm not the expert with whether one exists or not. People here know it better than me.

But the issue here is that. I would argue, also, that what we have seen from Europe is just that. It actually required fairly good pressure from payers to get doctors to try an experiment and begin to use biosimilars. And, frankly, in the United States, I expect that innovative drug company will keep on arguing the logic that the FDA used on every physician. And they have the boots on the ground. They're the ones who go to the physician and begin to argue why the logic the FDA used is wrong. And there will not be anybody there to argue the counterpoint. So once you begin to add more requirements, that's the risk you take.

SUSAN DESANTI: OK. Aaron Kesselheim?

AARON KESSELHEIM: I just wanted to make the quick point that I think that the transparency and the accuracy of the medical record is important, but it's also important to know who actually wants to know the information. And in the case of the interchangeable-- which company is prescribing which interchangeable-- I'm not sure that it's as necessary for the individual physician to know as it is for the people who are keeping track of pharmacovigilance and the pharmacoepidemiologists and the researchers at the government level and at the other larger levels who are compiling information from pharmacies and from insurers and from payers rather than from individual patient medical records.

Those are the people who are going to be able to identify and detect signals for safety sooner rather than the individual physician who only has a very small number of patients. And I think this was a point that Geoff brought up earlier that you need aggregation of this information accurately to be able to do these kinds of signal detections that you're looking for. And trying to make sure that the patient's medical record accurately identifies which various manufacturer made which interchangeable drug doesn't necessarily help that process.

SUSAN DESANTI: OK. Sumant and then Mark and then Geoff.

SUMANT RAMACHANDRA: Yeah, just a clarification so to at least comment. I am not saying the communication to the physician is for biosimilars only. We're talking about biologics and interchangeable biologics too. They both are part of that communication. So I just want to make sure. And at this point a designation of interchangeability on the biosimilar to the original biologic, today, the state of the science we know as a developer is very, very good-- it's excellent-- but it's not, today, equivalent to the same as a small molecule in terms of understanding everything at exactly that point where the molecule is made. That's the only point I'm making. This for the field of biologics and not about just biosimilars. Both are subject to communication.

MARK MCCAMISH: Sumant and I have argued about this for quite a while in terms of what the clinical relevance is and in this situation, the way that we state is the variability of the reference product if you could be within the variability of the reference product with your biosimilar then there's no clinically relevant difference along that line.

But let me go back to the issue you mentioned about a sales forces, Susan, which I think is an important question. And what we are trying to do is, if you have a standard approach that's there-- I mean, if you can get interchangeability at the state level and if it's consistent, it actually aides those companies that don't have a sales force.

If it's multiple different types of approaches in different states then you're going to have to address those different states from an educational perspective differently. So it's actually a disincentive if you don't have an organized approach that's there. So it gets back to this state component.

The last thing is on pharmacovigilance, and it comes up and it'll come up in the naming situation. And I agree with what Emily said that we will have a huge knowledge base on the biologics that you then make a biosimilar to and so we know where the immunogenicity will likely stem from. We will document that we'll have data around that. So the knowledge base you know about the safety of a biosimilar is actually greater than it is with the original biologic that you launched years before.

And the question is, why is pharmacovigilance coming up now? When biosimilars are being launched. And we had the same issues for years on this, and how do you differentiate a biologic or any other drug? And I think if we're going to put effort into this, it shouldn't be around biosimilars. It should be around pharmacovigilance per se.

How do we get a bar code integrated that's there and so we can track down to the lot-- it's the lot that's important, not that you name it some 47 letter word that the physician will never know. It's the lot we have to trace and we've got technologies to do that. Let's talk about how we do that from a safety perspective. That applies to all biologics. It's there. So I think it is, when you talk about pharmacovigilance just for biosimilars, it is a little bit challenging to understand why it's arising now.

SUSAN DESANTI: Geoff.

GEOFFREY EICH: I'd like to just echo and take right of from where Mark left off and also Aaron. It's really important that everybody understands how pharmacovigilance happens in this country. So UPenn cites it at about 90%. FDA's Office of Epidemiology at 95%. 95% of all adverse event reports come to the manufacturer of the individual product, assuming that that manufacturer can be correctly identified.

The next point that's really important to know is that that's how the information gets from a spontaneous reporting, which is hypothesis generation that there may be a quality issue, to the FDA. That's the way that this happens. This is our sort of ready made alert system for a change in quality. And I think to Emily's point no one has any question that the FDA is going to be approving these products to be safe and effective. And I want to really underscored that.

