FEDERAL TRADE COMMISSION

FOLLOW-ON BIOLOGICS WORKSHOP

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FEDERAL TRADE COMMISSION

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I N D E X (Continued)

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WELCOME

MR. GAVIL: Good morning everyone and welcome to the FTC's Follow-On Biologics Workshop. My name is Andy Gavel and I'm the director of the Office of Policy Planning here at the Federal Trade Commission.

We all appreciate the level of interest in the workshop and are very grateful that so many of you have joined us today, especially in light of our cancellation in December and rescheduling. We hope many others will also take advantage of today's proceedings via our webcast and the record of today's proceedings will be on our website, along with the webcast for future reference.

Before we get started, I need to review some administrative details and ask for your patience. First, please turn off or silence any cell phones or other electronic devices that you have. Second, if you leave the building for any reason during the day, you will have to go back through security. Please keep that in mind in planning ahead, especially if you are participating in a panel, so we can remain on schedule.

Please try to avoid having conversations out in the hallway, directly outside the auditorium, while panels are in session. The background noise from the hallway carries into this room and can sometimes

disrupt the discussion. Also, the microphones that we are using for the webcast are very sensitive, so some of those hallway conversations may be picked up by the court reporters or the webcast. So if you do speak in the hallway, speak loudly so that everyone in the world can hear you.

Fourth, the restrooms are located out the lobby behind the elevator banks and to the left of the security guard desk. Fifth, in the unlikely event of an emergency and the building alarms go off, please proceed calmly to the main exit in the lobby and assemble across the street on the sidewalk in front of the steps of the Georgetown Law School. The security guards will let us know when it's safe to return to the building.

I'd also like to remind all presenters and panelists to speak directly into the microphone so that everyone can hear your remarks and that we have a clear record of today's proceedings. And please speakers, be attentive to our time keepers, who will be right in front of the podium.

Finally, if anyone has questions throughout the day, feel free to ask our staff. We are wearing FTC staff badges, or those sitting at registration desk, and we will be happy to help you with anything

that comes up.

To open today's workshop, it's my great pleasure to introduce FTC Chairwoman Edith Ramirez. The Chairwoman has been especially interested in continuing the Agency's long-standing commitment to promoting competition in the healthcare field and we are really delighted to have her join us to open today's workshop. Chairwoman Ramirez.

OPENING REMARKS

CHAIRWOMAN RAMIREZ: Thank you, Andy. And good morning everyone and welcome to the FTC's workshop on Follow-On Biologic Medicines. At the outset, I wanted to start by thanking the speakers who are joining us today, especially those of you who flew in back in December when we had to cancel the workshop due to the storm.

I also wanted to thank staff from our Office of Policy Planning who have now organized this workshop twice, including in particular Elizabeth Jex, Susan DeSanti, Erin Flynn, and Chris Bryan.

What I wanted to do this morning was just to take a few minutes to set the stage for today's discussion. As all of you know, biologic medicines are among the most important pharmaceuticals available today, providing life-saving therapies for difficult-to-treat diseases such as cancer, diabetes and multiple sclerosis. There are also among the most expensive, with costs often exceeding tens of thousands of dollars per year. Others have a price that is substantially higher and these costs may prevent some patients from accessing potentially life-saving therapies.

Introducing competition into the biologics

market place represents one of the most promising ways to reduce prices and expand access to these critical drugs.

Most consumers are familiar with the cost savings associated with the introduction of generic drugs to compete with traditional brand name drugs. The abbreviated FDA approval process created by the Hatch-Waxman Act to introduce safe and effective generics has spurred price competition and expanded consumer access to many widely prescribed small molecule drugs.

Recognizing the benefits of the Hatch-Waxman process, in 2010, Congress passed the Biologic Price Competition and Innovation Act, which created a statutory framework for follow-on biologic competition. This law required the FDA to develop an abbreviated approval pathway to promote competition for follow-on biologics, including both biosimilars and interchangeable biosimilars.

While the FTC's 2009 Follow-On Biologics report found that a number of factors may result in different competitive dynamics and markets for follow-on biologics, it concluded that their introduction is likely to resulting in lower prices.

Of course, savings are less likely to be

realized if there are regulatory or other hurdles in place that inhibit the development or adoption of follow-on biologics. Before businesses decide to invest millions of dollars in developing any new product, they assess the market to determine whether it's conducive to new product entry. One important factor that can affect entry is the regulatory landscape. Does the landscape facilitate new entry or create unwarranted obstacles?

Although the FDA has yet to approve any biosimilar drug, the evolution of that regulatory landscape, beyond the FDA approval pathway, already appears to be underway. Accordingly, the time is right to consider this future market, particularly since policy positions being made today may have a crucial impact on how competition for biologics plays out in the years to come.

While it appears that, under federal law, an FDA approved interchangeable biosimilar may be substituted for a reference biologic without prior prescriber consent, there is substantial uncertainty at the state level surrounding how follow-on biologics will compete with their reference products.

State legislators are considering, and some have already passed, laws that may affect the ability

of follow-on biologic medicines to compete with existing biologic drugs. Last year alone, at least 15 states considered bills concerning follow-on biologics. The different laws provide some means for permitting interchangeable biosimilar substitution, but they vary in the effects and, some argue, the burdens associated with substitution.

For example, this past fall, California Governor Jerry Brown vetoed, as premature, a bill that would have permitted interchangeable substitution, but would have required that a pharmacist provide the prescribing physician with notice. Meanwhile, Florida enacted a law that requires notification only to the person presenting the prescription, typically the patient.

A key question is whether such notification requirements and other kinds of restrictions have valid justifications. And if they do, whether they are no broader than necessary to address legitimate concerns.

Other regulatory efforts could also affect competition for biologics. Some parties are requesting that regulators change the existing paradigm for naming medicines that compete with an original reference drug. In the case of traditional small molecule drugs, each of brand-name drug usually has at least two names, a

proprietary or branded trade name and a nonproprietary name that is based on the drug's active ingredient. A small molecule generic drug has the same active ingredient as its reference branded drug, which means that a generic drug typically has the same nonproprietary name as its branded counterpart.

Biologic medicines in the US also have at least two names, a proprietary branded trade name and a nonproprietary name that reflects certain scientific characteristics of the product. Some argue that biosimilars should have unique nonproprietary names that differ from the referenced biologics nonproprietary name.

This naming process may have profound implications for how the marketplace will receive follow-on biologics and therefore will influence company decision-making as businesses evaluate whether to invest in follow-on biologics development. These regulatory choices will directly affect whether and how follow-on biologics enter the market, as well as how competition will develop once entry occurs and they may also have crucial implications for patient safety.

The ultimate goal, of course, is to develop policies that protect patient health and safety, but to do so without unnecessarily chilling competition and

deterring investment in follow-on biologics. The FTC brings an important perspective to this dialogue. Our policy work in pharmaceutical markets dates back to the 1970s, as policymakers were grappling with how to regulate follow-on generic versions of traditional drugs. At first, many states responded by prohibiting pharmacists from substituting generic drugs for branded drugs. At that time, the FTC studied the competitive effects of states' anti-substitution laws. A staff report concluded that the FDA's review process would result in the approval of safe and effective generic drugs and determined that if pharmacists were free to dispense generic drugs without unnecessary regulatory hurdles, then generic drugs would stimulate price competition that would benefit consumers. Many states agreed with those conclusions and enacted the substitution laws that are essential to generic competition today.

Now we see analogous questions raised about different state laws relating to biologics, biosimilars and interchangeables. And let me emphasize the word analogous. Biosimilars and interchangeables are certainly more complex than small molecule generics, but the basic principle of competition in the context of healthcare markets still applies.

We have convened today's workshop to explore both state laws and naming conventions, how they could affect competition for biologic drugs. We believe that, with necessary safeguards for patient health and safety, competition from follow-on biologics can benefit patients through lower prices and expanded access to important biologic treatments.

So thank you for joining us for this timely and important dialogue and I'm going to turn the floor over to Susan DeSanti.

Thank you very much.

ROAD MAP TO MORNING PRESENTATIONS

MS. DESANTI: Thank you very much, Chairwoman Ramirez. She is unable to stay because Congress has called her to testify, which is one of the occupational hazards of being a Chairwoman of the FTC.

I'm Susan DeSanti. I am formerly the Director of the Office of Policy Planning and now an attorney with the FTC's office in San Francisco. Today, we are here to discuss policy issues involving biologics and their potential substitutes. As you heard from the Chairwoman, biologics are obviously very valuable and also very expensive. And in light of their high cost, healthcare purchasers and consumers are interested in whether, and if so when, FDA-approved biosimilars or interchangeable's could be automatically substituted for biologics just as generic drugs can be automatically substituted for brand-name drugs in certain circumstances, which has saved U.S. consumers and purchasers literally billions of dollars over the past 30 years.

Although -- as the Chairwoman mentioned, although the market dynamics for biologics, biosimilars, and interchangeables are likely to differ from the market dynamics for brand-name and generic drugs, with lower discounts being offered than for

generic drugs, it still appears that significant savings from competition could be achieved. Indeed, Congress passed legislation that permits certain FDA-approved biosimilars, those that the FDA determines to be interchangeable with a given biologic, to be substituted without the intervention of a physician, that is automatically substituted. So when we say automatically substituted, we mean the physician does not have to specifically give permission for the substitution. It's something that the pharmacist can then implement at the pharmacy and this is one of the primary ways in which generic drugs have led to so many savings.

In fact, this type of automatic substitution happens thousands of times every day with FDA-approved generic drugs. But that happens in part because there are state laws that permit that automatic substitution of FDA-approved, therapeutically equivalent generics, unless a physician writes the brand name on a prescription and specifies dispense as written.

So our first topic involves whether state substitution laws for biologics should operate in a similar manner. Now, the parameters have been set, to some extent, by federal law. Federal law describes two types of follow-on biologics. One is biosimilars. By

statute, the FDA must determine, among other things, that biosimilars are highly similar to the original biologic. Despite that similarity, however, biosimilars will require a separate prescription. Federal law does not provide that biosimilars can be automatically substituted for a biologic.

Second, there are interchangeable biologics which federal law does specify can be automatically substituted for a biologic. And federal law has more stringent requirements for a biosimilar to be approved as interchangeable.

Now, as the Chairwoman mentioned, currently in the U.S., the FDA has not yet approved either a biosimilar or an interchangeable and has so far provided draft guidelines only for biosimilars. Nonetheless, some states have started developing laws that will apply to the substitution of interchangeables and, in some cases, biosimilars for referenced biologics.

This morning, we will discuss whether it makes sense to develop those laws now and if so what, if anything, they should say to maximize competition and protect patient safety.

Now, let me move to some introductions. As Chairwoman Ramirez said, we are very grateful to

accomplished speakers for their time and effort in preparing for and attending not only this workshop, but also the workshop in December. And I encourage all of you to read their very impressive bios, which we have distributed. Because we have a jam-packed schedule, we decided to do all of the introductions for our panelists at the beginning of the morning, at the beginning of the afternoon, so we reduce the in transition from one speaker to the next. So we ask that, as one speaker finishes, the next speaker should simply just come up to the podium.

And as I give very brief introductions for our morning presenters and panelists, you can follow along in the agenda to see the topics they'll be addressing.

Our first speaker is Aaron Kesselheim, who will help us understand the statutory and scientific framework for the evaluation of follow-on biologics as compared to generic drugs. Aaron is an Assistant Professor of Medicine at Harvard Medical School, a faculty member in the Department of Medicine at Brigham and Women's Hospital in Boston, and a primary care physician at that hospital. Then Emily Shacter will speak about FDA practice related to biosimilars. Emily regulated therapeutic proteins at the FDA for 18 years,

serving most recently as the Chief of the Laboratory of Biochemistry and CDERs, Division of Therapeutic Proteins in the Office of Biotechnology Products. She now works as an independent consultant.

Next, Leigh Purvis will bring a consumer perspective to the issues around biosimilars. Leigh is senior strategic policy advisor with AARP's Public Policy Institute, where her work focuses on prescription drug pricing, biologic medicines, and prescription drug coverage under Medicare.

Following Leigh, we will hear about the current marketing of follow-on biologics from Ronnie Gal. Ronnie is the senior research analyst covering the specialty pharmaceutical industry at Sanford Bernstein, which provides research for institutional clients.

We will then have a ten-minute break and I should emphasize that we will start precisely at the end of the ten-minute break, so that we don't get behind on our schedule.

After the break, Jessica Mazer will provide us with an introduction to state laws related to biosimilar substitution. Jessica is the Assistant Vice President of State Affairs for the Pharmaceutical Care Management Association, which represents prescription

benefit managers, known as PBMs.

Following Jessica, Jeffrey Eich will give the perspective of a reference biologics manufacturer on state substitution laws. Jeff is the Executive Director of R&D Policy at Amgen.

Next, Stephen Miller will speak from the perspective of a PBM that administers prescription drug benefits. Steve is Senior Vice President and Chief Medical Officer for Express Scripts.

Bruce Leicher will then provide the perspective of a biotech company, Momenta Pharmaceuticals, which seeks to develop interchangeable biosimilars, among other things. Bruce is senior vice president and general counsel at Momenta.

We will then have another 10 minute break. And following the break, we will have a one-hour moderated panel discussion of state substitution laws. All of our morning speakers will join us on that panel, as well as some other representatives, who I will now introduce, some of whom will also speak in the afternoon.

Bruce Lott is Vice President of State Government Relations for Mylan, a leading generic and specialty pharmaceutical company.

Mark McCamish is a Global Head of

Biopharmaceutical Development for Sandoz International, a division of Novartis.

Suman Ramachandra is Senior Vice President and Chief Scientific Officer of Hospira.

Marissa Schlaifer joined CVS Caremark as Head of Policy in April 2013. She's a pharmacist with experience in both the managed care and community pharmacy segments, as well as leadership positions in other organizations.

Krystalyn Weaver is a pharmacist and serves as Director of Policy and State Relations at the National Alliance of State Pharmacy Associations.

After that panel, we will have one hour for lunch and you are on your own for that, but there are a variety of sandwich shops and delis close to this building. FTC staff would be happy to point you in the right direction to get a quick lunch. And you should feel free to bring your lunch back here and eat in this room.

Finally, after lunch, we are going to have an initial presentation by Elizabeth Jex, who is the prime mover and shaker behind this panel. And I'm going to introduce her now, so she doesn't have to introduce herself. She's going to give you a brief introduction to the naming topics that are the focus of the

afternoon.

Elizabeth has more than 20 years of experience investigating pharmaceutical, biotech and medical device mergers, acquisitions, and intellectual property licensing arrangements. Her work on the FTC's 2009 follow-on biologic drug report won her one of the Agency's top awards. And now, please welcome our first speaker, Aaron Kesselheim.

LESSONS FOR REGULATION OF FOLLOW-ON BIOLOGICS
FROM EXPERIENCES WITH SMALL MOLECULE DRUGS

DR. KESSELHEIM: All right. Well, hi. Thanks to Elizabeth and Susan and Erin for organizing this and for inviting me. It's a pleasure to be here.

And I guess I'm here today to start things off with a little bit of historical comparison between the issues that we're talking about today and a lot of the issues that have come up before in the context of small molecule drugs. And so I think starting with a few quotes from stakeholders might be a good way to kick off the day.

So here are some thoughts on the issue of interchangeability of pharmaceutical products. This is from a pharmacist, "From a technical standpoint, there is really no such thing as complete drug equivalence."

A drug industry executive is quoted as saying, "Not only has the pharmaceutical industry been successful in maintaining the conviction with many physicians and buyers that not all drugs are like, but even has succeeded in persuading them that all products are different."

And finally from a congressman who said, "I simply say to you that anyone suggesting that one drug firm is as good as another is a fool or naïve or both."

The interesting thing is that I found all of these quotes in the context of passage of the Hatch-Waxman Act in the early 80s, in the context of interchangeability and substitutability of small molecule generic drugs. And looking back on that issue, those quotes now look somewhat quaint.

The Hatch-Waxman Act in 1984 had a number of different features to it and I think that a lot of these features will come up again during the course of today's conversations. The Hatch-Waxman Act created this abbreviated new drug application process that allowed a product to show that, if it -- a manufacturer to show that if it's generic product had the same active ingredient, route of administration, and dosage form, that it could apply for approval from the FDA based on bioequivalence data alone and was not -- did not have to go through the same clinical trials that the originator product went through, saving both time and money and also subjecting patients to trials that were unnecessary.

It provided the manufacturer with data exclusivity from five years from the date of approval from the original product, providing a guarantee period for which this competition through this abbreviated process was not allowed to begin, no matter what the

status of the underlying patents.

It provided this patent certification and litigation process that I think is not really going to be a lot of the basis of the discussion today, but I put it in there just for completeness sake.

And of course, a lot of people also don't necessarily remember that the Hatch-Waxman Act was a compromise between the generic and the brand-name interests and also provided an additional market exclusivity period for brand-name drugs in the form of patent term restoration.

After the Hatch-Waxman Act was passed, the FDA established, over the subsequent years rules, for the establishment of this bioequivalence process. That bioequivalence could be established and the basis of identifying the maximum serum concentration of the drug, judging the area under the curve based on the serum concentration of the product, and establishing general parameters that required 90 percent confidence intervals for the ratio of branded generic products. These were the basic principles that the FDA established, but it also provided some flexibility for the FDA's scientists to evaluate the particular circumstances around a generic small molecule drug and adapt their requirements to a particular circumstance.

So if a brand-name drug caused nausea or vomiting for patients taking it in a fasted state, then the FDA may not require, necessarily, fasted testing to go along with the fed testing. And so there were some flexibilities that were able to be established.

The outcome of this process of development of these rules and regulations in the small molecule field was that, overall, over the subsequent decades, it became clear that small molecule bioequivalents mirrored the clinical equivalents of the products. And indeed, there is no good evidence that generic small molecule drugs are less effective than their brand-name versions, as clinicians have come to trust in the intervening decades.

I've done a couple of studies looking at this and looking at the specific literature and here is a forest plot for one of these meta-analyses where we looked at cardiovascular small molecule drugs and indeed found that there is no -- that bioequivalents does indeed translate to clinical equivalents in this field. And FDA reviews have shown that, even though their confidence intervals require this 10 percent boundary, that most small molecule drugs come within a much tighter interval than even the regulations require.

So the outcomes of the Hatch-Waxman Act were fairly astounding over the next few decades. The percentage of generic drugs prescribed, which was as low as 19 percent at the time leading up to the passage of the bill, rose to about 50 percent of all prescriptions by the year 2000. And more recently, small molecule drugs make up 84 percent of all prescriptions for -- generic small molecule drugs make up about 84 percent of all prescriptions for small molecule drugs. And a recent report by the GAO suggested that this system has saved the healthcare system 1 trillion dollars in unnecessary spending over the last ten years.

And then this chart on the bottom shows approval of new molecular entities by the FDA over the last five decades. The passage of the Hatch-Waxman Act comes about halfway through the chart there and what you can see is that the number of originator products approved by the FDA, in the years following, doesn't diminish and indeed rises up until there is this peak in the mid-nineties and then it comes back down to the historical mean. But overall, the amount of innovative new products coming through the FDA remains fairly consistent.

Nonetheless, one of the most impressive

things to me is how successful the Hatch-Waxman Act has been, despite the multiple barriers that exist in the marketplace to generic drug use. Surveys of physicians and patients even today show that there is substantial skepticism on the part of physicians and patients when they hear the word generic and despite the fact that generic small molecule drugs are so prevalent.

There is substantial marketing on behalf of brand-name manufacturers, some of which is explicitly anti-generic and anecdotal in lay media reports, providing skepticism, again, in the face of no evidence to the contrary, providing skepticism about the safety of generic products. And the generic products industry has flourished, despite the fact that estimates suggest that brand-name manufacturers spend about 60 billion dollars a year marketing their products and this same outlay is not spent by the generic small molecule industry.

There are studies that show that physicians don't know about the costs of drugs to their patients and tend not to talk about them to their patients. So you know, that conversation isn't necessarily happening at the level of the physician. And there are also studies looking at physicians' prescribing practices, suggesting that that 80 percent of them continue to use

to the brand-name product when they're referring to multisource drugs for generic products.