There is no question about these products. The question is, what if one lot or one half lot of one manufacturer's product sits on the loading dock too long and it starts to have a temperature excursion and aggregates? That can result in a product quality issue. There are many, many other insidious quality issues, and really, to go from Mark's perspective, this is about all biologics.

Biologics are increasingly being made by a range of companies and these are the right standards in place. But, again, do we now become vulnerable, all of us, collectively, with our biosimilar products to any other problem with any other product that may not even be something that the FDA can enforce and that may not be anything to do with the individual sponsor or their product? That's the question.

And it's not a question at NDC or a distinguishing name or the ability to have a complete record. The point is, do all of them? There's absolutely no downside to doing all of them. And I think where we've all found consensus is, if we treat this from all biologics, look at them from all biologics to make sure, quite frankly, that the exchange of information is consistent across all biologics. Then there is no advantage or disadvantage. It's fair. And the most important thing is it puts the patient first and foremost in the policy decision.

SUSAN DESANTI: OK. We're going to get into pharmacovigilance and the naming issues in detail this afternoon, so I'm going to move on from that and simply ask--

BRUCE LEICHER: Could I just make one comment about the substitution issue, which is that we completely agree with Geoff on the point that pharmacovigilance is important. We just think the notice provision is not the way to do it. The way to do is to allow the doctor to look at a system like Surescript, which is universally available, if there's a need to know what was dispensed and look it up. And then you're not providing any differentiation, discrimination, disparagement.

SUSAN DESANTI: OK. One question that relates to the issue of, if there are particular provisions that may have anti-competitive effects, what are the justifications that support the need for those provisions? Are there any data from Europe that suggest problems, in particular, with switching from a biologic to a biosimilar. I know there have been a variety of other

problems, but we haven't seen data on switching from one biologic to one biosimilar or any other kinds of switching problems. And I'm wondering whether the manufacturers who are here or Ronny know anything about this.

MARK MCCAMISH: So. Ronny do you know anything about this?

SUSAN DESANTI: Mark, Mark, I was calling on you.

MARK MCCAMISH: I'll share some slides this afternoon as well that goes to the naming component of why I have additional names to it, and our basis of this is about 200 million patient-days' experience in Europe with our products and worldwide. Europe does not use a different INN. So it's the same INN throughout Europe. And in reporting it-- gets back to the spontaneous events that Geoff was talking about-- when it's a spontaneous event that the doc reports or the patient reports, generally 99% of the time, it's the brand name that's used. They don't use the INN, and so, again, the INN or a different INN or a modified INN, at least in our hands, doesn't impact the reporting of adverse events.

But our experience in Europe-- and we know that there has been switches, and we know that entire countries have been exploring this. And now Norway is trying to sponsor a switching type of study to really do this. But this happens in the sense of tenders. So in certain countries, there's a tender that goes forward, and the company may win that tender. It's not often just the lowest price, but it's price as well as quality, as well as delivery, as well as call chain, and other types of things, because the country doesn't want to get a product that then the manufacturer runs out of it or can't provide it et cetera.

So it's complex in that sense, but with these tenders, they are switched from year to year from one product to another. And that includes treatment of kids. So in Poland, for example, one of our biosimilars is a growth hormone, and in Poland we won the tender for the growth hormone, so all people were switched to that biosimilar. The next year, we lost that tender, so they were all switched back to the originator in that sense. And, again, it's not perfect because we're not prospectively studying every patient that is switched. But with the databases that are available, there's no sign of adverse events, untoward events from that switching component.

We have had other studies where we proactively monitor patients coming into studies. And we are interested in, before they get on our product, how many different products were they on? And often this is in a nephrology setting. As Steve mentioned, they document very well what products the patients are on, and of patients coming into that study, only 22% were on the same product for the last six months. We had patients on 17 different products in the six months prior. So there are switches going on, and it's based on tender and other types of things.

Now, we've looked at the data to see if those patients that had switches responded to the product they were put on, either ours or the originator, in our study going forward. There's no relationship to switches versus efficacy. So if it's related to immunogenicity that causes an interference with efficacy, there's no data to support that.

So our experience is fairly robust that there are switches that happen. There's not some untoward signal that we've been able to pick up with our biosimilars in Europe and the rest of the world. And we follow the same pharmacovigilance system in our biosimilars as we do with our novel biologics. So there's nothing different in terms of the way that we're follow it.

Now, I agree the pharmacovigilance system is not perfect, and we need to fix that. But I don't think we need to fix it for biosimilars per se. That's the data at least that I have.

SUMANT RAMACHANDRA: So we're the second company that actually, within the panel at least, that actually sells biosimilars in Europe. And our experience mimics Sandoz's almost exactly. And we've published on this. We actually, as part of our approval, made a commitment to do post-approval registries as part of actually formally tracking patients in a registry format, as well as spontaneous reports that come out of market use. And in that we have not actually seen any untoward safety signals that have come there.

But it's important that we did that for a variety of reasons. And it's important we did that because it actually built up our database and our confidence, because it's part of our requirement to make sure that our product that we put out there continues to be safe and effective as part of our original intent for registrative market authorization. So that is our commitment from a Hospira perspective. And that's a commitment we have to make for patients to safely the drugs and ongoing safety of the drugs that are out there in the market. And we did see the same.

If we think the US is complicated, Europe is not about states. It's different countries, and each country handles its own way. You will see data I'll show you in the afternoon talk about different profiles of countries and how extreme it can be in terms of adoption. I also have to say that Hospira got the first, along with our partner Celltrion, the first monoclonal antibody biosimilar approved Europe, which is infliximab. Biosimilar-- our brand is Inflectra.

And in that experience, we've also seen that people are asking for-- that even though you do have that approval with the full range of indications, that's great. But we want to understand the safety and efficacy within my area of specialization I'm going to treat the patient in. Because our studies were done in ankylosing spondylitis and rheumatoid arthritis that on a full proponent extrapolation in fact that is one of the foundational bases of biosimilarity. It just doesn't make financial sense anymore to do biosimilar drug development if we don't have extrapolation.

But despite that, they have asked for the data. The practitioners have asked for data. And Europeans have been used to biosimilars for so many years. So if Europe, which has had biosimilars for that many years, gets a monoclonal antibody biosimilar come to the market, but they're still asking for data, what do you think is going to happen in the US community?

And that's why I talked about this being a transition point. 10 years from now, we're going to have a very different conversation in the US. But today, our conversation has to be based on scientific data and clinical data to drive confidence and communication. That's what we're stressing. Not that biologics are different than anything else or biosimilars are different than biologics. But you have to build the market with confidence and data, not opinions. You'll hear a

lot of opinions, but data actually drives that confidence. Not suppositions and going out there and saying, trust me. I'm great.

GEOFFREY EICH: Yeah, I'll just bring it home because we also have a European experience. And, again, our European experience thus far is on the brand side, and I think that underscores what we mean about, this is about all biologic medicines. And so our experience with other brand manufacturers is that an adverse event that was insidious and had nothing to do with the regulatory approval-- it was a post market change by another manufacturer in the market-- was misattributed to our product in the market. And this is the lesson learned for all of us with biosimilar medicines, but also with any other kind of biologic medicine, interchangeable or brand.

Going exactly from Sumant's point. If it is difficult to ascertain the root cause, and if the patient may have an adverse event at a time when they're taking one product, but the root cause is actually a product they've taken before. You have to have the data. I mean I imagine that circumstance-- and this is what we don't want to imagine-- is that these circumstances occur with any of our products, brand, biosimilar, or any other. We want to ensure that we can represent the post market safety benefit risk profile of our medicines without having that confounded. It's simple.

SUSAN DESANTI: Bruce?

BRUCE LOTT: Just one very quick point with regard to--

SUSAN DESANTI: Can you get closer to your et

BRUCE LOTT: One very quick point with regard to this. In Europe, there is no such thing as an interchangeable biological product. They are all biosimilars, so it's a process that's more similar to the US biosimilar. So when we're talking about the notification and the need for this, it sounds as though we've heard very clearly that there's very limited issues or problems. But even in Europe, we're talking about biosimilars, not interchangeables. We're talking in the US about applying notification to interchangeable biologics, which is a higher standard. And I think it's important to keep that in the context.

SUSAN DESANTI: OK.

MARK MCCAMISH: I think that's a good point. And I just want to, one thing. In Europe, interchangeable doesn't mean what it means here. So in Europe, interchangeable means the physician actually orders a different drug. Substitution is what interchangeable means here. And it is dealt with on a country by country basis. I want to go back to Geoff's point on this. And Geoff, the only thing that is a little bit disingenuous about this is the timing, because the issue with Eprex happened 10 years ago. And if it was an issue there from a labeling prospective or you wanted to change it and you felt that the product was falsely attributed to you, why now? I mean, that's the only issue that makes it a little bit challenging.