So how is it that the Hatch-Waxman Act has been able to have such an incredible impact on the generic small molecule marketplace? And the answer is, it's because of the state drug product selection laws, that generally do -- that allow, in some cases, automatic interchange and in other cases, permissive interchange, of A-rated generic products. So if the FDA approves a generic drug as pharmaceutically-equivalent to the brand-name product, the generic gets its therapeutic equivalence code and the automatic substitution is allowed to happen at the level of pharmacy.

Now, there is variability among the various states in their code. Some states have a mandatory system of substitutability and others have permissive substitution. Some require patient consent at the level of the pharmacy, as opposed to calling the physician and requiring the physician to change the prescription. A lot of this patient consent can happen at the level of discussion between the pharmacist and the patient itself. So there is some variability in these drug product selection laws.

There's limited evidence about the effects of

these laws as well. So we did a study looking more recently on this question and found that variability in the state drug product selection laws does lead to substantial differences in small molecule generic use rate among patients within those different environments.

We found a 25 percent lower substitution rate among Medicaid patients in states that had patient consent requirements, that required that before a pharmacist could substitute a small molecule product. And we estimated that, if you looked at three top-selling small molecule products, Lipitor, Plavix, and Zyprexa, that this difference could lead to over 100 million dollars in excess spending in Medicaid alone, which is only about 10 percent of the total U.S. drug spending in the first year after generic entry.

In the same study, we found that the costs of prescription drugs were much lower in the states with outpatient content. And other studies have shown that some of these -- some state laws initially required substantial recordkeeping, in addition to consent, and that this extra recordkeeping requirement on the part of states also led to lower substitution rates by pharmacists that weren't just -- that didn't have the capacity to do that.

Evidence in other fields of small molecule drugs were non A-rated approved generic drugs have been approved by the FDA suggest that there's less competition, lower savings, and less substitution of these non A-rated generic drugs that are then -- where there is then competition between the generic and the brand-name product, instead of just substitution.

So now we get to the topic of the conversation today, which is the Biologics Act. And again, the Biologics Act in many ways mirror the principles provided in the Hatch-Waxman Act. They provide two levels of biosimilarity, highly similar and interchangeable, which I know we will, again, over the course of the day, we will talk a lot more about. And the other aspects of the Biologics Act also did mirror some of the aspects of the Hatch-Waxman Act, including the patent dispute resolution process and it provided a 12-year period of guaranteed exclusivity before any follow-on can be authorized.

So want to end, in my last couple of minutes, with what I think are three lessons from the story about the comparability of the small molecule and biologics market. First, that FDA biologic drugs are potentially scientifically viable and can be used interchangeably.

In fact, there is a great deal of experience so far with some limited biologic drugs that have been approved through the ANDA and the Hatch-Waxman process. Here's one example, a generic calcitonin nasal spray, which is a polypeptide hormone that is used in osteoporosis and made up of 32 amino acids and a disulfide bond.

When the FDA was considering this product, the questions that they asked themselves, you know, do we need to require in vivo immunogenicity testing? Do there need to be clinical trials showing a similar clinical effect between the brand name and the generic product of this? And the FDA ultimately reviewed the science and determined that these sorts of testing were not necessary and allowed chemically synthesized generic versions to be approved on the basis of the fact that the impurities were, in this case, easy to characterize, monitor, and control, and that the primary structure was a major driver of the structural ordering of this complex molecule.

Another example that I know we're going to hear a lot more about today is generic Enoxaparin, a mixture of oligosaccharides that uses an anticoagulant. The FDA approved the generic in 2010, again, not the basis of formal clinical trials, but on the basis of

five principles that, again, you know, after an investigation into the science of this to determine provide a product that is safe and effective in the marketplace. And so if these five different requirements were met, then no additional clinical safety efficacy data would be necessary and consumers could feel confident.

So indeed there's also been substantial European experience so far in this field, since the first European follow-on biologic was approved in 2006. There is now experience with about a dozen follow-on products made by four manufacturers in Europe in the epo and growth hormone spaces.

And so I think the general principle here -- now again, you know, these are the successes. There are also warning cases out there where immunogenicity has emerged. So I think that the ultimate lesson here is to follow the science. That interchangeable biologics are possible in some cases, not possible right now in other cases, and as the science evolves, that these principles will be able to change. And that the regulatory sphere and the state laws should be able to adapt to the fact that science will continue to evolve in this space. And that the FDA will gain -- has access to and will continue to gain expertise

necessary to make these decisions.

Second of all, that the science, although important, is not enough. The name is actually critical. And the state product substitution laws and the similar namings of the small molecule and brand name products were key to the implementation of the Hatch-Waxman Act. Non-interchangeable generic drugs have limited market penetration, higher costs, and reduced savings. And that's because, even today, it remains true that the public is skeptical about things labeled generic. And generic biologic drugs will have to compete by providing a substantial investment into marketing against the brand name products, if there isn't this sort of interchangeability that's allow.

And so blanket anti-substitution carve-outs are highly problematic for those products that the FDA, using currently available scientific tools, has judged to be interchangeable.

And then the final lesson is that creating a viable generic drug market, which I think is the goal for part of the discussion today, is talking about creating a viable product market in biologic drugs, did not reduce brand-name innovation, that the five-year data exclusivity period is effective for maintaining strong innovation in the strong small molecule field,

and that the 12-year period in the biologic space may actually be much longer than is necessary, because what -- and I just wanted to end my comments with the thought that the end of the market exclusivity period is what drives innovator companies to develop new, genuinely approved products that will contribute to the next generation of therapies in medical progress, which is, I think, what everyone today is here to talk about.

Thank you.

THE RIGOROUS FDA REVIEW PROCESS FOR
BIOSIMILARS AND INTERCHANGEABLES

DR. SHACTER: Good morning, everybody. I am Emily Shacter. I was at the FDA for 18 years and regulated protein products almost exclusively during that time. But ten years ago, I took an interest what, at the time, was called follow-on biologics and started immersing myself in that subject, initially from the scientific perspective, since I ran a research lab for my entire career, until the day that I left the FDA, but also eventually taking an interest in the policy issues that came up over the years, which allowed me to contribute, in one way or the another, to the FDA draft guidances that came out a few years ago. I have a couple of FDA colleagues here in the room and they can either support or correct anything that I have to say today. But I will focus on the science of the issue.

So what I'll talk about is FDA's approach to the review and regulation of biosimilars. I have to say, in our training rooms at the Center for Drugs, which is where I left, I started out in the Center for Biologics, we had these two screen situations, which are a nightmare for somebody who likes to actually connect with the audience. And I kind of feel like this bobbing doll, that you're looking back-and-forth

at the screens. But also now, having a third screen, I can't even access you over there, so I apologize to the people on the far -- on that side of the room.

I'll also talk about the role of analytics and the development of biosimilars. See that's the problem, you can't like -- good, thank you. And then I'll talk about the scientific determination, how do we make a scientific determination about when a difference matters and when it doesn't.

To get back to the definition then of what is a biosimilar, as defined in the statute, from the BPCI Act? And I've abbreviated the definition for the purposes of conversation. What I want to point out is that a biosimilar protein product has to be highly similar to the U.S. licensed referenced product, notwithstanding minor differences in clinically inactive components. And there has to be a demonstration that there are no clinically meaningful differences.

So in two places in the statute the term difference is used. And I'm going to talk about that in just a moment, because it's very important. But first, let's talk about how a biosimilar is made. And there are many people in the room here who have actually done this. I personally have not, but there

are folks in the audience who can speak to this actual process.

So first, you choose the U.S. licensed reference product to which you want to make a biosimilar. You characterize many lots of that U.S. licensed reference product to determine, well, what is this protein? What does it look like? And what are the critical attributes of this product that are responsible for it's clinical activity? So then, you try to make your product. You reverse engineer your biosimilar product to try to match what you've understood about the U.S. licensed reference product. And if you find differences that appear to be significant, then you are going to try to manipulate either the cells that generate that product or the process that is used to make the protein product, in order to try to match, as closely as possible, the reference product that is on the market.

Any differences that you see that raise uncertainties about the predicted clinical performance of that product would be addressed through a variety of different kinds of studies, including functional studies, the bioactivity of the protein, non-clinical and potentially clinical studies.

The fact is that, thanks today's -- the

power of today's analytical techniques, small differences between a biosimilar and a U.S. licensed reference product are expected, unavoidable, and will be detected. The challenge is how to rigorously justify -- and this is the responsibility of the sponsor making the product -- how to rigorously justify any observed differences in order to ensure that there are no clinically meaningful differences between the products. And that doesn't mean words, it means that actually that product will perform clinically the same way as the U.S. licensed reference product in all important aspects.

According to the FDA Scientific Considerations Guidance that came out in 2012, there are three different kinds of studies that go into the assessment of similarity. One is the analytical studies, which is the area in which I have my greatest expertise. One is animal studies, or nonclinical studies, to evaluate the activity of the product or toxicity of the product in a small animal model system or also nonhuman primates, and then the clinical studies, which will include pharmacokinetics, (“PK”) pharmacodynamics, (“PD”), and immunogenicity in order to ensure that there actually are no clinically meaningful differences.

The agency has the discretion to determine that any element of these three components can be waived if there actually are limited uncertainties about how the product will perform clinically. And this is very important, because the FDA now has discretion to determine, well, what is a highly similar product. And in my opinion, and given my experience working on biosimilars for many years at the Agency, the FDA is not going to waive any element of that analysis if there is any residual uncertainty that the product will have basically identical clinical performance compared to the U.S. licensed reference product. They are just not going to do that.

And how are they going to make these determinations? Well, first of all, these are very experienced reviewers that are going to be analyzing all of these submissions. Think about it. They have seen every protein product that has come through the Agency. And so they have deep knowledge of protein products and what to expect from them and what's important and what isn't important. There will be numerous internal meetings and working groups to determine what are the important aspects of the protein product. There will be multiple levels of supervision to make sure that the messages are clear and consistent

across products and to different sponsors. And importantly, there's a lot of cross-disciplinary teamwork to determine -- so as a group, the CMC reviewers, the nonclinical reviewers and the clinical reviewers, and our legal folks, of which we have some here in the room, can make a determination that a product should be approved as a biosimilar.

In my opinion also, the FDA is only going to approve a biosimilar that can reliably be expected to perform clinically similarly to the U.S. licensed reference product. They have no motivation to do otherwise. So although biosimilars don't meet an unmet medical need, except for access and cost, so that is an important medical need, but many of these clinical reviewers, for example, would rather be working on, let's say, a breakthrough product, for example. Because they want to actually deal with issues that have not been met clinically for patients. So they have very little motivation to approve a biosimilar if it's not highly similar to the referenced product.

The Agency is conservative by nature and very risk-averse. The Agency is particularly risk-averse to having one of the first biosimilars out of the gate actually end up having clinical problems and clinical differences, because this would really sink a program

in which there has been tremendous effort, conscientious effort, put. So there's a lot of risk-aversion to approving a non-highly similar biosimilar protein product. And so all scientific expertise will be brought to bear. And any residual uncertainties that the biosimilar would behave similarly to the referenced product will have to be addressed by various kinds of studies.

In my opinion, and I'm outside the Agency, so this is a good thing, I can say whatever I want, I think that this really ensures virtual interchangeability. Now, maybe not in all cases, but if a product is approved as a biosimilar by the FDA, the FDA is pretty darn certain that it's going to behave clinically, highly similarly, to the reference product. They're not going to let it out if it doesn't.

And I'm not an expert in the laws and all of that, but in terms of how a product would perform clinically, I do have a lot of experience, especially with protein products. It's as though they are going to be virtually interchangeable.

Now I'm going to shift to analytics, because this is my greatest area of expertise, and bring forth the fact that I remember, 10 years ago, when we were talking about follow-on biologics and there were some

legitimate arguments as to whether the analytics were sufficient in order to be able to highly characterize a protein product well enough to be able to say that it's highly similar. That was 10 years ago. Analytics have progressed so much in the past 10 years that in my opinion, again, it's not really true. It's the power of analytics that have even made biosimilars a reality today.

Consequently, and for many reasons that I'll explain, the foundation of the similarity assessment is the analytical studies, because this is the part that we can best characterize. So why is this? Well, analytical studies evaluate a protein product down to the atomic level. Every aspect of a protein product will be evaluated. They are highly sensitive and highly discriminating to determining whether there is a difference between a protein product and a reference product. This is very different from animal studies, which were much more crude. They serve an important purpose in certain cases, but you need to use a lot of animals in order to make a discriminating determination of similarity and difference and that's not the way most nonclinical studies are done for biosimilars. Six animals in a group, what are you going to do? The reviewers hardly know what to do when a difference is

seen.

And then clinical studies are even less discriminating than analytical studies. So for this -- the clinical studies, especially safety and efficacy studies, have to be quite large in order to be able to detect a difference between two products and everybody in the room knows this. And so it's the analytical studies that have the most discriminating power.

For this reason, if there is a significant difference in the molecular attributes of two protein products, they actually can't be overcome by clinical studies. And this is the main reason why the FDA came up with this, and I was in the Agency at the time, this pyramid paradigm where, if you look at the right-hand side, this is really the desired program for development of a biosimilar protein product. Where you have extensive analytical studies, relatively minimal nonclinical studies, and then you have your clinical pharmacological studies and pharmacodynamics, if you have a relevant model, and those actually will be pivotal studies. And there's going to be no getting around those for the foreseeable future. And then using additional clinical studies to reduce any residual uncertainty and, if necessary, to also look at immunogenicity. So this is the paradigm and this is

the foundation that's being followed, analytical studies.

How do you get a reduced nonclinical and clinical requirement for developing your protein product as a biosimilar? You have to demonstrate to the FDA and convince them that your product is highly similar to the U.S. licensed reference product. That ain't easy, but it can be done. And when I say it's not easy, I say that because the FDA is setting a high bar and I think my FDA colleagues in the room can attest to that.

So speaking of the analytics, what is a protein? For the lawyers in the room. It starts with the amino acid sequence, which comes from the gene that is used to generate the protein product in the host cell that is doing it. It takes on what is called secondary structure, which is the form that these amino acids naturally take next to each other, so alpha helix, beta sheet, and then it folds into the active moiety that is actually responsible for the clinical activity of the product. It's also what the body sees. So it's this folded protein that is enacted. If you boil it and you lose that folded structure, you lose activity. You'll have the same amino acid sequence, but you won't have the same clinical activity.

And then also, if you have a multi-subunited product, for example, like a monoclonal antibody, then it's the coming together of those different subunits that is also extremely important. So I called these two here the higher order structure -- actually, the three of these, the high order structure of the protein product. Without that highly similar high order structure of the protein product, you will not have the same clinical activity and you may run into immunogenicity issues with the product.

Protein products are extremely large. There are many amino acids, almost uncountable compared to a small molecule generic drug. And there are many ways where -- I'm sorry, I can't point over there. There are many ways in which the protein product can be changed. I won't go through this list, you have the slides, but many different aspects of a protein product. So actually, a protein product is a mixture of heterogeneous molecules that have a lot of similarity to each other, but you don't have a population of identical molecules. So even that is an exercise in analytical discrimination, what is my population of protein products.

The good news is that, thanks to today's analytics, protein products can be deeply analyzed and

characterized. So the complexity that you find in our protein products can be addressed with a large array of powerful analytical techniques. If this were not true, we would not be having biosimilars today. We would not be talking about it. They would be too much risk.

And again, I won't go into this list, you have it as a reference. But basically this is to sort of summarize some of the many techniques that we have available to analyze every single aspect of a protein product. And I would say that today, the only two elements that we can't fully predict are immunogenicity -- and we still have some issues in determining the folding of protein products, given that you have a mixture. That doesn't mean that that inability isn't overcome in many ways, but we're still a ways -- we don't have perfect analytics to comprehensively evaluate every aspect of every molecule in a protein product.

But one of the techniques that I'd like to show is, for example, these studies that came out of my colleagues in England looking at the higher order structure of a crystallin protein. And what they did is, they wanted to determine whether this technique, for high order structure, this is circular dichroism, can actually tell if you have a single mutation in a

protein product.

And so they introduced a mutation into one amino acid and looked at the wild type and then two different mutations, one of which had a change, an influence on high order structure, and one of which didn't. And if you do the technique right, as for any technique, if you do it right, you can tell if you have a difference or if you have a similar protein product. I'm getting flashed my five minutes.

Monoclonal antibodies are among the most highly studied, actually, products that we have on the market. And even though they are large and complex, we know an awful lot about monoclonal antibodies and what the various different amino acids in this large molecule do to contribute it its clinical activity.

So what do you do if you do find differences between your biosimilar protein product? You have to determine if those differences might be impacting clinical activity. And you'll do this through multiple analyses of biological activity and also looking for potential impact on PK. So it's not just the activity, but you also have to make sure that the biodistribution of the molecule is the same. How do you do this? State-of-the-art analytical techniques. You have to be able to detect and characterize the molecule so that

you know actually, if you don't find a difference, it's because you applied the correct analytics and, in fact, there is no difference. And not just that you used poor techniques.

Sponsors using blunt analytical techniques need not apply. Now, while I was at the Agency, I saw some -- let me say subpar submissions regarding characterization of protein products and they need to go home and do a better job.

And so, at the end of the day, you are going to put together all of your powerful analytics to be able to determine whether you have a similar or different protein product.

So the similarity assessment will be comprehensive. There's going to be a deep analysis and comparison of the biosimilar to many lots of the U.S. licensed reference product. Different state-of-the-art analytical methods will be applied. There will be stress-testing to make sure that there isn't some -- some buried very difference in the molecule that you can't detect by just looking at the molecule on the surface. And the latest paradigms for the sensitive clinical pharmacology studies will also be applied. And one day we will actually see the Clin Pharm guidance document coming out.

So I would like to -- just a couple more points. I think that the old stories about how we had adverse -- unexpected adverse events from protein products, in other words adverse events that did not derive from the expected pharmacological activity from the molecule, because that's where you have most of your adverse events with proteins, it's the pharmacological activity of the molecule.

So there's the famous case of Eprex, which caused a very severe disease, actually, in patients who received a product that underwent a manufacturing change, unexpected immunogenicity of the product, and knocked out a physiological system. I don't think those events are going to happen -- let me say this. I think the likelihood of those events happening is greatly reduced today, compared to what it was so five, ten years ago. And that's because we have better analytics and we have more extended use of those analytics.

So on the continent of immunogenicity, because this is important and it's used as a reason for why a biosimilar protein product actually might be unsafe, because you don't have the same extended clinical studies, well this could be true. But what does immunogenicity come from? It comes from the amino

acid sequence, the folded structure. It's essentially what the body sees of this molecule after it gets injected into the system. And the immune system is actually one of the best discriminators of similarity and difference. The immune system has such a great capacity to tell if proteins are similar and different, so this is extremely important.

The consequences of immunogenicity can be many. You can lose efficacy, as has been the case in some cases, where you lose the activity of the protein product of interest. You can knock out a physiological system, as happened with thrombopoietin and erythropoietin. You can have hypersensitivity reactions, et cetera.

Most licensed protein products do have some level of immunogenicity. Most of the immunogenicity is inconsequential. I think, in many cases, it actually knocks out the ability for a patient to be able to use that drug, so you want to have some backup drugs that are similar, but different, in order to be able to compensate for the loss of that activity. I'm getting my flag for one minute left.

So I would like to close by saying that FDA-approved biosimilars, in my opinion, would be one of the most deeply analyzed and predictable protein products to

hit the market. Maybe one exception is Enoxaparin, and some of the folks who are responsible for developing that drug. That was certainly deeply analyzed as well, but it's really -- it's a paradigm setter for the discussions that we're having.

So will they be determined interchangeable by the FDA? I don't know, I'm on the outside now, so this is to be determined. But I can assure you that all scientific rigor will be brought to bear.

So I want to just thank my former colleagues from the office of biotech products and the office of new drugs and actually a couple of my legal friends here in the room, Janice Weiner, with whom I worked very closely at the Agency, for helping to inform my opinions about biosimilars. Thank you very much.

CONSUMER OVERVIEW OF BIOSIMILARS

MS. PURVIS: Hi, my name is Lee Purvis and I've been asked to come here to provide the consumer perspective on the issues being discussed today.

I'd like to start off with explaining why biologics and biosimilars matter to our 40 million members. First and foremost, I think it's very clear to us, and probably clear to everyone in this room, that biologics represent the future of the drug industry. There are a growing number of products on the market and there are hundreds more in development. We've also seen projections that they are eventually going to represent more than 50 percent of spending in the next few years. We also are aware that there are large number of popular biologic products that are either off-patent or due to go off patent shortly, and thus far, we haven't seen any sort of impact or noticeable change from that.

Something else that's caught our attention is that, for the products that are on the market already, there are a rapidly increasing number of indications, sometimes dozens for a single drug. So basically more of them are coming to market and more people are using the ones that are already here.

I think it's safe to say that one of the

primary reasons that AARP is interested in biologics is there are markedly high costs. The average annual cost of a branded biologic is estimated to be roughly 35,000 dollars right now. However, annual costs can range anywhere from 25,000 to 200,000 dollars or more, with many drugs coming on with prices at the higher end. For example, 12 out of the 13 new cancer drugs approved last year were priced over 100,000 dollars annually. And some drugs are coming to market with prices closer to 400,000 dollars.

Something you probably heard us say repeatedly in public, when we are speaking on prescription drug issues, is that older Americans use more prescription drugs than any other segment of the population. Over two-thirds are taking three or more drugs and three-quarters are taking two or more drugs. So they are a population that are using a lot of these products.

Also, biologics are used to treat conditions that are more commonly found in older adults, many of which are chronic conditions. So when we talk about our members using biologics, we are talking about people who are probably going to be taking them for the rest of their lives.

Now, to put some of the numbers I'm going to

be presenting next in context, I wanted to start off by dispelling some myths that seem to be out there about Medicare beneficiaries.

Number one, they are not wealthy. Their median income is just over 20,000 dollars and more than 25 percent have less than 10,000 in savings. So we are not talking about people with substantial assets.

Second, they are not in good health. More than two-thirds are currently being treated for concurrent chronic illnesses.

So the Medicare program, which is a topic of constant discussion for us. Medicare Part B, which generally covers services associated with doctors visits, is spending a lot of money on biologics. Under Part B, beneficiaries are responsible for 20 percent of their prescription drug costs and there is no out-of-pocket cap. So anyone taking a biologic facing 20 percent of costs is going to be facing that same scenario playing out year after year. I've heard people respond to our concerns by saying yes, well a vast majority of Medicare beneficiaries have supplemental coverage. And that is the case; however, the 12 percent who don't are in serious trouble. And for those that do have supplemental coverage, it's not like the costs associated with these products just

disappear into the ether. They will come back to beneficiaries in the form of higher premiums or cost-sharing, which can ultimately make that type of coverage unaffordable. Or alternatively, if they have supplemental coverage from a tax-payer funded program like Medicaid, it increases government spending.

And of course, we also have concerns about the Medicare program, in terms of its longevity, and the 80 percent share of the costs associated with biologics that is shouldered by Medicare is non-sustainable.

Another part of Medicare that we spend a lot of time on is Medicare Part D, which covers outpatient prescription drugs, or those that you tend to pick up at the pharmacy. Under Part D, a lot of plans are increasingly using coinsurance, or where the beneficiary is responsible for a percentage of the cost as opposed to a flat copayment. That coinsurance tends to range from 25 to 33 percent, which can be thousands of dollars for a drug that is extremely expensive. And it's particularly expensive for someone who is on a fixed income. Fortunately, unlike Part B, under Part D there is an out-of-pocket catastrophic cap of around 4,500 dollars. Unfortunately, in order to reach that, you're spending roughly the equivalent of a quarter of

a Medicare beneficiary's median income on just Part D cost-sharing, which obviously is problematic.

It's also worth noting that, even after you reach catastrophic, you are still responsible for some level of cost sharing. For example, Humira, a common biologic, is still -- the cost sharing associated with catastrophic is still over 100 dollars a month.

We also have noticed that there's no real incentive for Part D plans to control spending on biologics because the beneficiary who is prescribed one tends to blow through the benefit pretty quickly. And after catastrophic, the Medicare program is on the hook for 80 percent of cost-sharing. Again, much like Part B.

We also keep track of private insurance. We have a lot of beneficiaries who have employer-sponsored coverage. And typically where Part D goes, employer-sponsored coverage tends to follow. So we are seeing an increase in coinsurance and we are also seeing an increasing number of plans that have created a fourth, or even higher, tier with an average copayment of around 80 dollars and an average coinsurance of around 32 percent.

This population is different. They are typically not on a fixed income, but paying for a third

of a drug that costs thousands of dollars is not going to be easy, regardless of your income. And it can be difficult for even those with good insurance.

Something else we've noticed is reports that the relatively low cost-sharing associated with biologics is threatening to increase cost-sharing for drugs that are non-specialty. So basically -- relative to the cost of the drug, the amount the beneficiary is paying is actually pretty low. And if it's going to maintain that same level, it's going to increase cost-sharing across the board.

We've also been keeping an eye on the plans that are going to be offered in the exchanges. Beneficiaries under those plans will benefit from new out-of-pocket maximums; however, a lot of the exchange plans are going to be relying on coinsurance for tier three and tier four, which can result in extremely high cost-sharing.

For example, you can see here, the average cost-sharing is around 40 percent, but it can reach as high as 50 or 60 percent. That level of cost-sharing could put drugs out of reach for a vast majority of Americans. However, saying all of this, while cost-sharing is a problem, the underlying problem is the cost of the products. Even if the cost-sharing

were lower, the cost associated with these products would eventually come back to consumers in the form of increased premiums.

Something else that is usually pointed out to us when we raise concerns about the price of drugs is patient assistance programs. We do find them helpful; however, they can be less than generous. They typically do not help insured patients and they tend to have very low income thresholds. Some also require beneficiaries to spend a certain amount of their income before they can participate.

Each company has their own qualifications, their own forms, their own processes and rules for refilling. They can even have a different program for each -- a single manufacturer can have different programs for each drug. The net result is a kind of complicated system that can make it difficult to access certain drugs.

So as evidenced by this meeting, the passage of BPCIA obviously did not signal the end of the issues surrounding biologics and biosimilars and AARP still has a number of lingering concerns. Probably first and foremost, the one we are most vocal about is exclusivity.

Our long-standing position is that the 12

years provided by BPCIA is too long. We've also been surprised by a lot of debate over the definition of what type of exclusivity was provided in BPCIA. Is it 12 years data exclusivity or is it market exclusivity?

Something else that has been brought to our attention repeatedly is the risk of evergreening. I understand there have been people saying yes, that's never going to happen, but we've also been hearing a lot of concerns that it will.

Another concern is the possibility of reverse payments. Unlike Hatch-Waxman, BPCIA does not require companies to report settlements to the FTC.

As far as what we are mostly discussing, briefly -- I know it's going to be discussed in greater detail, so I will just provide AARP's perspective on it generally, and that is that we think that the state legislation that we've been seeing is designed to make interchangeable biosimilar substitutions so onerous the prescribers and pharmacists don't bother trying.

We also don't understand why it's necessary, given that the FDA has yet to approve a biosimilar. Our feeling is that, if we can trust the FDA to regulate and approve biologics, we can trust them to approve and regulate biosimilars. And we have yet to hear a valid reason why substitution should not be the

same as it is for traditional chemical-based drugs.

If this legislation were to be enacted, and in some cases it has been, our feeling is that it's going to reduce substitution and subsequent competition that is needed to reduce the costs associated with these products and it's going to increase healthcare costs across the board.

The AARP perspective on naming is rather similar. We're not quite sure what the rationale is behind it. We think mostly it's going to led to prescriber and patient confusion and possibly impact patient safety. We also think that it kind of is intended to create the false impression that biosimilars have a different clinical effect than the original biologic drug.

And we also have some serious concerns about the fact that having different names would separate the existing safety information from the biosimilar.

Again, we believe that different INNs would reduce substitution and subsequent competition which, again, increases healthcare costs.

So how do we see things in the future? I think our biggest concern is whether the stated purpose of the BPCIA act is going to be fulfilled. Supposedly, there is going to be price competition, but there seems

to be a lot of activity on the market that might thwart that.

Another concern is whether the pathway will actually be used. We have heard the FDA saying that some people have started the approval process; however, we've also heard a lot of companies saying there are so many problems with it, they don't intend to use it, at least for the foreseeable future.

And I think the biggest concern is that we want to make sure the competition develops and right now, we are not quite sure that it will. There seem to be a lot of roadblocks that are being thrown up that makes it less likely that companies who could potentially provide biosimilars will actually enter the market.

Another concern that has come to our attention is that, this might be the tip of the iceberg. There may be other opportunities for additional delays in the market. For example, a biologic manufacturer might decide to kill their old product and launch a next generation product just as soon as biosimilar competition approaches. Another option would be constantly tweaking the reference product, which would preclude substitution indefinitely.

They could also compete on price, since they already have the manufacturing facility set-up, which kind of reduces the incentive for a biosimilar company to enter the market.

And finally, something we may already be seeing, they could raise fears of reduced efficacy or increased risks of side effects from biosimilars.

So what if this never happens? What if the market never develops? Well, for the first -- I think the one word that we constantly hear related to prescription drug prices, particularly biologics, is that they are non-sustainable for patients or payers. something has to change. I think if nothing happens, more patients and many patients may not be able to afford biologics if the competition does not provide some level of price relief.

And I think one final thought that we need to keep in mind for the rest of the day is that the best medical advances in the world are meaningless if no one can afford to use them.

Thank you.

CURRENT STATE OF FOLLOW-ON BIOLOGICS
IN THE UNITED STATES AND EUROPE

DR. GAL: Good morning. I'm Ronny Gal. I'm an analyst with Sanford Bernstein. My day job is to predict the success, commercial success of drugs and drug companies. And I come from the perspective of Wall Street, which is we don't really care if certain drugs do well, biosimilars do well, any particular drugs do well, our job is simply to predict it.

And I've done most of my research, for the last three or four years, looking at biosimilars first from a viability perspective and now from a commercial perspective, based primarily on the history of small drug molecules and what we know right now about adoption in Europe and the technology.

I'm only going to make three points here. At the first one is around the commercial rationale from a corporate perspective around developing biosimilars, the second one is what we can learn from adoption in Europe, and the third one is some observation about the current U.S. drug system and the holes that are in it that are essentially producing opportunities to delay biosimilars.

So first, when I went to school and studied biochemistry, the process of making what I'm going to

call antibodies and other drugs was very much of an art. That has changed over the last 30 years. Successive process, standing on the shoulders of giants in engineering improvement, have turned the process from an art to a science. The skills required to make biological drugs have advanced to the point where you can actually outsource most of the manufacturing and even the development of the drug and get a reasonably quality answer.

The other thing that happened in parallel was a great reduction in the cost of making a biological drug. As yields improved and processes got to be more scientifically sound, the cost of making drugs greatly decreased. What did not decrease and actually increased, with successive generations of drug introduction, was the price.

So price points of biological drugs, as we've heard from previous speakers, 25 to 200,000 dollars, gross margins are roughly running now in the high 90s. So the cost of making biological drugs coming out of facility, net of any royalties you have to pay to universities, is right now about 2 to 4 percent on average of the price actually being obtained realistically in the marketplace in realized prices.

Now, if you are basically a drug company and

you look at this and you go, hmm, 96 percent gross margins, patents are about to expire on the first generation of biological drugs, obviously the laws of economics dictates, on very large revenue drugs, that you will seek to develop follow-on products. Skills are available to be hired, money is available to be gained, and therefore companies go out and try to develop this.

The two side effects of this process? Obviously if you are the guy who owned the original molecule, guess what? You will try to innovate a way and improve the molecule into a better drug. One example I will give is Roche, who has done a wonderful job of improving their Herceptin and Rituxan franchises with a new generation of drugs.

And second, innovation in manufacturing to produce some lower cost and higher quality. Previous people spoke about the quality of analytics. I would argue the quality of analytics has to do, to a large extent, with the need to better characterize your drugs for the process of making biosimilars. Essentially, it was a push for the analytical science that you had to get to that level of accuracy.

Second, adoption in Europe. The short answer -- the one background word I would say here is

that the EMA has been a lot more aggressive than the FDA, in terms of developing biosimilars. As a matter of fact, the first slide they always put up when EMA people speak on the issue of biosimilars is the cost and the imperative to reduce cost. The FDA has been a lot more shy about using the directive to reduce cost as a rationale. The EMA has been very open that their objective is to help in reducing healthcare costs in the countries in which they serve.

Adoption of biosimilars in Europe has not been even and that is the point I'm trying to make here. This is kind of like a May of 2012 perspective. Even with the availability of biosimilars, it is critically dependent on the setup in every country in how they pay for the drug and who decides to -- how drugs are reimbursed and the influence payers have, or national payers have, on the decisions by physicians what to prescribe.

So essentially, the availability of product is necessary, but insufficient to drive adoption. Biosimilars can easily fail. And what we've done is we spoke with a bunch of payers, in individual countries, and a bunch of pharmacists. To give you two examples, I spoke with a doctor in the U.K. who is in charge of the National Healthcare Trust and he basically says, look,

there is NICE guidelines. If nice tells me I can use this product and it's cheaper, guess what? I'm using it. Okay? But they can also rely on the naming.

I spoke with a pharmacist in hospital in Italy about the use of anti-TNF drugs. And I asked her, what is done when you are running out of budget midyear? And her answer is, well, my job is to find budget. The doctors get to prescribe what they want and my job is to find the budget to allow them to prescribe what they wanted. It was not, I need to manage the budget.

So differences in countries -- and by the way, I'm not picking on Italy. This is all clearly changing because of the economic crisis in Europe, but clearly the approaches by different payers and different healthcare systems mattered dramatically for adoption of those products.

Third, about the emerging dynamics in the United States. One thing I would say is clearly the drug company have picked up developing biosimilars. If I look at the elite table of companies, almost each and every one of them as some sort of biological biosimilar initiatives.

This is the new 2012 picture. We keep on updating it and we are always running three months

behind, just because. There are at least ten highly credible biological manufacturers who are involved in making biosimilars. There clearly is an interest in coming to this market.

And when I first saw that, I said, “Aha.” We are going to have those drugs coming out, there will be multiples; therefore, the prices will come down and therefore this will be a great benefit to the U.S. system and frankly a great reduction in costs to the consumer and those are great.

As the last couple of years progressed my opinion has become a lot more sour on that thought. I am now far less convinced that biosimilars will have the impact that one would hope they would have as a cost reduction for the U.S. consumer.

And I'm going to mention on essentially some barriers. This is far from an ultimate catalog, but there is a bunch of things you can do before a drug comes to market, in terms of changing the reference product and in terms of introducing new IP that most of the world would not be given, but in the U.S. would. There are some bugs in the U.S. patent system that allow for patents to progress for a very long time before they are actually issued. This is now changed, with some new changes in IP law, but it will clearly influence

the first generation of molecules.

And there are essentially multiple other tools I haven't even thought about, about challenging the law that just passed. We know that the Hatch-Waxman law went through about 20 years of court challenges and fixes before it got to where it is today. The first generation of the biosimilar law will almost certainly have to go through the same round of adoptions.

But a more interesting question is what will actually happen when those drugs come to market. And there is a variety of payers for adoption that already exist today and I'm going to just give you two examples. I am just putting up this long list as kind of a catalog of problems we've already identified. I'm just going to mention two of them.

The first one is the issue of the rebate. So rebates on biological drugs are now around 50 percent, 45 to 50 percent of the price of the drug in certain categories, anti-TNFs, insulins. What happens is there is a list price and, if you are a big buyer of the drug, you pay half the price, as long as you got the drug on a preferred tier.

What happens if the biosimilar comes in and you would actually want to move the old drug to the

non-preferred tier and use the biosimilar as the preferred tier?

I will give you an example of this case where a list drug, the innovative drug, is about 10,000 dollars. It is obviously higher, but I am just giving an example. Post rebate, if you are talking about a 50 percent rebate, is 5,000 dollars per patient. Let's take a sample of 1,000 patients, a 5 million cost for the payer, okay?

Now, let's assume the payer wants to introduce a biosimilar. Well, it's a 10,000 price on the list price, once you have taken away the preferred position of the innovator, it is still 10,000 dollars. And let's assume you've got 500 patients still on the innovator drug. That will cost you now, since the price is twice, again 5 million.

Now, if the biosimilar developer even drops the price by 50 percent, then the cost per patient on the biosimilar drug is 500 dollars, that's an extra million dollars, the total cost of acquisition of taking care of those 1,000 patients is now higher than it is to continue to use the innovator drug.

So essentially -- and you know, I speak to drug companies that only very subtly mention it as one of the tools in their portfolio, the level of rebate is

essentially used as a barrier to adoption of biosimilars.

If you want to adopt a biosimilar, you must switch your entire patient population. If you grandfather existing patients in, and existing patients are often 80 percent of the ongoing patient population over a year, you essentially have a barrier for adoption here that is quite material.

A second adoption is, what if the patient gets his first dose and one he's on that first dose, what happens next? So for example, I've done some work on drugs that are being used in Medicare Part A. You've got a patient coming out of hospital who is going to long-term care. He's going to stay in long-term care up to 100 days and long-term care providers are capitated for that period of 100 days.

It is highly -- they are highly incentivized to essentially pay less money for their drugs. The drug companies are highly incentivized to give the drugs to the long-term care providers in Part A for a much lower price point. Why? Because then they capture the patient on their drug.

When the patient leaves the long-term care and goes back home, or just as that period ends and he goes on a PDP program even in the long-term care

facility, he is now subject to another set of prices. The prices here might be a lot of higher for the innovator drug than to the biosimilar, but you would have to switch the patient from the existing drug to a new drug, as opposed to a new patient start, which the patient did not (inaudible) one of the drugs and the efficacy is presumed to be the same. And we are seeing that right now with small molecules.

I am just kind of giving two areas where I actually did some more work and I am somewhat more familiar with the details for small molecules.

So essentially as one biological company told me, the price in the United States for a drug is also the lowest and the highest. We would be the lowest price globally for our drug in the United States for some payers, which are the critical payers for us to be able to capture the patient, and obviously we charge the less interested parties a lot more for the price of their drugs.

So essentially there are multiple barriers here that already exist in the system, multiple -- simply because our system is very balkanized. There is no central planning of how we pay for drugs. Multiple organizations make decisions based on their own economic incentives and the drug companies are

being very, very smart in taking advantage of that.

I'm going to give you one more piece of data and that is, we ended up doing a lot of work on why drugs, small molecule drugs, with moderate differentiation still do well. The FTC will probably be very familiar with the example of Nuvigil versus Provigil, which are drugs that were very similar. You can think of this has a twice per day versus a once per day drug or a chewable drug versus a simple, non-chewable drug.

And I was so surprised by the fact that those second generation of drugs, despite a very, very modest differentiation, are able to maintain market sales despite the introduction of multiple generics for the first generation drugs, which has got only a very small difference from the original drug.

So I did a survey of managed care organizations and the full survey is actually in the back of this note. But the short answer is, if you ask them why you guys keep on covering those drugs that have very, very moderate differentiation, they did acknowledge that it's not that those drugs are better, they deny that it's because they have an agency problem on their own, but they would basically tell you that we have a major problem with drug companies being too smart and finding

ways around the barriers they erect and they have a problem with their own clients, the employers, not quite willing or not quite understanding everything they need to understand to provide more pressure.

So we kind of look at biosimilars, which are clearly a new concept in medicine, doctors are going to be less comfortable with them than with generics after 20 years, and they are typically larger drugs and larger percentage of sales for the drug companies that are promoting them, okay? And the same gaps, in my view, will be used prominently, and even more so than in the small molecule world.

`So the only comments I would have here for the regulators is, you know, please don't add any barriers to what we already have, to what biosimilar developers will already have to contend with. Overall, frankly, I am more optimistic because of these issues that we actually cannot afford to continue to have innovative medicine unless we find a way to cut the costs on the older drugs. That over time, we will have successive rounds of introductions where, over time, we will have faster and faster and more comprehensive adoption of biosimilars, but that adoption process could be 20 years or it can be 10 or it could be 5. And right now, I am kind of tending to think more

towards the latter, and that's towards the earlier end.

Thank you.

MS. DESANTI: Okay, we will have our ten-minute break now. Please be back at ten after ten.

(Whereupon, there was a brief recess.)

INTRODUCTION TO STATE BIOSIMILAR SUBSTITUTION LAWS

MS. DESANTI: Would you please take your seats and we will get started again?

Our first speaker now will be Jessica Mazer.