GEOFFREY EICH: And I think it's important for everyone to consider this. So since that particular set of circumstances, which took an inordinate amount of time, two to four years, to be able to identify the root cause, which is completely inappropriate and would be absolutely inconsistent with our aspiration for the biologic market, we've continued to work with regulators for many years. We have implemented changes in the label of our products and others that indicate that the product needs to be tracked appropriately in the patient record.

We've advocated before the European Parliament and Commission on behalf of legislation which is called the Pharmacovigilance Directive in Europe, which goes to ensuring that every member state will create circumstances by which every patient, every physician, and every pharmacist can accurately report an adverse event and know which product the patient received.

So it's a great question, Mark. And I think that it's important to note that this takes a lot of time. Our view for the US, guys, is that this is an opportunity. We have the opportunity to set the circumstances to take the lessons learned from Europe and have a highly, highly successful biosimilar, interchangeable biologic market in the US. We don't have to learn all of these lessons all over again in the US.

And this is why, really, I hope you get a sense, we have tremendous respect for our colleagues all of whom are developing biologics, biosimilars, and interchangeable that are going to be absolutely everything that the FDA says they're going to be. But at the end of the day, every one of them is a biologic medicine, vulnerable to all the same sets of circumstances. If we get it right, we will have a very, very successful, pro-consumer, pro-patient market. If we take steps to just ignore our relevant history, we do so at our own peril.

SUSAN DESANTI: OK. One question I want to get out. In some legislation, there's a requirement for pharmacists, for the State Board of Pharmacy, to maintain a list of biologics and their reference interchangeables. Would that be necessary if the FDA created a new publication, say comparable to the Orange Book, that provided an authoritative listing of FDA approved biosimilars and interchangeables and their reference biologics? Is there anyone who thinks that--

KRYSTALYN WEAVER: I'm happy to jump in and say, no. I think that it's just an extra step for the state boards. The state laws now that refer to the Orange Book can refer to the list that the FDA maintains. There's really no reason to have that be a state by state issue. The state boards don't have any special knowledge about interchangeability of medications.

SUSAN DESANTI: Marissa.

MARISSA SCHLAIFER: I think that was said perfectly. I mean, state boards, should they create a list, are going to need to turn to the FDA, to resort to an FDA list, and reproduce it at the state level. If a state produces anything that's different from the FDA, it's not accurate. So it's just a duplication in 50 states of the same list.

SUSAN DESANTI: OK. And, finally, there are other provisions in some state laws that mandate particular lengths of time that pharmacists need to keep records of what drug or biologic or

biosimilar or interchangeable was prescribed. Are those lengths of time similar? I mean, what do pharmacies typically do in terms of keeping records?

KRYSTALYN WEAVER: The requirements vary state by state, but I would say that the most appropriate thing that should happen is that biosimilar interchangeable medications are kept for the same amount of time as every other prescription.

GEOFFREY EICH: We would totally agree with that. That's been our advocacy as well is that it just is the same for any other medicine. There's no reason to have it. It needs to be, roughly speaking, it should be longer than probably 12 to 24 months so that if there is something that takes longer to manifest, that there is a record. But really just matching existing statute is perfectly sufficient.

SUSAN DESANTI: Does anyone disagree with that?

KRYSTALYN WEAVER: And I don't think that there's a need for it to be in a separate physical location either and I think that's what's suggested.

SUSAN DESANTI: OK. Yes, Emily.

EMILY SHACTER: I wanted to make a comment and ask a question. The question may be naive, but, if a doctor prescribes a biosimilar and the clinic doesn't have it available so they give the reference product instead, does the doctor have to be notified?

BRUCE LEICHER: So is that interchangeable, biosimilar, or, in your parlance, the virtual interchangeable?

EMILY SHACTER: Any biosimilar.

MARISSA SCHLAIFER: It would depend on how the prescription's written. So if it was written, assuming that we're looking at one naming, and not suffixes or prefixes right now--

EMILY SHACTER: Might be a wrong assumption.

MARISSA SCHLAIFER: Right. So if it was written with one name and specifically it said I want to prescribe this drug by Sandoz and you use the reference drug and your changing in the manufacturer, you would definitely need to notify the physician. If it was just written with the generic name, the INN name and nothing else, then any one of those products. whether there it was the reference product or the biosimilar product, would meet that name and that definition. So there would not need to be any notification.

EMILY SHACTER: OK. I also just want to make a comment about the experience in Europe with switching. So the absence of immune responses and all of that to the products that are switched through the tender mechanism in Europe is consistent with the science, the underlying science. There actually isn't any underlying science that the switching of one highly similar biologic to another is going to result in an immune response.