MS. MAZER: Thank you. As Susan said, I'm Jessica Mazer. I'm the Assistant Vice President of State Affairs at PCMA, the Pharmaceutical Care Management Association. PCMA represents the nation's pharmacy benefit managers that administer prescription drug benefits for more than 200 million Americans across the country who have health coverage provided through Fortune 500 employers, labor unions, health plans, and Medicare Part D.

So in my position at PCMA, I have kind of the privilege of setting legislative trends as they go across the country each year because I cover all 50 states, D.C. and Puerto Rico. And so one of the interesting legislative trends, at least last year, was the introduction of biosimilar legislation across the country. And so that's why I've been asked today to kind of run through with you what we saw last year, what was enacted, and what we are seeing this year, briefly.

So first, the typical requirements of the biosimilar legislation that we have seen include a

requirement that the pharmacist notify the prescriber within a specified amount of time after substituting an interchangeable biosimilar. There is also patient notification requirements by the pharmacist, as well as recordkeeping requirements, mostly for the pharmacy and, in some states, for the prescriber as well. Also, a requirement that the Board of Pharmacy maintain a list of -- either on the website or some kind of accessible list of the FDA-approved interchangeable biosimilars.

So what did we see in 2013? So in 2013, 28 bills were introduced in 18 states, which is pretty significant and kept people very, very busy last session working on the legislation. It was rejected in ten states, as you can see I've listed them there. And I'll talk a little bit about California in a few slides and the story about what happened there. Enacted in five states, and I'll cover each of those states so you can kind of see the differences and comparisons between them. And also it carried over in three states, so those bills are still working this year, along with a whole bunch of new ones that have been introduced this month, in January.

So I just wanted to first cover with you, before we hit the states, some of our concerns at PCMA

about the legislative activity that we've seen. You've heard multiple times that the FDA is in the process of approving -- of putting a pathway together to approve biosimilars as well as determining interchangeability. So we are really concerned that the legislation we are seeing is premature, specifically with the notification requirements. We are worried that it will cause confusion in state substitution -- state laws with substitution, and that the legislation essentially attempts to undermine public confidence in biosimilar medications.

So we worked in this last year in opposition with, PCMA, a lot of folks. We had national groups working together, we had state-specific coalitions working together. It varied state-by-state. Often times our national partners were GPHA, AMCP, NACDS and then on the state-specific partners, AARP had their terrific state chapters who were really critical in helping us oppose legislation in a number of states, as well as AHIP, with their state health plan association comrades, health insurers across the country, Kaiser, Blue Cross/Blue Shield worked on it with us, retail and independent pharmacies, Rite Aid and Walgreens are some examples. The generic manufacturers, Mylan and Teva worked to oppose the legislation with us. Unions, a

number of unions specifically in California worked on the legislation in opposition and those included the AFL/CIO, the Teamsters, the United Food and Commercial Workers Union. There was a large number there. And also a number of state pharmacy associations across the country worked in opposing the legislation.

So starting with the states. North Dakota. North Dakota Senate Bill 2190, which was enacted, we consider this one of the most onerous legislation that was enacted in the country last year. It has some really stringent requirements, including a 24 hour notification after the substitution by the pharmacist to the prescriber. There is also individual patient notification as well as the pharmacy and the prescriber have to keep records for no less than five years.

It also has that board of pharmacy requirement that they maintain a list of their current FDA-approved biosimilar products that were approved for interchangeability.

Moving on to these three, Oregon, Utah, and Virginia. I put these three together here because what they have specifically in common is the fact that they have sunset provisions on the prescriber notification requirement. All three have patient notification requirements and then, in Oregon, you have three

business days. So the pharmacists, within three business days, have to notify the prescriber of the substitution of the interchangeable biosimilar.

The same requirement, three business days, in Utah. In Virginia, it is five business days. So as you can see by the next column, all three states, that specific requirement actually sunsets in two years from the effective date of the enactment of the law.

Additionally, the pharmacy recordkeeping requirements, three years in Oregon, it is unspecified in Utah, Virginia it is two years. And interestingly, in prescriber recordkeeping, there is none in Oregon, none in Utah, two years in Virginia. And specifically in Oregon, the actual prescriber recordkeeping requirements were in the bill as it moved through the legislature and ultimately it was stricken in order to remove some of the opposition to the legislation from some of the medical groups.

One thing that I find curious about that is that the pharmacy is required to notify the prescriber after the substitution of the interchangeable biosimilar, how come the prescriber isn't required to keep some kind of record of that? It kind of doesn't make a whole lot of sense.

But an interesting thing to note, in Oregon,

they do have the board of pharmacy website list requirement and that is not required in Utah or Virginia.

Florida, as I think it was mentioned earlier, is unique in the fact that the notification requirement was stripped from the bill right before it passed. Literally, seconds before it passed the legislature. And therefore the legislation essentially attempts to mirror the generic substitution law in Florida. So no notification law requirements and a patient notification requirement which is similar to what you have to do for a standard generic substitution in the state. A written record requirement for the pharmacy of two years and the board of pharmacy also has to keep a list, in Florida, of those interchangeable biosimilars available.

So California. California was a long, drawn-out and interesting battle last year. And the introduced version of the legislation required notification of the substitution within five business days, to the prescriber, and it was specific to just interchangeable biosimilars.

Now, early on in the legislative process, the prior to January 21, 2017, you see there tacked on, that sunset provision, was amended into the bill.

Additionally, the language was changed to include a notification of either a biological product or an interchangeable biosimilar, which was unique to California.

Now, there were huge coalitions on each side of the issue in California and we, on the opponents side, worked with more than 30 organizations. We had health plans, insurers, pharmacists, retailers, unions that I mentioned earlier, of course PBMs, generics, some of the brands. It was a big, big group of folks on our side. And ultimately, the bill went through the legislature and went to the Governor and the Governor -- a lot of folks weighed in with the Governor, including CalPERS, who weighed in with a veto request. And ultimately, the Governor vetoed the legislation.

I think it's interesting, I put the Governor's veto message, Governor Brown's veto message up there, where he ultimately found that the legislation struck him as "premature" and I think that's important to note.

An example for you of kind of what's going on here, this leads from last year to this year, Massachusetts has a carry-over rule. Massachusetts was unique in itself last year because it tied the notification requirements to the interoperability of

the electronic health record systems. So in Massachusetts, the pending legislation doesn't require notification until this full interoperability of electronic health record systems is actually reached. An entry into the patient's electronic health record shall constitute notification.

Now, the reason why this is unique to Massachusetts is because, in 2012, Massachusetts enacted a law that required all providers by 2017 to implement fully interoperable electronic health record systems that connect to their state-wide health information exchange. This is unique to Massachusetts, the requirement for providers, and there is no additional notification requirement, at least for the prescriber, that are included in this version of the legislation.

But as I move on, this kind of leads into this year and the trends we are seeing this year. Now, this was as of last Thursday. I just got an email that Vermont introduced a bill and I think we've got one coming very soon in a couple other states, but here's what we've got pending so far.

The unique thing about 2014 that we're seeing is this tie to this interoperable electronic health information exchange showing up in a lot of bills.

However, most states don't have a requirement for providers to connect to those kinds of systems.

What's also unique to the 2014 legislation is that, if the state doesn't have this electronic exchange available, then notification is still required to the prescriber within ten days, is the average of what we've been seeing.

So it really doesn't solve the issue. It looks like a great idea, but it doesn't actually solve the problem because most states don't have the requirement like Massachusetts does, so it's interesting to note.

Another unique amendment that we are seeing being added to some of the legislation across the country relates to including, in the notification requirements and the restriction on substitution, on insulin products. We are seeing that attached in a couple of states. Where that goes remains to be seen, but I thought it was important to note as well.

So in summary, as you've heard a million times, the FDA is the only regulatory body with that scientific expertise to determine interchangeability. And as I've stated, we're really concerned about the onerous requirements on substitution of interchangeable biosimilars. We think it's premature and we believe

that it may conflict with the national standards the FDA is currently developing.

I thought I'd leave you with one quote from the FDA. Now, the FDA doesn't engage in state legislative battles; however, this quote was said publically by the FDA Commissioner and I think it's important. "The high standards for approval of biosimilar and interchangeable products means that patients and health care professionals can be assured that when those products go to market, they will meet the standards of safety, efficacy, and high quality that everyone expects and counts on. Efforts to undermine trust in these products are worrisome and represent a disservice to patients who could benefit from these lower cost treatments."

Thank you.

INDUSTRY PERSPECTIVE ON STATE SUBSTITUTION LAWS

MR. EICH: Good morning. I'm Geoff Eich, Amgen's Executive Director for Research and Development Policy and a member of our Biosimilars Policy Group.

As Susan mentioned, we are going to represent an industry view, but I wanted a caveat that the industry is not necessarily one of the reference product sponsors and what I'll represent is also our biosimilar perspectives. We and many others that are engaged in a lot of these issues, I think Ron sort of put together a really nice slide, an overview of what this industry looks like.

The biologics industry is increasingly a mixture of small companies partnered with large biologics companies partnered with generics companies. So what you see, in terms of the industry that is evolving, is a very different mix than what we've seen historically, so I'll try to represent that view.

My colleague, Gino Grampp and I, who is also here today to speak on naming, we represent Amgen's very significant investment in research and development of biosimilar products for the U.S. and for other regions of the world. And so our commitment to the success of the U.S. biosimilar program really cannot be dismissed.

There are three things that FTC must consider as it evaluates biosimilars and policy surrounding it. First, and it is fundamental, biologics are not generic drugs. We've heard this before and there are many good examples of this.

The issue of state legislation, naming of the products, and also the way that the FDA labels the products are going to be collectively important to biosimilars and I'm going to talk more about how that evolves.

And also the empirical data demonstrate the need for a complete and accurate patient medical record. We are going to talk about what exactly is behind the concept of communication between the health care team and the objective is a complete and accurate patient medical record.

We have the benefit of being both a pioneer in biotechnology and a leading developer of biosimilar products. We know and understand the complexity of biologics and can state categorically that there are important differences between these products and generic drugs. Every biologic medicine, every single biologic medicine is, in fact, unique and this fact is absolutely fundamental from a scientific, regulatory, and health care policy perspective. We can tell the

difference between a process change for a product that we've known for years and a biosimilar product to a reference product that we've just met. Along with regulators in the scientific community, we can empirically tell the difference between three biosimilar products of the same reference product.

Amgen and other leading manufacturers have long experience managing manufacturing risks and designing rigorous quality systems, both to prevent errors and to quickly identify errors that cannot be prevented. We've seen both predictable and surprising changes in product quality with our products and with others. We know that hubris is for the uninitiated. We have pioneered systems to perform post-market surveillance and statistical signal detection for each lot of our biologic medicines. We've also experienced misattribution of adverse events to the wrong manufacturer and we have experienced also that these can change the benefit/risk profile of an entire class of medicines.

Biologics are materially different than chemical drugs, oral chemical drugs. They are utilized differently in patient care and these differences are central to discussions on product selection and nomenclature. Biologics are injected and infused, as

you've heard today. They are frequently in doses that are specific to the patient and her disease. They have unique degradation profiles, limited shelf-life, and are rarely stocked in quantity in pharmacy inventories.

Approximately 70 percent of all biologics in scope of the biosimilar law are dispensed in physician offices, clinics, hospitals, and other institutions with their own procedures. 25 percent are dispensed via mail order and only 5 percent are distributed in traditional brick-and-mortar retail pharmacies. This is a distinctly different scenario than in 1979 when the Federal Trade Commission considered product selection laws the first time.

It looks like I'm missing a slide here. This is a new kind of product in a new era and all appropriate policy options should be considered and our history of generic drugs should not guide us to overly narrow or false choices.

Must we choose between increased access or the ability to monitor specific medicines reliably? Must we choose between low cost medicines or for patients to have an incomplete or a complete medical record? Must we choose between vigorous competition or enabling manufacturers to voluntarily stand accountable to the patients we serve? Why not transparently label

biosimilars to engender patient and physician confidence? Why not enable patient medical records that clearly identify specific products? And why not select distinguishable nonproprietary names for distinguishable products?

Increased access to biologic medicines can and should include policies that are appropriate to these classes of medicines. We believe in "and" not "or."

Let's be clear. An inability to identify a specific product reliably jeopardizes all biologic programs equally. That's fundamentally important to understand. And people who understand ask me why Amgen is so passionate about this and the answer is, it's simply the right thing to do. This will stand the test of time and of rhetoric. We do not have to make false choices.

Framing the debate based on our history with generic chemical drugs or the state of affairs years before the recombinant DNA medicine were first introduced is misguided and will not lead to a lasting or robust biosimilar marketplace. However, this 1979 FTC report is a valuable reminder for some regarding the characteristics of a model product selection law and how it can be distinguished from a mid-century

anti-substitution measure.

The U.S. health care community today is well-educated, globally aware, and increasingly knowledgeable in the science that underpins biologics. Patients and their families share highly-informed perspectives and were pleased by the interest of policymakers. We are paying close attention to the perspectives of the pharmacists who will dispense these products, the clinicians who prescribe and often administer them, and the organizations that will pay for them.

It is clear to us that successful competition in the biosimilars marketplace will be grounded in patient and physician confidence. Indeed, in its 1979 report on the subject, the FTC noted, and I quote, "Increased communication, as well as lower prices, may explain why most pharmacists report that product selection laws have had a positive effect on their relations with patients." Surprising? We think not.

Efforts to describe biosimilars as generics in all but name do a fundamental disservice to health care professionals, patients, and their families. They intentionally obscure, from pharmacists, patients, and providers, the scientific reality that each biologic is unique and hence these are anticonsumer. They are

often a conscious effort, on behalf of special interest, they are offensive to protein scientists, and increasingly disparaged by academia, regulators, and competitors as misleading.

Some, even journal articles, argue emotionally that biosimilars have to be foisted on patients, switched furtively at a pharmacy before administration. Others want the physician removed entirely from the conversation about which biologic medicine has been administered. These views demonstrate an inferiority complex and it's a belief that biosimilars are not as good as their reference product. We fully reject these views.

We have no inferiority complex about our biosimilars and we have no shyness about the important potential enabled by FDAs regulatory construct. It allows significant design, development and product flexibility. We appreciate and will use the freedom allowed by the biosimilars pathway here and around the world.

We want our biosimilars to have distinguishable names because they are distinguishable substances. We want patients to have complete and accurate medical records so we may be accountable when they are administered to patients. The product

selection approach we advocate for, along with patients, physicians, scientists, and the leading biologic and biosimilar manufacturers, is to update existing state product selection laws to include interchangeable biologic medicines when determined by the FDA to be appropriate for alternating or switching between products.

The legislation also seeks to address an unintended but important consequence of product selection. Absent some level of interoperable health records, or after the fact communication between the pharmacy and clinician's office, the patient's medical record will be rendered either ambiguous or inaccurate. This is fundamentally important. The patient's medical record will be rendered ambiguous or inaccurate, and that is an important record.

The records help accountability and this is the only area where the proposed biosimilar legislation differs from the model product selection acts that the FTC has helped to advocate for. Communication between the health care team for the purposes of recordkeeping, after product selection and administration, hardly constitutes an intervention and those who suggest as much are confused.

So why does this matter? Here's a chart of

European patients experiencing an increased rate of adverse events. The actual medicine doesn't matter and nor does the setting, but the important thing is that each line that you see here represents a patient's medical history, as reconstructed by a researcher in Paris. By the way, these are all brand medicines before the EU approval of biosimilars.

The different colors on each line represent different biologic medicines, or routes of administration, administered to each patient. If you look closely, and I realize they are small, the red dots note the onset of clinical symptoms and the green dots represent diagnosis of a rare but serious adverse event.

At the time, records were not as accurate as they needed to be and determination of the manufacturer having a problem took too long. But what is also important is where the green or red dots occur on a product other than a yellow line. We now know that the agent the patient was receiving at diagnosis was not the root cause of the problem and that the products administered previously were the likely cause.

This is the point on records. This is not a hypothetical scenario, it is our reality in the biotechnology space. In the U.S. today, a lengthy

process to identify or resolve a quality problem in the context of multiple manufacturers, because medical records were rendered ambiguous or inaccurate, will neither engender confidence nor enable or collective objectives for biosimilars.

Patient medical records also play an important role in data collection and communication of adverse events. This is information that serves often as the first warning of a quality problem with the medicine. The information on past drug history and suspect medicine or medicines in a report are of important value.

When it comes to post-market surveillance and accurate recordkeeping with biologics, it is neither wise nor reasonable to invalidate experience-based procedures and processes for drug safety.

So here, in a single figure, depicting the concentration of a biologic medicine in a patient's body, we can actually examine the problem posed by product selection, absent any level of communication or an interoperable health record. We model the biologic monoclonal antibody that is frequently used in self-administration. For purposes of argument, we've assumed here that it's an identical set of product characteristics, including absorption, clearance, and

immunogenicity.

In practice, we expect subtle differences between all products, some that could result in important but latent events or quality changes that occur throughout the product's life-cycle.

The red, yellow, and blue sections depict the concentration of each medicine in the patient's body and the graph shows exposure of what it would look like with the patient receiving a recommended dose every two weeks. Given current practices, the patient could well receive a product from a different manufacturer every 30 or 90 days. Here, conservatively, we have assumed every 90 days.

What you can see in the tail of these curves, in the red, the yellow, and the blue, is that biologics persist in the body for a much longer period of time than most small molecule drugs. Overlap to exposure to circulating biologics from different sources is likely. To make this more clear, the patient may have two or three of the biologic medicines in their body at a point of which they report to their physician and are having a loss of efficacy.

There is also a black hash line that shows the rate at which anti-drug antibodies are detected in patients when treated with just one source of the

biologic. Many patients develop an immune response against some biologics and, as stated before, this can manifest in a loss of efficacy or allergic-type reaction.

The immune reaction starts on the first injection, but it can take many months to be detected. This occurs with the original medicine and is equally expected to occur with the biosimilar.

So let's take a look at the blue vertical line. The blue vertical line highlights the question of what happens seven to eight months into a patient's course of therapy if they are losing response to the medicine. Which product is responsible? Which one is not? How can this be ascertained in a timely fashion so that patient care is optimized?

As you all know, our immune systems have long memory and vaccines frequently provide ten years of immune surveillance. For a biologic medicine that elicits a strong immune response, this can last for over a year. The immune system is ready to react vigorously should the foreign substance appear again. So this is the reason that we need to ensure complete and accurate medical records with all biologics. When a problem is identified, the initiating biochemical event may have occurred long before.

Our scientists are motivated by the work we've done on biosimilars and many of our biosimilar candidates are now in their pivotal trials. Our manufacturing scientists and experts have risen to meet a number of vexing challenges. We have not yet talked about virtual interchangeability, but that is certainly something we can address with the Agency.

Biologics are not generic drugs. State legislation, naming, and labeling are collectively important for biosimilars and empirical data clearly demonstrate the need for a complete and accurate patient medical record. Rules that would impede transparency or frustrate post-market drug surveillance will not be successful in this age of technology.

We believe if we are transparent, specific, science-based and, most importantly, accountable, we will earn the trust and confidence of physicians, of patients and their families, and we will see a meaningfully more successful biosimilar program in the United States. We believe in "and" not "or."

CUSTOMER PERSPECTIVE ON BIOSIMILARS

DR. MILLER: I want to thank the FTC for inviting us today. My name is Steve Miller. I'm the Chief Medical Officer with Express Scripts.

Germane to my comments today about the consumer and their views on biosimilars, I need to give you a little bit of my background. My career started as a transplant kidney doctor. I was a basic scientist throughout most of my career, doing primary drug discovery and actually hold patents with several of the companies that are represented here today.

After that, I actually opened a dialysis network for the University and we became the largest provider of dialysis services in the state of Missouri during the 1990s.

That was followed by a stint as the Vice President and Chief Medical Officer for Washington University and Barnes Jewish Hospital, at which time I actually had the opportunity to oversee 13 hospitals' pharmacy practices. And most recently, for the last nine years, have been the Chief Medical Officer for Express Scripts.

This unique background gives me an opportunity to talk about almost every aspect of the channels in which biologics are used. And my comments

reflect that of the 65,000 pharmacies in the United States, including the specialty pharmacies that dispense speciality drugs, but it also represents the thousands of clients that we service and the 100 million patients that we represent.

Biologics are a really challenging part of the future of healthcare, as demonstrated by this pie chart. If you look at drug spend today, so if you thing about this pie as being about a 300 billion dollar pie, about 30 percent of drugs right now are specialty drugs, the vast majority of those being biologics.

As you've already heard, by the year 2018, 50 percent of pharmacy spend will be for biologic drugs or specialty drugs. If you dissect this and look at who is using this, this is 1 to 4 percent of any given population. So you're talking about 4 percent of the patients in the United States who will be consuming 50 percent of the pharmaceutical spend, most of it for biologics.

Now, you can't read the drugs in these stack charts, but all you need to do is look at the colors to understand what I'm talking about. In 2010, as you can see, seven of the top ten drugs in blue are traditional oral solid drugs. So as you can see, the vast majority

of the drugs that are big spend drugs right now are traditional oral solids.

If you just fast-forward to 2016, what you see is seven of the top ten would be biologic drugs. And so we have a complete flip of what spend is going to be for pharmaceuticals going forward.

And the great news is that the innovative community of the pharmaceutical and biologic industry has really hit a stride where they are having great success. They continue to bring to the market truly remarkable new products. And our view is, you want to save every dollar possible to spend on these new products.

And so when you can have substitution to a cheaper, equally-effective biosimilar, that's a great opportunity not just for consumers, it's a great opportunity for the pharmaceutical industry because those dollars can be repurposed for patients who need these great new drugs.

And these drugs truly work. They are incredibly remarkable. When I was a med student and I would go to the nursing home to see family members, you'd see family members or old people with these incredibly swollen, painful hands. They could not even grip the utensils at the table and needed these special

little bumpers to actually hold their forks and knives.

If you go to a nursing home today, because of the advent of phenomenal new drugs, you don't see this. Your kids and you won't have this same experience as your grandparents did. So these products truly are not just life-saving, they are life-altering and they are really important to have in the marketplace.

Now, we did a study to look at what would happen if biosimilars actually made it to the United States. And we've been talking about this for a long time and so we've actually had the opportunity to do this study on several occasions. We've looked at 11 products that will be losing their patent protection over the next decade and we've made some assumptions. And the assumptions are relatively conservative.

Whereas in Europe, you are seeing discounts of 30 to 50 percent, we said the largest discount you will see in the United States ever is 30 percent. We start at 30 percent and it never goes up, despite more competition coming into the marketplace. We thought that inflation would slow, so that if you had a biosimilar enter the marketplace, the brand inflation would drop so we put in a drop for brand inflation.

We thought that there would be modest switching, that often times we would only be able to

get the new patients, so that many patients would be grandfathered. So we assumed that there would be very modest switching to the products. And we assumed no interchangeability to the year 2020.

On top of that, we put almost no growth in the market. We put a 0.1 percent increase in utilization annually over time. So we made every assumption as conservative as possible.

And for these 11 products, what you see is that this is the trajectory of their spend over the next decade. If you have biosimilars for these products, with slow uptake, what you see is a delta that occurs that, over the next decade, you can have a quarter of a trillion dollars of savings in the United States for just these 11 products.

Now, will we be wrong in these projections? The answer is probably right, we will be wrong. Sometimes we will have guessed too low, sometimes the discount is going to be way greater than 30 percent, sometimes the uptake is going to be way greater than 0.1 percent. But we know directionally this is correct and we know that the opportunities are enormous if we can get biosimilars into the marketplace.

But as you've heard over and over today, there are several concerns and these concerns are

around two things that we'll address today. That is, the nomenclature, what's the naming of these products, and what are the state substitution laws.

As you've heard from several speakers already today, the United States actually has a robust and vigorous system that has protected patients over the course of the last many decades, even with the advent of generics. We know have generic substitution 84 percent of the time and patients are being well-served by this.

And so now we have new arguments coming about the purity of the medical record. I can tell you, as a practicing physician, the medical record is ambiguous. And I will also predict the medical record will continue to be ambiguous into the future, but we can't let the perfect be the enemy of the good.

On top of my other credentials, one of the things I didn't mention is that I am also the Chairman of the Board of Surescripts, the number one router of electronic prescriptions in the United States. The idea of bidirectional interoperability is not only unlikely in the near future, it's actually not often even desired by doctors. When we had transactions that the doctors actually thought they wanted to get often times, in reality, they don't.

I'll give you an example. When we were first creating the system, we asked the doctors, would you like to be notified if a patient picks up their prescription at the pharmacy. You would think that a doctor would want to know that, but we found out, when we started piloting it, is that the doctors, in fact, did not want to get those notifications. Not only did they not want to keep the records, but they wanted to limit their liability and they did not want to be liable for that period of time when the patient doesn't pick up their drugs. And so this assumption that doctors want all of this data is actually often misplaced.

There are four major channels in which biologics are distributed and you heard about those already today. They are delivered to the pharmacies and that includes both the retail pharmacies but also the specialty pharmacies. They are delivered through the hospitals, they are delivered through the hospitals' clinics. So those are the pharmacy, the hospital, the hospital clinics, and the third place is mainly through dialysis units and the fourth is physicians doing buy and bill and dispensing in their office space.

It turns out the records in the pharmacies

are extraordinary and we will show you the data for that coming up. It turns out that the records in the hospital are extraordinary, and it's mainly because the hospitals want to be reimbursed from their clinics or inpatient facilities and they need to have that data. It turns out that the dialysis units, which I worked in for many years, are phenomenally capable of keeping great records and know which products they are dispensing.

The only hole in the system is actually when it is the physicians who are buying and billing. So physician notification to physicians, who are already failing to keep the records in their own buy and bill, is unlikely to add safety to the system. And so this idea that bidirectional physician notification is the key to this whole problem is actually misplaced.

So what we all want to do is we want to improve access and we want to create the savings that are out there. It turns out that the reason pharmacy is so effective is because the amount of data that is available to every single pharmacy, every single hospital, every dialysis center is actually an extraordinary amount of data because of the way we bill.

Every product already has three unique

identifiers on it, besides the INN. It has a trade name, it has an NDC, and it has a manufacturer. If you require the use of one of these unique modifiers for billing purposes, for reimbursement, doctors, hospitals, dialysis units are phenomenally effective at collecting that data and submitting it.

And so the idea that we can have big pharmacovigilance is actually true, because we already have very accurate records in most settings. The idea that the biggest hole, where physicians do buy and bill, that notification would close that hole just leads to inefficiencies in the system, it's fear mongering, it adds confusion, but it does nothing to make the system safer.

So let me show you some data. This is -- we looked at the prescribing habits of doctors and we looked at several things. We looked at, not only could we track every product that went out the door, we looked at how the doctor prescribed it.

Atorvastatin is the generic for Lipitor. And as you've heard already today, the vast majority of times, even when products are generic, the doctor is using the brand name to prescribe the medication. So making the INN unique for the product will not add safety. So even when it comes to atorvastatin, the

vast majority of those scripts come to my pharmacy looking to be -- written as Lipitor.

But if you take a drug even well older than that, azithromycin, we still get the majority of our scripts as Z-packs. And so the reality is, physicians prescribe by the branded name.

Now, atorvastatin, in a one-week period, we dispensed about 160,000 prescriptions for Atorvastatin. We adjudicated these and they went out from almost 52,000 pharmacies from 15 different manufacturers. We could tell you the exact product in the hands of every patient because of the use of the NDC codes that are required for pharmacy reimbursement.

If you look at the biologic drugs, 419 scripts for growth hormone, 11 different trade names, 1 INN, 145 different pharmacies, 7 different manufacturers. Again, we could track, down to the individual patient exactly, not just what product they got, but what vial size they obtained the drug in. And finally for Epo, 333 claims, 285 pharmacies, 2 manufacturers.

The reality is, the system that the FDA has created in the United States is safe and effective. It's safe and effective for the biologic companies to use today and it will be safe and effective for the

biologic companies and the biosimilar companies to use in the future.

If we're going to have effective biosimilar regulations, we need payers and plan sponsors to work together, because they are phenomenally concerned about the rising cost of this. This is an unsustainable pace we are on and we need to do something so that we have more money to spend on the great new products people want to bring into the marketplace.

The high price of speciality drugs clearly represents a barrier for patients able to use these drugs and patient assistance programs are inadequate, in and of themselves. If we are going to have success, it has to be all the stakeholders in the room today, working together to create a system that works better, to keep safety the way it is and to drive down costs so that we have a more efficient system.

Adding inefficiencies like doctor notification is nothing more than adding confusion to the marketplace, putting in inefficiencies that will cost time, cost money, and prevent patients from getting the products they need. And the PBMs and the pharmacies are going to play a crucial role in this going forward.

Thank you all very much.

INNOVATION OF INTERCHANGEABLE BIOSIMILARS

MR. LEICHER: I feel like I don't need to say good morning anymore. I'm Bruce Leicher, I'm here for Momenta Pharmaceuticals. And I guess like my prior colleague, Geoff, I'm also here to represent the industry viewpoint, I guess, which isn't necessarily unified.

What we are focused on at Momenta is actually the innovation that you heard a little bit about from Ronny earlier and from Dr. Shacter about how the pathway is driving innovation. The idea, the notion that we need to invest in developing the characterization and analytical tools to demonstrate biosimilarity and interchangeability is based on the fact that there would be a return on investment. I'm sorry, I should get closer to the mic. And we think we are seeing the fruits of that now.

Momenta is much like many other biotech companies. Let me just say that we were a spin-out from MIT and we are largely focused on it and we were -- the company was principally involved in the original characterization and development of Enoxaparin, as you heard about earlier.

So you know, in short, let me just say that our view on this is much -- I'm going to try to

synthesize some of what we heard this morning, because much of what I was going to say, I think, was covered by many speakers, but we think that the biosimilar and interchangeable biologics policy that's adopted should be designed to promote innovation and attract investment, like the investment Momenta and many other companies are making in making innovative interchangeable biologics. And that it should be designed, as Steve Miller was just saying, to address the patient needs as well as patient safety. And that it should avoid using anti-competitive restraints to do so.

And I think what I'm going to focus on through much of what I'm saying this morning is that I think when you tie together the proponents of the state law, what you are going to see is one common denominator, in that this is really, in our view, part of a commercial marketing campaign to make interchangeable biologics look like biosimilars. In other words, they are really not interchangeable, they are different; and to discourage substitution at the state level and to have a forum where you can make disparaging-type comments without the risk of enforcement.

So one way to -- we really need to put this

in context. There has been a long-established campaign against biosimilars from well into the -- well over ten years. The first message was generic biologics are impossible. And then it translated into, well, they have to be biosimilars and we shouldn't have an interchangeable part of the pathway. And the whole point, in either case, was to prevent substitution.

And then the same messages reappeared in the comments from opponents at the FDA in the biosimilar guidance documents. They were -- they were used in support of citizens petitions to delay biosimilars and to put in place the naming restrictions that you've heard about. And you may have also -- you heard this earlier in a presentation, but there's an effort underway to seek to use restricted access, to limit access to a comparative product as well.

You know, it's interesting to me listening to the talk from Geoff this morning that there's a key part, and maybe I have to add another one to the list here, a key position strategy that seems to have fallen out of the talk, and it was the argument that planned products drift and are made in different manufacturing facilities and therefore it is not really -- since we have differences, just think of the differences we'll have with interchangeable biologics or biosimilars.

And that one seems to have gone away, but the point I want to make on that subject is the whole benefit of having the interchangeable pathway was what Emily Shacter described earlier, which is it created a fertile field for companies like Momenta, we're not the only ones, to learn how to develop the science to make products that can be substituted and can be switched and were viewed by the FDA to demonstrate that that's possible.

And while yes, they may not exist today, the reason we fought for the interchangeability pathway in the law was to create that opportunity to attract the investment. And if we allow the states to put the barriers in place that make substitution a challenge, then I think we are going to remove the opportunity for that investment and the kind of innovation we've seen in the last couple of years is going to be diminished.

So now we are faced with the next tactic. And I think, you know, we heard the next tactic described perfectly and it's, you know, essentially the states are being asked to join in a campaign to say there is a problem with pharmacovigilance now. You know, just like there was a problem with brand drift. And if you think about, each of these arguments that has been made historically is true, in the sense that

there are problems with systems, but there is nothing necessarily unique about those problems to either biosimilars or to interchangeable biologics, and what should be fixed is the problem. It shouldn't be used as an anti-competitive tool.

So by example, by thoroughly characterizing, as Emily described, and understanding what is in a vial, one has the ability to substantially reduce the risk of brand drift and product changes at new manufacturing facilities. And it is the technology that is being developed by companies developing interchangeable biologics that is going to make that possible.

So we heard a little about this this morning, but why is substitution so important? Well essentially, and I think this is really the guts of it, it eliminates the need for sales and marketing to physicians and payers. And you know, you'll note that there are some companies that now support a so-called compromise that you've heard about, where it is going to say, well, we'll have interoperability at the state level, but when we don't have interoperability, we are going to still require a special notice. And what that does it is enlists the state in an effort to say, you know what? Interchangeable biologics are different.

And it's interesting, if you read the California statute, it described the interchangeable biologics in the statute as biosimilar. It didn't describe them as interchangeable biologics and I think there's a conscious effort, if you look at a lot of the presentations, to try to confuse, that there really is a higher level of proof associated with interchangeability, and it's something that the FDA would determine is substitutable and switchable.

And I think the other thing to look at as you are examining the companies that are supporting this compromise legislation is, are they really developing interchangeable biologics for innovation, which they may or may not be, and are they planning to market those through substitution or market those through a sales force? And I'll at least posit the hypothetical that the companies that have lined up behind the compromise are companies that are looking at using sales and marketing as the principle mechanism and they are trying to basically enact into law competitive restrictions so that those who can obtain substitutability won't be able to achieve the benefit of it and that would be a shame.

And it's really -- just to make this point, the notice provisions are really just designed to make

the point that interchangeable biologics really aren't interchangeable, they are different and that they're suspect. And you know, this point was made quite forcefully by bio recently in the food area where, you know, there were a number of state laws being proposed to require labeling of GMO foods. And the legitimate response to that is that that's just an effort -- that's just a disparaging comment.

So in the end, what I think you heard from a number of the folks here on the pharmacy and on the payer and consumer side is it matters to patients, it matters to physicians, it matters to payers. And we think it matters, because we are a novel development company as well, we think it matters for novel products as well. Because in the absence of the presence of interchangeable biologic competition and biosimilar competition, there won't be headroom in the budgets to pay for novel products as they launch.

Last year, I think there was quite a bit of press around the issue as the laws came out and people were catching on to the fact that this really was a commercial campaign. And that's probably why we saw some of the toning down of the message. And I'm not going to dwell on this, because Steve did such an excellent job, but it really does matter, just looking

at the Express Scripts data, to have this competition available.

You know, this is one set of data that shows, if you look at specialty products, we could be looking at close to, you know, over 65 percent cumulative price increases just in the next three years.

So what is Momenta doing? And I actually want to thank Emily Shacter, she described a lot of what we're doing. This is a standard biosimilar and this is what people had in mind, perhaps, ten years ago when they thought about what was being developed and raised concerns, before people started thinking the way the FDA is, and perhaps the way we were when we were developing generic Enoxaparin.

And that there were going to be things that you might now that are the same about it, there are things that you might know are different, and there are things you might not know at all about it. And what we have focused on, and I think what other companies are starting to focus on, is you actually can get to a much higher level, a high similarity, which is really the middle segment, by focusing on the thorough characterization. It's not the clinical trials that are going to provide the differentiation. They will provide explanations to whether anything that remains

is an issue or not.

And ultimately, we believe we can get to where it's blue and blue. And we are not saying that we can get there today, but if we have state laws that take away the economic advantage in investing in that innovation, I think the opportunity for that to occur is really put in jeopardy.

From our perspective, we think this isn't fantasy. This is -- you know, everyone made the same arguments on the opposition when we were working on the development of generic Enoxaparin. And you'll see from Dr. Sherman's quote, you know, in her view, she felt this was about as complicated as any biosimilar application would be, in terms of demonstrating similarity.

Now, let me switch to what's wrong with special notice. And I think what's -- essentially the reason I said before, the reason they argue for it is really to get a competitive advantage in the marketplace, the companies that have sales forces and can deliver the message. If the state determines that you are not substitutable or it's hard to substitute, it's going to be a lot easier for sales reps to go out there and point that out. It's going to indicate they are different. If they have different names, it's

going to indicate they are different.

And as you heard from Steve Miller, and I learned some more about it today, there already is an existing Surescripts network that largely covers, or has the opportunity to cover, most pharmacies. It's interesting to hear his comments about doctors' interest in actually getting the information, but you know, the advantage of this system, if you look at it, is it allows a physician not only to know what was dispensed, but to know what was dispensed before. So that patient, when a prescription is written, you can take into account conflicts. The real purpose was to prevent prescription error.

And what I'd also add is the adoption -- this is just an example, because I'm from Massachusetts, but the adoption in Massachusetts, which is not mandatory for another couple of years of interoperable health records, which is a bigger system, but the adoption of E-prescribing is in the high 90 percents and it has grown at very substantial rates in the rest of the country. This is an innovative way to make available information to doctor if they want to know.

And what's also important for people to know is that the National ePrescribing Patient Safety Initiative was set-up recently and it makes available

access to this system for free to any doctor in the United States who wants. This is not -- there's no barrier to entry. A doctor can write a prescription on a script pad, but they can join this system if they really -- if they want to know what the patient was dispensed, they can look it up.

So as you heard earlier, Massachusetts adopted a law which doesn't effectively put in place a notice requirement and there's no intervention required, no prior notice, no special recordkeeping. And it uses the interoperable health records as the mechanism so that it doesn't disparage or distinctively label an interchangeable biologic as different.

And one of the interesting things that I noticed is that Mass bio had a legislative breakfast in Massachusetts about a year ago and they invited a panel of speakers, some of whom are here today perhaps, to speak to the legislature about what the biosimilars bill ought to be. And I think they expected it to be the message that biosimilars are different.

And they invited Professor Hancock, who is one of the leading researchers in the United States on analytics, to speak. And when he got up and said, I want people to -- he got up and basically said what Emily said, I want people to know that the state of the

science for analytics in the last ten years has dramatically improved. And he said, others may disagree with me but I can show the two proteins are the same. And I think that kind of affected the power of the commercial message that was being displayed on the legislature, which caused them to be a little more innovative in their approach.

And you know, as you heard, the California bill similarly was vetoed as people focused on it.

So just to briefly summarize, you know, we see that the state laws conflict with the BPCIA, which provides that a biologic may be substituted at the pharmacy without the intervention of a physician. We believe that the special notice requirements are designed to get physicians to intervene and are designed to create negative disinformation about biosimilars. And we see that it is a real burden on the statutory provisions.

What is important to note is Hatch-Waxman never provided that generic drugs are substitutable at the pharmacy, but this law expressly provides that they are. So it seems to me, and this is really what we think the FTC ought to recommend and what we think FDA and CMS ought to do, is to put into their guidance documents that these provisions, that restrict

substitution, are in violation of the provisions in the BPCIA and that we should just solve the problem simply.

So I'm going to take the last couple of minutes just to make a statement or two about naming, which really, I think, follows the same path. You know, I think you've heard people believe that biosimilars, when they are approved by the FDA, are going to be therapeutically equivalent. And the interchangeable biologics, to get approved by the FDA today, have to be substitutable and capable of being switched. So the standard for approval is going to be quite high.

And it would seem to me there's no defensible basis for creating a distinction that would interfere with their appropriate use. And the notion that you would have a different name for an interchangeable biologic, which is intended to be substituted and switched, just seems beyond what is intended by the law.

Here are some examples of the messaging around this issue that we collected. And you know what I think you -- you know, you may hear a little less today, because we've been criticizing it for some time, but I think over the course of the past year and the past ten years, it's always been a campaign of,

biosimilars are different. Interchangeables are biosimilars, therefore they are different, and this is all about patient safety.

And you know one of the things that I reacted to when I was watching the presentation on pharmacovigilance earlier is, when you're making a biologic and you have multiple manufacturing facilities or you may have multiple manufacturing changes, there are often, not all the time, but there can be often multiple manufacturing company versions of a product on the market at the same time. And you know, none of the companies are suggesting that they have a different name or that they have a notification at a state level of which particular flavor of the brand is being dispensed. That's, for some reason, not a safety issue, but it's a safety issue when you dispense an interchangeable biologic, which has actually been proven to the FDA, with tests, that were not necessarily conducted in doing comparability testing, to be switchable and substitutable.