And I had a lot of arguments-- discussions-- with some of the best immunologists at the FDA, my very close colleagues, and asked where's the underlying science? What is the immune system going to be doing that's going to have it react to the second one coming in or if you go back and forth?

There isn't an underlying science for it. The immune system hasn't demonstrated that. So I think that your empirical experience, actually, is consistent with what we would expect.

MARK MCCAMISH: I have just one quick question for the pharmacists and Steve. I mean, you've got a lot of experienced to come to bear on this. And the question is-- again, I'm just trying to balance these things out-- is it better for you and who you represent to have a standard across the states?

Or how much of it is an issue if you have multiple different states doing multiple different things going forward? And you have like a North Dakota and you have a California. You have a Florida and totally different there in terms of those and the risk of being very conservative in some states that are there. I just don't know. Do you balance that? And what do you think about that in terms of when you're weighing this in a sense of pragmatism?

STEVEN MILLER: So I'll start and my colleagues can speak. We actually have differences across the states on a lot of different pharmacy law. As you know, because of the Constitution, pharmacies are regulated at the state level and 10th Amendment, the policing, and so we're always going to have differences in the states. We have it on narcotic regulations and record keeping. We have it on many other substitutions, on different drugs, as we've heard Tennessee or others.

And so we're used to dealing with it. We would like it to be most standardized. We believe that, in this particular case, the FDA has the knowledge on this. And the FDA's ruling on this should apply across all 50 states. We also believe that pharmacovigilance is important but it is separate from this issue. And trying to tie pharmacovigilance to getting biosimilars into the marketplace is just a tactic to delay biosimilars' appearance in the market. OK. Geoff, you can have the last word.

GEOFFREY EICH: Sure. I think the first point is that we're very, very proud of the work that we've done with our biosimilar development programs. We're very excited about the prospect that biosimilars bring to increase access. I think all of us would agree that our number one objective is to make sure that every patient who needs a biologic medicine has access to a high-quality biologic medicine, full stop.

I think that the biosimilar pathway offers tremendous opportunities. It is complicated, because the practice of health care is regulated at the state level. And we've heard a lot of conversations about, the federal government should do this. At the end of the day, the FDA will determine that the products are safe and effective for their intended uses. And those uses may include, at some point, the interchangeability or the alternating or switching between products.

And I think I would agree with Emily's perspective that the burden lies on the sponsor to meet the standard, the standard that's been laid out in the federal law is an opportunity. The opportunity is clearly there. And it is the right standard. And just to be very clear, the standard is that there's an expectation of the same clinical result in any given patient, and that there's no decrease in safety or efficacy as a result of alternating and switching for these that are used more than once.

That's fundamentally important. It's the right standard. It's a great opportunity. What we're trying to do is work with many other colleagues and stakeholders who are developing biologics and biosimilars for this market and make it a real opportunity for patients.

SUSAN DESANTI: OK, Geoff, I'm sorry. You're not going to have the last word. But I do have follow-up questions because you've emphasized Amgen's interest in biosimilars. Can you tell me, does Amgen have biosimilars in Europe currently? And for the US biosimilar market, when it comes about, whenever that is, have you made projections for what your profit margins on biosimilars are likely to be in the US versus your profit margins, as you currently have them, on biologics in the US?

GEOFFREY EICH: So a couple of questions and I'll just take them in order. As we discussed with you, we've made publicly clear our six biosimilar portfolio. All six of those products will be designed and developed to be marketed worldwide. Those are obviously biosimilar candidates, and, like I said, we've got-- I think I mentioned earlier-- three of those six are in pivotal trials now.

I'm an R&D policy person. I work in regulatory affairs so I don't have any insight into the financials or the commercial interests of biologics. I can tell you, though, which I think is really important, is that our scientists are learning a tremendous amount about these products. The development of biosimilars has been for R&D organization, manufacturing, and process development organizations really quite profound in terms of what we're able to learn. And we're going to apply those skills. And I actually very much agree with much of what Emily has said today.

Not only will the individual manufacturers be able to apply this knowledge, but so will the regulators around the world. We have tremendous opportunities in the US. And, honestly, this is a little bit of a lay up, because Europe has done a lot of the hard work. And manufacturers like Sumant and Mark have done a lot of the hard work.

The challenge before us is to make sure it's the right system, the right place for biologics and biosimilars to be successful in the long term in the US. And then we have challenges around the world, because biologics are absolutely in great need in many other regions of the world.

SUSAN DESANTI: Thank you very much. Thank you all for your patience. We will start again at 1:35.