And it's also interesting to get feedback from the EMEA, where they are increasingly paying attention to the issue of characterization and recognizing that the variability in the brand products should more than encompass the variability that could

be made in an interchangeable.

And I'm just going to close on this one note. The other thing I just want to bring up, I saw it in a few other presentations, is that there are a number of companies, and I don't know that it's become prevalent yet, that are looking to use restricted access programs to affect competition, and I would encourage the Agency to pay attention to that as well.

So let me just conclude with the following points. We think that the policy should be driven and measured by how it promotes innovation, through the development of interchangeable biologics, and that we have an ability to attract investment by having a pathway available. We think it's important to address patient needs and patient safety and we think that a policy should be picked that avoids using the least innovative and most anti-competitive solutions. And we'd encourage the FTC to encourage the FDA and CMS to interpret the statutes to properly restrict these laws.

Thank you.

MS. DESANTI: We'll have another ten-minute break. Please back here at 11:30 for the panel discussion.

PANEL DISCUSSION: STATE SUBSTITUTION LAWS

MS. DESANTI: I want to say a word of 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 are 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.

AUDIENCE MEMBER: Excuse me. Could you speak into the microphone. It is very hard to hear over here.

MS. DESANTI: Woah -- no broader than necessary to protect -- are they -- yes, it's on.

All right, is this better? All right. Okay, a working mic always helps.

So basically competition should be legislatively restricted only if it is 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 of -- obviously, if there are no likely anti-competitive effects, then there is 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 a first question -- we need to get our questions up. Okay, so the first question is, how would particular provisions in new state substitution laws, or similar legislative proposals, likely effect 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 have 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?

MS. SCHLAIFER: Sure -- am I on?

MS. DESANTI: Closer in.

MS. 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, or as the drugs will become available, pharmacies, speciality 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 between --

MS. DESANTI: Excuse me, Marissa. Where?

Where are the requirements for physician notification?

MS. SCHLAIFER: Well, today, if a pharmacy dispenses a medication that is not a generic equivalent or, in the future, an interchangeable --

MS. DESANTI: Okay.

MS. SCHLAIFER: -- medication, you cannot make a change without physician notification or prescriber notification.

MS. DESANTI: And that applies to biosimilars, that will apply to biosimilars --

MS. SCHLAIFER: That applies to any drug that is not a generic -- that is either not a generic equivalent or an interchangeable biosimilar.

So that would apply to if a substitution was being made for a therapeutic interchange between two -- 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 are creating unnecessary communication between the pharmacy and the physician's office. And I think that it's very important that, 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 the physician's office about. When we are 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 are not producing or introducing unnecessary noise into that interaction between pharmacies and the physician's office 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 when you look at, 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.

MS. DESANTI: So you're saying that you believe that physician notice, and perhaps other requirements in state laws, could convey a false notion that interchangeables are not --

MS. SCHLAIFER: Right, exactly.

MS. DESANTI: -- equivalent with the reference biologic.

MS. SCHLAIFER: Correct.

MS. DESANTI: Okay. Krystalyn Weaver, could we hear from you?

MS. 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 were the epilepsy drugs in this case.

And in that case, I think there was pretty clear evidence that it affected the competition and changed behaviors. There was a 29 percent increase in the brand usage in that instance, where those barriers were put up, including physician notification, that really inhibited the substitution of those generic products and resulted in increases in costs to the state in 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.

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

DR. 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 with a brand name would increase and the prescribing and substitution of the generic would decrease.

MS. DESANTI: Thank you.

MR. EICH: Just a quick second. I need to ask a question, in terms of how this is structured. If we actually have the Tennessee bill, and there is a

distinguishing feature that it's prior notification, do you want to talk about that now or how do you want to --

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

MR. EICH: 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 that record can be brought to bear. There is no need for sort of a, you know, this needs to be sent to the physician for their approval. It's not an intervention at all.

DR. KESSELHEIM: I guess I would just -- I agree with you that this is a different construct, but

I think that in reality, a situation where a biologic manufacturer -- that all of this notification is required after the fact, 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 are going to be calling the physician and the physician is going to say I don't know what went on. And then the pharmacy is going to call the patient and then you've got this very expensive drug that you 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 probably would implement that as a pre-dispensing notification. So practically speaking, it is probably more similar than you think.

MR. EICH: I think it's a really good point. And just another quick point on that, I think that what we need to remember though is that patients and physicians are generally groups that are advocating for a fewer number of days, you know, before the communication takes place.

From the perspective of ensuring a complete and accurate medical record, you know, from our perspective, the hypersensitivity issues, if you will,

between any of these biologic products, regardless of how they are 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's -- but it goes to the point that patients and physicians, if we are 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 that are going to rely on these medicines.

DR. GAL: Geoff, the following question is to you. I can completely understand why a physician would want to have access, would want to make sure if something happens, everybody can tell what doctor, what drug exactly this patient was prescribed.

But from my experience with physicians, the last thing they want is the accountability that would exist with them having to maintain the electronic medical record themselves because, you know, they don't trust the guy in their back office or the attendant in the physician room. And you are hearing here that, hey, the guys who actually provide the drug actually have a system to do that.

How do you answer that concern that physicians would have?

MR. EICH: Yeah, that's exactly right. And I think that 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 and 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 are 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 with a 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 are fundamentally misguided. All biologic manufacturers are going to have to follow their products in the post-market setting. And the Agency has made this very clear in their -- article in 2011.

MS. DESANTI: Okay, 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.

MS. SCHLAIFER: That's an interesting suggestion. I mean, I hadn't -- with the new proposed legislation, obviously once the legislation is passed, we would be figuring out how to implement.

From just a practical point of view, and for

any of you who have spent, or haven't spent and have looked from the outside what goes on in a pharmacy, the idea -- more likely than not, any notification would take place during the downtimes in the pharmacy, which tend to be in the evening or, you know, during the lunch hour. Not necessarily, if a prescription is being filled at 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, you know, calling or 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.

MS. DESANTI: Krystalyn?

MS. WEAVER: I agree with the hectic nature of the pharmacy for sure, 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.

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 is a level of creating anxiety of the safety of the product if you have to do that notification, even if it is 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.

MS. DESANTI: Okay. I'm going to have to ask all of our speakers, including myself, to speak more closely to the microphone because people are having terrible trouble hearing.

In particular, in the center section, some of you wouldn't know this, but there is 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 mics.

Okay, so thank you very much for both of those observations. I'd like to move on --

DR. KESSELHEIM: I think we've got a comment over here.

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

MS. DESANTI: Sure.

DR. MCCAMISH: And that is, you saw Ronny's presentation talking about Europe and the variability of responses within different countries, it's something we face all of the time, in terms of moving things forward.

In the states, there is the issue in terms of state legislation, which is 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. And you can go down this pathway, it's not identical, it's not a generic, it is a biosimilar. It is not identical to and 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've tried to take a little bit of a pragmatic approach because we are 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 would 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. Not that we have concern about a safety issue, not that we have concern about a documentation issue, but is there a way that you can say, okay, only for those interchangeable biologics, and this is what we 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 that it is not pejorative to the biosimilar. That's what we want to avoid, is any suggestion that the biosimilars have a lower class, a lower quality than the originator.

And so what we have thought through is, can you have it so that it is agreed upon where you would then communicate with the physician whatever the drug

was, whether it is the biosimilar, whether it is the originator.

So they are getting this communication within, I don't know, ten days or something so they can document for their records. And if it is a safety concern, they have it documented, that's there.

Now, I don't think that's magic, but what I'm trying to instill here is, without some kind of a pragmatic approach, there is a risk that you'll have North Dakota all over the place, some Floridas some places, some Californias 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 there isn't, and the data around that.

So I am just interjecting, is there a pragmatic approach. And that's why we've tried to come up with some kind of language, not that it's perfect or great or whatever, but if it is standard and everybody can apply toward it and understand it, would that be better for access? Would that be better for patients? Would that be better for competition?

MS. DESANTI: We are going to take a comment from Sumant and then I want to ask Steve Miller.

DR. RAMACHANDRA: So we are the third company

actually, with Amgen, Novartis, and Hospira, and it's actually not a compromise, it's a consensus. It is very important to understand that we want to move the topic forward.

There are a lot of issues on biosimilars. This a market-forming event. It doesn't happen very often in the history of medicine to have a market-forming event. There are going to be follow-on biologics in the next few years in this market and the first thing that 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 are not asking for some burdensome process. This is a post-dispensation communication between the pharmacist and the physician. So that if anything does happen, and Geoff is right, a patient may go on an original biologic and then on a biosimilar, and then eventually may go back on the original biologic at some point, depending on the pharmacy and the pharmacy benefit manager.

And what we want to insure is that when a market-forming event happens, there is 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 are asking for transparency in the system. And it's very difficult for me, as a prescribing physician, to understand why there is such opposition to that, especially since we are a 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 are the only U.S.-based company, with the 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 are asking for.

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

DR. 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 in ten years from now, 15 years from now, we will be talking a different language, but I think that 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 him 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 is what really matters at the end of the day. This is a pro-patient approach, by closing the loop between a pharmacy, 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.

MS. DESANTI: Bruce Leicher, you've been waiting for awhile. And then I'd like to ask a question of Steve Miller and then we will get back to you.

MR. LEICHER: Just to clarify one point, we are in complete favor of transparency of information, we are just in favor of transparency in a manner that doesn't create a 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 of the

pharmacies, and the ability today to 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 is very carefully used by people forming the coalition. They talk in terms of biosimilars when we are talking about laws that are for interchangeable biologics. And there's a big difference between the two products, in terms of the approval at the FDA. The interchangeable biologics are intended to be substituted.

And you know, in terms of the question that you asked, I just want to make one point. One of the fundamental problems with the compromise is that it doesn't define what an interoperable health record system is. 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 their 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.

MR. EICH: That's for brands, too, right?

MS. DESANTI: Excuse me.

MR. EICH: The laws effect the brands and the interchangeable equally.

MR. LEICHER: No, they don't. Because the --

MR. EICH: How so?

MR. LEICHER: -- brands are already signing with a sales force.

MR. EICH: No, no, no. The communication --

MR. LEICHER: Let me finish, Geoff.

MR. EICH: 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?

MR. LEICHER: It does not provide for notice when a biosimilar is prescribed, for example. Let me just --

MR. EICH: But we've already agreed the pharmacy doesn't have discretion. We had that conversation --

MR. LEICHER: I understand that and that's one of the competitive problems, is it creates a

scenario where a doctor is --

MR. EICH: But when it's an interchangeable, it's --

MS. DESANTI: Okay, guys.

MR. EICH: -- it just --

MS. DESANTI: All right, excuse me. Jeff, Bruce, we've got a lot of material to cover.

So Steve, you mentioned Surescripts, and that has been referred to here, so could you please describe how that works and to whom it's available?

DR. MILLER: Thanks. I'll just make one comment before I start and that is, you've already heard from the two pharmacists and I represent a pharmacy, a system already exists. You don't need a compromise, you have an existing system that is 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 PBMs and the pharmacies about a decade ago. And it is just pipes that communicate between doctors, pharmacies, PBMs.

So we currently have over 500,000 doctors that are enrolled in Surescripts, we have 65,000 pharmacies, we have all 5,500 hospitals. And 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 that 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 messages. Some of those systems are so immature they can't express even the formulary that a patient is 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 organizations have trouble consolidating the 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've lived over my life and the idea that you are going to have a comprehensive pull of all of 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.

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

MR. EICH: Bruce, do you want the Tennessee bill?

MR. LOTT: I have it memorized.

MR. EICH: Okay, good. We'll get the prior notification right this time then.

MR. LOTT: I worked on that legislation when it passed down there and I believe that, whether it is 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 is 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 is working to develop biosimilars as well.

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

MS. DESANTI: Please do, please do.

MR. LOTT: -- parts of your question, I'd be more than happy to just 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, you know, so called bio-betters as well. And as a result, this type of notification requirement is not really relevant in those types of scenarios, so it does bring into 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 has undermined competitive -- could undermine the competitive market that generates the 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.

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

DR. SHACTER: Is this working? Okay. Yeah, I'm a little bit confused by someone's comment that we know less about biosimilars than we do about other protein products.

Of course we know less now because we don't have any yet and we 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, especially for -- well, and as well for protein products, especially as well.

So I'm really confused as to why they should be treated differently when they are 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.

MS. DESANTI: This is exactly the question that I thought we should move on to now, which is, okay, if these prior or post-notice 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 is prescribed be recorded 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 the question then 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 those. Yes.

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

Pharmacists are relied on today to be -- it's where physicians go when they want to know what drugs have been prescribed by other physicians, are there drug interactions with prescriptions from other physicians, anything about whether 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, you know, it's the pharmacists right now that make sure that the patient gets the right drug at the right time. And I think it's very

important that we recognize that there is 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, you know, not looking at the big picture.

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

DR. MILLER: No.

MS. DESANTI: Okay.

DR. GAL: So a comment about this issue of adopting earlier -- and this is referring to what Sumant was saying and the question that was asked earlier. 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 this drug for 20 years, you are offering me the same drug at less money for someone, not for me, not for my patient, why should I use it?

And further, why should I use the drug from a generic company when there is this innovative company which keeps investing R&D dollars in my therapeutic area and in inventing new drugs. So why should I ever use a biosimilar?

So doctors don't really have a lot of

incentive, or historically they did not have a lot of incentives, to like low-cost options. It's just an unnecessary risk they have to bear.

So we ended up getting increasingly more concerned about the overall cost of healthcare, 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 required to use biosimilars, they have less and less incentive and you begin to add disincentive to participate in this market.

Obviously, that has to be balanced with true safety issues. So if one exists, and I'm not the expert in whether one exists or not, people here on the panel 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, they actually required fairly good pressure from payers to get doctors to try and experiment and begin to use biosimilars. And frankly, in the United States, I expect that an 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 are the ones that can go to every physician and begin to argue that the logic that they

use 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.

MS. DESANTI: Okay. Aaron Kesselheim?

DR. KESSELHEIM: I just wanted to make the quick point that I think it is also -- I think that the transparency and the accuracy of the medical record is important, but it's also important who actually wants to know the information.

And in the case of the interchangeable, you know, 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 -- the 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 patient -- or the individual physician, who only has a very small number of patients.

And I think this was a point that Geoff

brought up earlier was that, I mean, 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.

I just wanted to make that point.

MS. DESANTI: Okay, Sumant and then Mark and then Jeff.

DR. RAMACHANDRA: Okay, just a clarification to Emily's comment. I am not saying that the communication to the physician is for biosimilars only. We are talking about biologics and interchangeable biologics, too. Both are part of that communication, I just want to make sure.

And at this point, a designation of interchangeability on a 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 today to the same as a small molecule, okay, in terms of everything exactly at that point where the molecule is made. That's the only point I'm making.

This is for the field of biologics and not

about just biosimilars. Both are subject to communication.

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

But let me go back to the issue about the sales force, 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 aids those companies that don't have a sales force.

If it's multiple different types of approaches in different states, then you are 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 in -- it will 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 will have data around that. So the knowledge base you have about the safety of a biosimilar is actually greater than it is the original biologic that you watched years before.

And the question is, why is pharmacovigilance coming up now when biosimilars are being launched? I mean, we have the same issues for years on this and how do you differentiate a biologic or any other drug? And I think if we are 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 is there and so we track down to the lot? It's the lot that is important, not that you name it some 47 letter word that the physician will never know. It’s the lot, you have to trace it, we've got technologies to do that. Let's talk about how we do that, from a safety perspective, that applies to all biologics.

So I think that there is -- when you talk about pharmacovigilance just for biosimilars, it is a little bit challenging to understand why it is arising now.

MS. DESANTI: Okay. Geoff.

MR. EICH: And I'd like to just echo, take right off from where Mark left off and also Aaron. It's really important that everybody understands how pharmacovigilance happens in this company.

So UPenn cites it at about 90 percent, FDAs office of epidemiology at 95. 95 percent 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 is really important to know is that that is 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 sort of our 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 underscore that. There is no question about these products.

The question is, what if one lot or one-half lot of one manufacturers product sits on the loading dock too long and 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 know 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 it may not be anything to do with the individual sponsor or their product. That's the question.

And it's not a question of NDC or a distinguishing name or the ability to have a complete record. The point is, do all of them. There is 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.

MS. DESANTI: Okay, we are going to get into pharmacovigilance and the naming issues in detail this

afternoon, so I am going to move on from that.

MR. LEICHER: Can I just make one comment about the substitution issue --

MS. DESANTI: Of course.

Mr. LEICHER: -- which is that I -- 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 it is to allow the doctor to look at a system like Surescript, which is universally available, if there is a need to know what was dispensed and look it up. And then you are not providing any differentiation, discrimination, disparagement.

MS. DESANTI: 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.

DR. MCCAMISH: Ronny, do you know anything about this?

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

DR. MCCAMISH: I'll share some slides this afternoon that goes to the naming component of why have additional names to it. And our basis of this is about 200 million patient days experience in Europe with our products and worldwide. And Europe does not use a different INN, so it's the same INN throughout Europe.

And reporting it, it gets back to the spontaneous events that Geoff was talking about. When it is a spontaneous event that the doc reports or the patient reports, generally 99 percent of the time it is the brand name that is used. They don't use the INN. 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 you know, now that Norway is trying to sponsor a switching type of study to really do this -- but this happens in the sense of tenders.

In certain countries, there is a tender that

goes forward and the company may win that tender. It is often not just the lowest price, but it is price, as well as quality, as well as delivery, as well as -- and other types of things, because a country doesn't want to get a product that then the manufacturer runs out of it or can't provide it, 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 the treatment of kids, et cetera. 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, you know, biosimilar. The next year, we lost that tender, so they were all switched back to the originator in that sense.

Again, it's not perfect, because we are not prospectively studying every patient that was switched, but with the databases that are available, there is no sign of adverse events, I'm told, from that switching component.

We've 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 and, as Steve mentioned, they

document very well what products the patients are on.

And in patients coming into that study, only 22 percent were on the same product for the last six months. We had patients on 17 different products for six months prior, so there are switches going on and it is based on tender and other types of things.

Now, we 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 -- and there was no relationship to switches versus efficacy. So if it is related immunogenicity that causes an interference with efficacy, there is no data to support that.

So our experience is fairly robust that there are switches that happen. There is 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 are following it.

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

MS. DESANTI: You wanted to --

DR. RAMACHANDRA: We are the second company that actually, within the panel at least, actually sells biosimilars in Europe and our experience mimics Sandoz' almost exactly and we have 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. In that, we have not actually seen any untoward safety signals that have come there.

But it is important that we did that for a variety of reasons. It is important that we did that because it actually built up our database and our confidence, because as 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 registry and market authorization.

So that is our commitment from a Hospira perspective and that is a commitment we have to make for patients to safely drugs and the ongoing safety of the drugs that are out there on the market.

And we did see the same -- if we think the U.S. is complicated, Europe is not about states, it's different countries and each country handles it's own

way. And you'll 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 -- I get the first, along with our partner Celltrion, the first molecule antibody biosimilar approved in Europe which is infliximab biosimilar, our brand is Inflectra. And in that experience, we have 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, and I'm a full proponent of extrapolation -- in fact, that is one of the foundational basis 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 are still asking for data, what do you think is going to happen in the U.S.

community?

And that's why I talked about this being a transition point. In ten years from now, we are going to have a very different conversation in the U.S., but today our conversation has to be based on scientific data and clinical data to drive confidence and communication. That is what we are stressing. Not that biologics are different than anything else, or biosimilars are different than biologics, but you have to build the market and the confidence and data, not opinions. You hear a lot of opinions, but data actually drives that confidence, not suppositions and going out there and saying, trust me, I'm great.

MS. DESANTI: Okay, Geoff.

MR. 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, it 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. It's 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 are taking one product, but the root cause is actually a product they've taken before, you have to have the data.

I mean, 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.

MS. DESANTI: Bruce.

MR. LEICHER: Just one very quick point with regard to --

MS. DESANTI: Can you get closer to your mic?

MR. LEICHER: 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 U.S. biosimilar.

So when we're talking about the notification and the need for this, it sounds as though we've heard fairly clearly that there are very limited issues or problems, but even in Europe, we are talking about biosimilars and not interchangeables. We are talking, in the U.S., about applying notification to interchangeable biologics, which is a higher standard. And I think it's important to keep that end of the context.

DR. MCCAMISH: I think that's a good point. And I just wanted to add 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 wanted to go back to Geoff's point on this. Geoff, the only thing that is a little bit disingenuous about this is the timing. Because the issue with Eprex happened ten years ago and, if it was an issue there from a labeling perspective or you wanted to change it, and you felt that the product was being falsely attributed to you, why now?

MR. EICH: That's a great question.

DR. MCCAMISH: I mean, that's the only issue

that makes it a little bit challenging.

MR. EICH: And I think it's important for everyone to consider this.

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 have 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 have 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 U.S., 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 U.S.

We don't have to learn all of these lessons all over again in the U.S. 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 interchangeables that are going to be absolutely everything that the FDA says they are going to be, but at the end of the day, every one of them is a biologic medicine, vulnerable to all of 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.

MS. DESANTI: Okay. One question that I want to get out. There is, in some legislation, there is a requirement 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 --

MS. 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 and there's really no reason to have that be a state by state issue. The state board's don't have any special knowledge about interchangeability of medications.

MS. DESANTI: Marissa?

MS. 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.

So 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.

MS. DESANTI: Okay. 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?

MS. 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 any other prescription. There's no reason to have a separate amount of --

MR. EICH: We would totally agree with that. That's been our advocacy as well, 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 if there is something that takes longer, if it takes longer to manifest, that there's a record. But really just matching existing statute is perfectly sufficient.

MS. DESANTI: Does anyone disagree with that?

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

MS. DESANTI: Yes, Emily.

DR. 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?

MR. EICH: So is that interchangeable, biosimilar, or in your parlance --

DR. SHACTER: Any.

MR. EICH: -- the virtual

interchangeabilities?

DR. SHACTER: Any biosimilar.

MS. SCHLAIFER: It would depend on how the prescription is written. So if it is written, assuming that we are looking at one naming and not suffixes or prefixes right now --

DR. SHACTER: Might be a wrong assumption.

MS. SCHLAIFER: Right. So if it was written with one name and specifically it said I want to provide this drug by Sandoz and you use the reference drug and you are changing 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 it was the referenced product or the biosimilar product, would meet that name and that definition. So there would not need to be any notification.

DR. SHACTER: 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, who are my very close colleagues, and asked, where is 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.

DR. MCCAMISH: Just one quick question for the pharmacist and Steve.

MS. DESANTI: Sure.

DR. MCCAMISH: I mean, you've got a lot of experience to come to bear on this. The question is, and 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 Florida? Totally different there, in terms of those, and the risk of being very conservative in some states?

I just don't know. Do you balance that? And what do you think about that in terms of when you are weighing this, in a sense of pragmatism?

DR. 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, pharmacy is regulated at the state level in the Tenth Amendment of policing.

And so we are always going to have differences in the state. We have it on narcotic regulations and recordkeeping. We have it on many other substitutions of different drugs as we've heard in Tennessee or others, and so we're used to dealing with it.

We'd like it to be most standardized. We believe that, in this particular case, the FDA has the knowledge on this and the FDAs ruling 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 marketplace.

MS. DESANTI: Okay, Geoff, you can have the

last word.

MR. EICH: Sure. I think the first point is that we are very, very proud of the work that we've done with our biosimilar development programs. We are 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 has 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 is an expectation of the same clinical result in any given patient and that there is 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 are 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.

MS. DESANTI: Okay, Geoff, I'm sorry. You're not going to have the last word. 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 U.S. 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 U.S. versus your profit margins as you currently have them on biologics in the U.S.?

MR. EICH: So a couple of questions. I'll just take them in order.

As we discussed with you, we've made publically clear our six biosimilar portfolio. All six

of those products will be designed and developed to be marked worldwide. Those are obviously biosimilar candidates and, like I said, I think I mentioned earlier, three of those six are in pivotal trials now.

I am 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 very important, is that our scientists are learning a tremendous amount about these products. The development of biosimilars has been, for an R&D organization, manufacturing, and process development organizations, really quite profound in terms of what we are able to learn and we are 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 U.S. 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 U.S., and then we have challenges around the world because biologics are absolutely in great need in many of the regions of the world.

MS. DESANTI: Okay, thank you very much. Thank you all for your patience. We will start again at 1:35, because we ran five minutes late. You need an hour for lunch.

(Whereupon, there was a recess for lunch.)

ROAD MAP TO AFTERNOON PRESENTATIONS

MS. JEX: So good afternoon, again. I'm Elizabeth Jex, an attorney with the Office of Policy Planning for the Federal Trade Commission. I want to thank you all for coming back for the afternoon presentations, which will be focused on naming and pharmacovigilance.

As many of you are well-aware, policy makers in the U.S. and internationally are debating whether the existing paradigm for naming medicines should be used for biologics and follow-on biologics or should be changed.

Currently, reference biologic medicines in the United States have at least two names, a proprietary branded trade name and a nonproprietary name that reflects certain scientific characteristics of the product. Some parties argue that patient safety can best be protected if biosimilars and interchangeables have unique or distinguishable nonproprietary names that differentiate them from the reference biologic's nonproprietary name.

Others contend that unique or distinguishable names could diminish the viability of competition from biosimilars and interchangeables and thereby deter companies from investing in the development of such

medicines. They further argue that different types of patient confusion, resulting in possible patient harm, could result from the use of unique or distinguishable names for every biosimilar and biologic.

These issues intersect with the current pharmacovigilance system in the United States. This system aims to keep track of what medicine a patient receives so that it can be identified if it has caused a problem. The choice of what to do about nonproprietary names for biosimilars and interchangeables could affect how incidents involving biologics, biosimilars, or interchangeables would be reported.

By way of background, the term pharmacovigilance is derived from the Greek word pharmacon, which means drug, and the Latin word vigilare, which means to watch over. Doctors and their patients, pharmacists, manufacturers keep watch over drugs and other pharmaceuticals in the U.S. through a voluntary drug safety program overseen by the U.S. FDA.

The FDA receives some adverse event and medication error reports directly from health care professionals, such as physicians, pharmacists, nurses and others, and consumers, such as patients, family members, lawyers and others. Health care professionals and consumers may also report adverse events or

medication errors to the product's manufacturers. If a manufacturer receives an adverse event report, it is required to send that report to the FDA, as specified under regulations. The FDAs adverse event reporting system collects these reports in a database.

Our speakers this afternoon will describe how nonproprietary names have been used to date for generic drugs and their views on whether unique or distinguishable nonproprietary names should be used for biosimilars and interchangeables. We are looking forward to a lively debate.

Now, let me introduce the speakers who will educate us on these issues this afternoon. To begin with, we will hear from Angela Long and Tina Morris, who will provide further background information on drug naming issues.

Angela is a Senior Vice President of Global Alliances and Organizational Affairs and Executive Secretary of the Council of Experts for the U.S. Pharmacopeia.

Tina Morris is Vice President, Biologics and Biotechnology in the Global Science and Standards Division at the U.S. Pharmacopeia, which she joined in 2003.

Next, Mark McCamish, Global Head of

Biopharmaceutical Development for Sandoz International, a division of Novartis, will discuss his company's experience with biosimilars and how naming affects market penetration and customer acceptance in European markets.

Gustavo Grampp will then provide a perspective of a leading reference biologics manufacturer, Amgen, on naming issues. Gustavo is a Director of R&D Policy at Amgen.

Next, Sumant Ramachandra, Senior Vice President and Chief Scientific Officer for Hospira, will discuss naming issues and the worldwide development of the biosimilar market. Hospira is a leading provider injectable drugs and infusion technologies.

Following Sumant, Helen Hartman will discuss a case study of adverse event reporting. Helen is Director of the Worldwide Regulatory Strategy at Pfizer.

Next, Emily Alexander will discuss the views of AbbVie, a reference biologic producer formed in 2013 after it's spin-off from Abbott. Emily is the Director of U.S. Regulatory Affairs in the Biologic Strategic Development Group at AbbVie.

We will then hear from Alan Lotvin, an Executive Vice President of Speciality Pharmacy for CVS Caremark. Alan will discuss whether the

pharmacovigilance system, rather than the naming system, needs to be modernized and strengthened to protect consumers.

Finally, Harry Travis will offer the perspective of a private insurer on the growth of speciality pharmaceuticals and naming. Harry is Vice President and General Manager for Aetna's Specialty and Home Delivery Pharmacy.

Following these presentations, we will have a short ten-minute break. Following that, we will have a one-hour moderated panel discussion on naming and pharmacovigilance. To introduce that panel, we will have a brief presentation by Neal Hannan, who recently joined the FTC’s OPP Office from the law firm of Boies Schiller, where he was an intellectual property litigator.

At the conclusion of this panel, Andy Gavil, the Director of Office of Policy Planning, will share his concluding remarks. He is on leave from his position at the faculty of Howard Law School and is a leading scholar in antitrust, who has written and spoken extensively in the U.S. and abroad on antitrust law and policy.

So to begin our afternoon, I'd like to invite Angela Long to begin our presentations.

INTRODUCTION TO DRUG NAMING

MS. LONG: Thank you, Elizabeth, and thank you for including USP in this important discussion.

I am here to give you a primer on nomenclature in the U.S. I will talk a little bit about INN, we've heard a lot about INNs throughout the day so far. And I know a lot of you probably know and understand USPs role in naming, but that's not something that maybe not all of you do understand, so I'm hoping to clarify what the law states about naming in the United States and how USP is involved there.

I bring greetings from USPs new Chief Executive Officer. He joined yesterday, otherwise he would have been here. You can expect to see him in these future forums on these topics. His name is Ron Piervincenzi and he joins us recently from Biogen Idec and then before that McKinsey & Company, so I'm sure you'll learn more about him in the coming weeks and months.

And I do want to also say, for those of you who don't know much about U.S. Pharmacopeia is that USP is a non-government, standard setting organization. Most other pharmacopeias in the world are within the ministries of health. USP is not. There is only one other pharmacopeia, and that's Chile, and they modeled

themselves after us. So being a non-government pharmacopeia has its pluses and minuses.

I'm going to give the primer on nomenclature and then Tina is going to come in and really talk more about some of the scientific aspects and challenges as we go forward.

So as Elizabeth mentioned, here on the screen you see a label, a drug label. And we're talking about not the brand name that you see in the middle there, but the nonproprietary name that you see there. As you can tell, USP initials follow that name. That's not always the case, it's not required that USP initials appear there.

But let's first talk about INN and why those come about. Obviously, as drugs come through the pipeline in innovation, there is a point at which it becomes necessary to give it a name, as it starts emerging as a prospect, a therapeutic prospect. And so companies go to UNN and USAN, which I'll get to, to identify a name for it. And it's far in advance of when these products come to market.

So for the INN, the international nonproprietary names, it is sponsored by the World Health Organization and they are obviously facilitating those names and identification of substances. And so

it is drug substances that they're naming. And they are unique names and they are recognized to varying extents globally. So a regulatory authority has to take up an INN.

It's important to note that the U.S. does not follow INN and it doesn't have a role in federal law, but you'll see that we do follow the U.S. Adopted Names, USAN. We work very closely, the USAN works very closely with INN. But USAN is sponsored by practitioner organizations, the American Pharmacists Association, the American Medical Association, and USP, and it was started about 50-some years ago, and FDA participates. And AMA is the secretariat and USP publishes the book of USAN, the USP dictionary. But as I mentioned, INN is separate from USAN, but we do work together. Again, focusing on drug substances only.

So as this, you know, because so many drugs go to USAN and INN early in the pipeline, some of them do not emerge from the pipeline. So 75 percent of USAN that are published do not become therapeutic drugs.

And this is just a typical USAN entry, it's in your slides. You can kind of see what it does, but it does recognize the other nonproprietary naming authorities like INN or British Applied Authority of Names, JAN, Japanese names, as well.

And to go back to my example, here's the USAN entry for Insulin Human. And you can see that it shows the date that it was initiated. This is one that didn't have that big lead time ahead of the approval, but it gives all of the information that you need in the very beginnings of a drug entity.

So with the relationship with biologic naming is that, yes, INN and USAN have been working very closely together. We use very similar approaches for naming biologics and you can see there, in the sub-bullets -- and I'm going to try to speed up here, so Tina has enough time to talk.

But the biosimilars debate started -- at WHO started last spring and sort of carried on into the fall. And we're hearing about biologic qualifiers that WHO is now proposing.

But I want to talk more about USPs role in naming and so that comes through the Federal Food, Drug and Cosmetic Act. And it's very, very important to note that, you know, this role is grounded in law. I have some slides later that show you the provisions that those are in.

But if there is an already applicable standard in USP, when a drug is approved, then it is important that that drug meet the monograph

characteristics and also have that same official title.

If there is no applicable monograph when the drug is approved, which happens all the time, the FDA actually creates what’s called an interim established name. The established name comes later, with USP, when USP creates a monograph.

Now, USAN creates names for drug substances, but USPs role is broad, very broad. It applies to both drug substances and drug products and so that's important to note. And it also covers the biologics that are licensed by the Public Health Service Act. And these -- these branding and adulteration provisions do apply to the Public Health Service Act.

So the -- you know, FDA and USP have been working closely on these naming activities but it's important to note that this role, USPs role, in naming does not really come about until there is a monograph elaborated in the USP. And that is what USP is doing primarily. It's in our general notices that we indicate that.

So here are the details of USP in the law and they are in your slides, in your packet. But I wanted to show you now kind of how that role plays out. So in -- applying to both drug substances and drug products. And you can see here, again, my example of a drug substance

monograph and a drug product monograph. You see the route of administration has been added to the drug product monograph. And this is how it relates to the name in the monograph.

So this is an important link that the identification test links back to the name. And that links to publically available product quality standards and tests and criteria. And that's probably the most important aspect of USPs naming rule.

And how do we do this? We have expert committees. And it's not just one, we have a nomenclature safety and labeling expert committee that works on the naming, but they also work very closely with the scientific expert committees that establish the quality standards in the monograph. And throughout this process, we work very closely on naming with the FDA, in both the naming committee as well as the scientific monograph development committees.

It's also important to note that, for nomenclature, the nomenclature committee are practitioners who are out in the field, physicians, pharmacists, nurses and others who really know -- are connected to patients and know what patients need when it comes to drug product names.

So our perspective on biosimilar naming is

obviously we don't have a role in brand names. Those are determined by the Agency with the innovator company. But unique brand names, as biosimilars come on board, may be okay. Once a biosimilar is approved, if that drug meets the identification test of the monograph, it should use the same title. So it's very, very important. And Tina is going to elaborate on the science there.

And as we just heard in the recent panel, we certainly encourage FDA to pursue the idea of an Orange Book or list with states. That would certainly be a good idea, USP supports that.

So with that, let me turn to Tina to take you to our scientific piece.

DR. MORRIS: Good afternoon. Thank you, Angie. I'm going to go a little bit deeper on what goes into the scientific considerations that set up the naming recommendations at USP.

I am going to put a boundary assumption up there, just to make it very clear what the role of USP standards are. They really are a critical subset, but by no means an all-comprehensive set of parameters that describe the quality of an article in commerce, including a biologic.

We think that it can be a helpful resource to

the regulator in a licensing decision and I think there are examples for that where USP has monographs and then, later on, we know FDA has referred to them, but they are not intended for that purpose.

Why do I say that and why is it important? There are cases where a USP monograph under the same title and the same name, may describe multiple articles in commerce that differ in specific aspects of their licensed attributes that are not covered in the monograph. So the monograph can never be this all-comprehensive thing. So FDA may very well prescribe additional standards that are material to an article's sameness.

Going back to what Angie already introduced to you, that the key concept also that is very important to our naming is the compendial identity. And this is the direct quote on what identify means in the context of the compendium. It's taken from our general notices. "Compendial tests titled identity or identification is provided as an aid in verifying the identity of the article, as they are purported to be and to establish whether it is the article named in the USP-NF."

What does this mean for biologics in practice? I'm giving you the Somatropin example here,

together with the primary sequence obviously. And Somatropin in the USP and monograph has two identity tests, chromatographic purity, by separation HPLC, high performance chromatography, peptide mapping. The key here is that, for identity, usually several orthogonal tests that probe different aspects of the molecule, different attributes of the article, including the primary sequence, are used to identify what the article is.

In the case of biologics, in many cases there is an additional bio-identity test that speaks to the functionality of the product, which is very important as well.

I also used the Somatropin example here for you because it's an interesting course because there are seven products in the U.S. market right now and they have all come on to the market via the 505(b)(2) route.

The challenge -- I was specifically asked to talk a little bit about glycosylation and the challenges of glycosylation analysis in micro-heterogeneity. I think scientifically, a lot of people are in agreement that once you have a protein sequence, with today's technology, it's not very difficult to verify what it is. Glycosylation is not a template-driven process, it's much more complicated and

it is much more variable and susceptible to changes that can occur during the molecule synthesis for anybody.

And it may or may not matter for the protein or for the article whether it is glycosylated or not, in terms of how the article behaves. So it may or may not be a critical quality attribute.

One important thing that I want to point here, that a couple of speakers have already pointed to this morning, including Emily, the size of your magnifying glass is important. How well you see micro-heterogeneity depends on how well you can look, it depends directly on your analytical technology, and that technology doesn't stand still. Not for the manufacturers, not for the regulator, and not for the compendium.

This is an example that is well-known for Epo, where by isoelectric focusing, for example, you cannot distinguish between epoetin and alpha and beta. And so clearly, in this particular analytical test, you would say they are the same.

So what's USPs experience to date? We have a lot of experience with biologics, with very complex biologics. You heard about Enoxaparin this morning, we have a monograph for that, and for many others,

especially naturally-derived biologic in the recombinant therapeutic field. We have a couple of enzymes, but we have no monograph that actively addresses glycosylation, but we are currently considering one.

So what would our expert committee look at in a case like that? So they would obviously -- the science expert committee, as Angie told you, would consult with the nomenclature committee. They would look at the existing USAN naming precedent and other compendial standards that exist. They would consider the proposed tests, their specificity, and their power -- their resolving power in the context of the entire monograph. And they would also recognize that -- reconcile their recommendation with the existing naming practice that is already in the compendium for biological medicines.

And that, in a nutshell, is the science piece for naming at USP.

Thank you.

EFFECT OF NAMING ON COMPETITION AND INNOVATION

DR. MCCAMISH: My thanks to Elizabeth, Susan, and Erin as well, in terms of organizing this twice for us. It's a pleasure for me to be here.

Let me run through these slides really quickly to comment about naming and will it have an impact on uptake and competition. And the answer to that is yes, it will. And I'll present data around this. This is not my opinion, it's data that we have regarding the impact of naming on the uptake.

So first I'll talk about just a little bit of background in biosimilar development, because it bears on the topic. And I always start out talking about access. Access drives need, in terms of providing these wonderful biologics to patients that need them. And these are data that say that access is not uniform and there is inadequate access. I have family members that have not had access and it has had an impact on their lives and most of you have had that own experience, so it's a driving process. This is why I'm so passionate about what we're doing and trying to make it happen and push it forward.

The development of biosimilars, it's important to understand, that it really turns the world upside down when you're talking to a key opinion leader

or a physician or someone who is familiar with biologic or drug development.

Usually, as you see with the triangle, the upside triangle on the left, you will see that an original drug or a novel drug is based a lot on the clinical data. So you do your characterization, your talks, your PK, animal studies, pharmacology, et cetera, but the basis of it is clinical trials, large clinical trials that prove statistically safety and efficacy.

Now, when you go to the biosimilar, it's on the right-hand side, and talked about by Emily earlier, where the base is an analytical characterization, PK can be often pivotal, and the clinical trial is a confirmation of similarity. Now, if you talk to a clinician about your wonderful biosimilar clinical trial, they will look at that and scratch their head and say, well, what are you guys doing? Because they don't know what confirmation of similarity means, they don't know what the analytical data was, where there was a regulatory judgment that this was similar enough that you could use an abbreviated clinical trial to be there.

My point in sharing this is that it's very easy to convince a key opinion leader, knowledgeable

physicians, that a biosimilar is only similar and not the same and it connotes some risk of the product itself. And so it's easy to sway clinicians in that way.

This is a slide by Christian Schneider. He's the head of the Biosimilars Working Party at EMEA, a very well-known individual, just documenting the number of manufacturing changes in a normal biologic. These are not biosimilars, they are marketed biologics. And you see that it varies, in terms of the number, of manufacturing changes. You can see for Remicade or infliximab about 37 different manufacturing changes.

My point in showing this is regulators evaluate these changes over time and they know these changes will, in fact, lead to some clinical effect. And they are only approved if the manufacturing change has no clinical -- no expectation of a clinical difference that's there. Scientifically, it's valid to do this. There's nothing wrong with it, we are just showing that this is what happens.

And also, there is variability, even within a single biologic, batch-to-batch, with batch-to-batch variation. So it's key to understand that identity is not an issue with biologics. And people that say that

the biosimilar is not identical to the originator product are just using that to cast fear in that. And having a different name helps cast that fear that it's not the same, that it's not the same drug substance. So that's something to consider.

Now, EMEA has a lot of experience in this area and they've talked about similar but not identical and that it is a paradigm associated with all biologics. And it should not be used to fear biosimilars, because the original biologics are not identical to themselves, based on the changes that have happened, but there has been a regulatory determination that they are "the same" as the originators, without any significant clinical effect.

And the revised EMEA Q&A that recently came out really validates the principles of biosimilarity in this. If you read through, it says, "The active substance of a biosimilar and its reference medicine is essentially the same biological substance." And if it is essentially the same biological substance, i.e., its variability overlaps with the variability of the originator, why would you call it a different name?

There has also been, as Sumant will mention, been a biosimilar Mab approved in Europe and this was

just taken from the label. And you can see what it says under number one, that I underlined, Remsima contains the active substance called infliximab. It is not the active substance modified, it is the active substance called infliximab. So they are using the same terminology.

And in Europe, you use the same INN. There is no differences in INN with the various products.

So the biosimilar concept works in terms of we have a lot of experience with this in terms of our drugs on the market. We've penetrated a lot of markets. Zarzio is now the number one G-CSF in all of Europe by volume, it has surpassed the originator. So the uptake is substantial and moving forward. And each of our products are the number one product in the world as biosimilars. And there has been 18 other products approved in Europe and they all bear the same INN as the originator.

And then I had mentioned that, in fact, our Remsima is already approved by the FDA. And even complex biosimilars can be developed successfully today for this.

So we're talking about naming. So the USP presented this, basically it just says that these are the names. You see Genotropin and Omnitrope, just two

examples of somatropin. You see the label here having the brand name, the INN, the manufacturer, the NDC, lot number, J code, all of this identifies the product. And does it make any sense whatsoever to change the INN for a biosimilar? Where in that is it going to provide additional information for either pharmacovigilance or for the physician to know what drug they are using? It's just not necessary and there is data to back that up.

So here is our experience, if we talk about safety and adverse events. Even just our data, up until about a year ago, it would be about 200 million patient days now if you look at it, but the same data holds out. And essentially, we track how much the INN was used in spontaneous reporting, when a physician, nurse, patient reports an adverse event, how do they report it.

And you can see in all of the data, there is maybe one or two cases where the INN was used and all the rest are with the brand name. In the first category, you see Binocrit, which is erythropoietin, only 1 was reported by epoetin alfa, which is the INN. Omnitrope or Somatropin, same. We received 8 reports by the INN, but 6 of those were by the health care authority because everybody reports to the health care

authority for spontaneous events and then they report to all of the manufacturers of these and they use the INN for that. And the same for Zarzio, very few in terms of reporting via INN.

So by modifying the INN, it will not have a significant impact on pharmacovigilance.

So now what about penetration? Here is data from our U.S. marketed Somatropin, Omnitrope. This is a biosimilar every where else in the world, in the U.S. it is a 505(b)(2) because they didn't have the biosimilar route at the time. And you can see, this is competing with seven -- there are seven somatropes on the market, each one is a unique product, has the same INN, and none of them are biosimilars.

You can see, compared to Enoxaparin, which is approved as an AP substitutable complex product, we have about a 17 percent penetration. And that may not sound that great, but that's the second most prescribed growth hormone, because there are seven on the market. So it had very good penetration with the same INN and competing with the remainder.

And from a pharmacovigilance perspective, you heard from Steve earlier, no problem in terms of pharmacovigilance there. So although not 50 percent penetration, the same INN is helpful, in terms of using

the product.

Here is an example from Australia. Australia has mandated that a biologic with a glycosylation requires an alternate INN. So here you can see the traditional generic penetration in Australia is about 50 percent, you can see on the right-hand side you have filgrastim. Filgrastim is a non-glycosylated product and therefore it has the same INN. Epo is a glycosylated product, so TGA forced us to use a different INN. And you can see the penetration difference, 25 percent down to 2 percent, about a ten-fold decrease in penetration when you have to use a different INN. So data really shows that that's an issue.

The same in Japan, although the rates of generic penetration in Japan are very low, it still has an impact, the penetration for a biosimilar are really miserable. And you have to use a different INN or a different name there as well. So again, data showing you that there will be a difference.

In Europe, the same INN, we've been able to have a huge uptake. It's country specific, as was mentioned earlier by Ronny Gal, but overall, as I mentioned with G-CSF, we are the number one short-acting G-CSF in all of Europe right now. And you

can see that, not only have we had good penetration with the same INN, we've dealt with access. There's been a 30 percent increase in the use of the drug by volume because the cost has gone down. So we've accomplished that as well.

And so before we -- and I've got a couple of slides for summary, each biologic product is clearly identified by its brand name. INN identifies the active substance and is not suitable for product identification. The INN doesn't tell the physician what indication to use, it doesn't tell what dose, it doesn't tell anything specific. It is just saying what the active substance is.

A different INN for biosimilars leads to confusion of physicians, discrimination of biosimilars, and it does impact affordability and patient access.

The current naming system for biologics works well and should not really be dismantled.

So I have a couple of back-up slides. This one deals with drift and I want to quickly go over it. We had a little talk about it earlier. This is a slide from Christian Schneider as well and it presents our data, which was published, showing manufacturing changes.

If you go to the top right-hand corner, it's

a slide basically showing a manufacturing change with Enbrel. And you can see, in the far right top, where the light blue dots are very, very consistent until there's a manufacturing change and then there's a shift in that glycosylation.

So there's two things you can see here. There's no drift, it's very, very specific and very consistent and then there's a manufacturing change. So this whole concept of drift, that you're not going to have control of your biologic and it is going to drift somewhere and that you have no clue where it is and it's going to be totally different and now you've got a different product than the biosimilar because there's all this drift, doesn't happen.

If you have a loss of control of your manufacturing, you have to come in to regulatory authorities and say, listen, I can't release product because it no longer meets my release specs. So drift is really a non-issue. There are step changes, there are manufacturing changes, but not really drift, in that sense.

And then two slides. Basically this is from the Alliance for Safe Biological Medicine, it makes me feel nice and comfy. But taken directly from their website, this is data from the survey they do, and key

findings from the survey include 53 percent of surveyed physicians in Europe felt that an identical nonproprietary name implies identical structure, which would not be the case.

61 percent of surveyed physicians said that identical, nonproprietary names implies that the medicines are approved for the same indications, which is not the case.

24 percent of reporting physicians record only the nonproprietary name for biological products in their patient record. I'm not sure where that data comes from, because we showed you that it is the brand name that is used in terms of communicating.

And so all of this says -- it demonstrates the need for distinguishable, nonproprietary names to be given for all biologics. And how these products are named will clearly play an important role.

My only point is that, the term identical is abused to instill fear and foster misunderstanding. That one can take advantage of leading questions and misinformation in a survey to produce a desired outcome. Naming does, in fact, matter. And using a different nonproprietary name does communicate a different product, which it's not supposed to. And different nonproprietary names will cause doubt in

health care providers, which is the desired outcome of some.

Thank you.

INDUSTRY PERSPECTIVE ON NAMING CONVENTIONS

DR. GRAMPP: Good afternoon. I'm Gino Grampp, Director of R&D Policy at Amgen and a member of our biosimilar team.

I've been involved, most of my career, in manufacturing of biologics and that includes designing new processes for biologics, managing process changes post-approval, and also overseeing quality investigations where, at times, we've learned new things about our biologics years after they were approved.

Based on this collective experience, I know that biologics should not be treated like generic drugs for the purposes of naming, traceability and manufacturer accountability. So if you are looking for consensus among biosimilar manufacturers, as we were discussing this morning, you won't find it with this topic.

I'll spend the next few minutes discussing naming in three important aspects. First, the nature of biologics, the very nature of them, means that related biologics can be distinguished. And we believe that if they are distinguishable, then they should be distinguished. Second, naming is important to the long-term traceability of these products. First, any

biologic, after it is approved, as well as long-term, over its life cycle. And third, distinguishable naming does not necessarily impact market uptake.

So let's start with the science, the fundamental nature of these biologics. They are complex, they are large, they are sensitive to their conditions, they are made of living things, and they are variable.

Why does this matter for naming? As they are large and complex, that means it is difficult to define exactly their microstructures. As they are made of living things, it means that scientists like myself can't always predict how processing conditions could affect their quality. And as they are variable, which we've just heard quite a bit about, they are variable because they are composed of multiple components. They are variable within batches and between batches. And it is difficult to define precise boundaries for what is and what is not a given active ingredient. Instead, we have approximations.

So these three factors currently make it scientifically impossible to say that two active ingredients are the same. You can say that they are essentially the same, but you can't say that they are the same. And also, it is impossible to say that any

given drug substance will remain the same over time.

So how does this apply to naming? Well, prior to biosimilars, naming organizations have provided distinguishable features for related biologics, reflecting their different origin and nature of manufacturer, reflecting different glycosylation patterns, slight sequence variations, and other structural features.

So these rules have been taken into account for years. Oh, and I should mention, we heard about glycosylation, so that is particularly important as we talk about biosimilars, because it is something that is not templated, as Tina mentioned, and we have seen variation in glycosylation among products over time. Also, glycosylation can possibly affect safety and efficacy, so it's important to keep track of that.

So the INN rules, and other agencies like USAN that have applied these types of rules, have a common core to reflect common structure and function, so that prescribers and patients and others know about that, with a distinguishable feature. But this is not just about taxonomy -- there is a broad policy consensus that biologics should not be treated like generic drugs for the purposes of safety monitoring.

So regulators currently accept that, for

off-patent chemical drugs, that safety data can be safely aggregated across the whole class without specific regard for manufacturer-specific data. But it's clear that policymakers in the United States, Europe and elsewhere do not accept this paradigm for biologics.

We heard a lot about this this morning, but why have special rules for biologics? This is coming from the regulators that watch these products and they understand their complexity. So there may not be a consensus yet on specific policy measures to achieve this policy -- but there is consensus that biologics need to be tracked to the individual manufacturer.

So what are the implications of this in the U.S.? First, as we heard from Elizabeth, manufacturers in the U.S. are legally obligated to track the safety of their individual products and to report that to the FDA. In fact, 90 percent of reports in the U.S. originate, coming to the manufacturer first and then go to the FDA.

Second, some would argue that the pharmacist will know what product was dispensed. And I think that's the case, but the reality is that prescribers are in the best position to recognize an adverse drug reaction and, indeed, most reports in the United States

come via the health care provider.

Third, although brand names appear to be working very well in multisource biologic markets right now, there is no requirement going forward, and we're talking about a long-term plan here. There's no requirement that brand names will be used in the United States for future biologics or interchangeables -- biosimilars or interchangeables. In fact, there is a trend towards increasing use of nonproprietary names for prescribing, this being encouraged in medical schools and, because of computerized order entry systems, prescribers are seeing drop-down menus with the drugs listed by the nonproprietary name. So this is -- it could increase in the future.

So it's vital to patient safety, to the manufacturers who are accountable for the safety data, and to the FDA that the reporters that are providing these safety reports have access to all the information they need to identify the product. And that needs to account for all the different settings of use and all of the different circumstances, so we think that means that you need brand names, when they are available, that's the best identifier for a specific product; distinguishable nonproprietary names, when those may not be captured in a record; and other codes,

especially for pharmacists that have good access to them.

So how does this apply to biosimilars? It means the naming conventions that work well for generics do not apply. So we've shown that it is difficult to precisely define the identity of biologics, of related biologics. And indeed biosimilars, under U.S. law, are neither required nor expected to be identical to the referenced products. And I'm not saying that is a reference to any concerns about safety or efficacy, it's just not required to be the same. And there are no requirements to evaluate biosimilars against each other, either analytically or clinically.

So what's the consequences of that? You just need to look at the record so far. The record for biosimilars that have been approved overseas, there are differences in glycosylation between those biosimilars and the reference products and among each other. Furthermore, as developers, such as Amgen and other companies, pursue increasingly complex products, the possibilities for diversity could increase. So naming really cannot be used as a surrogate for interchangeability of all of these products just because they have a related structure.

So I just described the situation at the time of biosimilar approval. When you consider the life-cycle implication for biologics, for multisource biologics, it gets more complex.

So as I mentioned, the products start in a place where there is already some structural diversity. It is not clinically meaningful, those differences, but they may not be interchangeable. But now after time, process changes can occur and the history shows that that has occurred for reference products or originator products.

Those changes could be subtle, they may not affect the comparability of each product with each step, but you could end up with divergence of the products over time. Some of that might be significant, some of it might not be.

Add to that the fact that these products are immunogenic, and we heard about that also this morning. The immune response is natural for these large complex molecules. In most cases, there is no safety issue, but there are variable effects, in terms of safety and loss of efficacy for some of these biologics.

Some of these effects are very rare, so they won't be captured pre approval for the biosimilar or the interchangeable and some of them take months to

appear, after a patient would have been administered the drug. So it's important to be able to track this in the context of multiple products, some of which could be diverging from the others, some of which could have different, rare immune response than the others, not because there was anything wrong with the original manufacturing process, but just because of an unexpected outcome. We need to be able to track these individually.

So adverse event reports -- thank you. Adverse event reports will not be able to capture this product-specific information if there is a loss of information anywhere in the chain from prescribing, through dispensing, recordkeeping, et cetera. So if a common, nonproprietary name is used for prescribing, there is already ambiguity from the beginning in the patient record about what medicine the patient will receive. If the pharmacist has discretion to dispense various medications under the provisions of the institution or the pharmacy, there might be further ambiguity.

If those product identifiers are not captured in the medical record, that is accessible not just to the pharmacist, but to the prescriber, how will it get into the adverse event report? So we believe we need

to take into account that pharmacists, prescribers, and patients could all be sending in these adverse event reports and they need to have access to redundant -- or multiple sources of specific and retrievable information. That means brand names, when they are available, nonproprietary names that are distinguishable, and other codes, when that's appropriate.

So I mentioned life cycle challenges. I won't dwell on this slide earlier. You heard the example earlier today about the PCRA investigation in Europe. The key thing is, in order to complete this investigation, investigators in Europe -- and identify the suspect product, they needed to reconstruct the patient histories for each of these patients. And they had good records, because each of those products had distinguishable nonproprietary names and brand names and they were able to do that. So it was a rare event, but European policymakers took notice of that. As Geoff said earlier, the immediate policy response was to put warnings and precautions into the labels of all of these erythropoietin products in Europe that says that you must record -- or prescribers should record the exact brand or trade name of this product and make sure that that's reported through to the agencies.

But they went beyond that, as Geoff also mentioned earlier, Europe has now codified that into law for all biologics, biosimilars and biologics, that the brand name or trade name should be recorded in the prescription and tracked all the way through to the adverse event report. So this shows that policymakers do take this seriously and that biologics need to be treated differently than generics.

I mentioned earlier that, for generic chemical drugs, there has been an aggregation of safety signals without regard to specific manufacturers. What's the consequences of this? This is a figure from a recent publication showing the safety reports for a product that lost exclusivity.

As we know, generic drugs are very successful with regard to market uptake, a significant market uptake after loss of exclusivity. And from a safety monitoring perspective, this would be fine, as long as the share of adverse event reports similarly migrated commensurately with the market share. This is not the case.

In this case for Zoloft, the adverse event reports reported to the originator brand increased after the loss of exclusivity. So that means that the vast majority of reports went to the wrong

manufacturer.

We believe that there are data, contradicting what Dr. McCamish said, that distinguishable names have not impacted market uptake in biosimilar markets overseas and we will be presenting more data than I have here in our submission to the FTC docket. But just in this case, for Australia, we looked at the uptake of two different biosimilar classes last year, G-CSF and erythropoietin.

G-CSF shares a nonproprietary name with the originator product and Epo does not. It's hard to distinguish that there is a meaningful difference in uptake between these product classes in Australia. So it really is -- excuse me, it's coverage and reimbursement policies that dominate the uptake in these markets.

So a broad cross-section of stakeholders also share these views that distinguishable names are important. Surveys of prescribers in Europe and the U.S. show that 80 percent of those responding believe that there should not be these identical, nonproprietary names for biosimilars. Although some payers clearly oppose this policy, in a survey of payers, 93 percent of those responding in the United States believe the same thing, that the nonproprietary

names should not be identical for biosimilars. And policymakers overseas have also implemented policies toward this end, including in Japan and Australia, where they have rules for nonproprietary names.

So in closing, we have shown that the nature of these complex medicines dictates that they need to be treated differently than generics, and that's justified by global experience. Biosimilars have already demonstrated that they have differences, analytical differences, from the reference products and from each other. The quality of biologics can diverge over time, can evolve over time, and even diverge for products that shared origins. Product-specific safety monitoring will remain critical throughout the product life-cycles and this is best accomplished by distinguishable names.

So we believe that the U.S. biosimilars program will thrive with these policies that encourage accountability and transparency and instill confidence in patients and prescribers.

Thank you.

LESSONS FOR THE U.S.:

BIOSIMILAR MARKET DEVELOPMENT WORLDWIDE

DR. RAMACHANDRA: Good afternoon, everyone. My name is Sumant Ramachandra and I'm the Chief Scientific Officer and head of R&D for Hospira, which is an injectable company that found it's core actually out of generic injectables as well as infusion devices. So we operate actually both in the technology space, with integration to electronic medical records, as well as in the generic space.

About six or seven years ago, we made the decision -- a little bit over seven years now, that we made the decision -- of getting into biosimilars in Europe because we knew that the laws were being passed and that the regulation was ripe for our entry.

So I will be giving a brief discourse on our experience in Europe and what we have learned from there and how we are applying that to the United States. First and foremost, why is this even an important topic? I mean, there's a lot of money involved here. It starts with Bs, billions. That's why there is a lot interest. Is this about patients? Absolutely. But there are a lot of billions to either defend or to capture, right? So there is going to be a lot of discussion, a lot of stakeholders in that

process and we have to understand that these billions have come from innovative products that have really benefited a lot of patients, but it comes at a cost. It comes at a cost of access, at times. It comes at a cost for the fact that many people either can't afford this, so access becomes an important issue throughout the globe.

So as the biosimilar pathway started getting defined, because legislation started getting passed, many of the markets, starting with Europe, started opening up to the concept of biosimilars. People understood the state of the science was there to make a product as similar as possible to the originator product that met the regulatory hurdles in those particular markets.

So here, in this particular slide, you can see what the size of the game is over here and that many of these drugs are going to face biosimilar competition by the end of this decade. And this market is still growing by a growth rate, a compound annual growth rate of close to 9 percent. So there is no slow growth in this particular market. And obviously as originator companies come up with new innovative drugs biosimilar companies will come with options for the original drugs in the past.

It's important to note that biosimilars are not generics. I am going to emphasize that multiple times. I said it in the panel earlier, I am going to say it now, and I'm going to say it in the next panel again. Biosimilars are not generics. And people who try to use the generic paradigm to push this forward are not doing it a service. And that requires us to think about some things very, very carefully.

We are speaking from the experiences we have had in Europe, not just in a simple biosimilar called filgrastim or a more complicated one called erythropoietin, or even a more complicated one that we are launching right now called infliximab, or Inflectra is our brand, this is a progression of science and understanding the science, and we have to apply those particular rules.

But it also takes a lot of money to develop these drugs and we have to ensure that this is not a market about just driving to the bottom most cost possible and it is not going to mimic the generic market, because that will kill the biosimilars market, also.

So you have to get an even ground where the access is given to patients, but not the price that goes so low that there is a disincentive to actually

participate in this market. Anti-competitive behavior can go to both extremes, okay? So we have to be careful, in both extremes, to make sure that this is a viable market.

I made the comment before, we are in a market formation mode. In a market formation mode, you have to ensure that you actually keep your eyes peeled for things that occur at both ends of the spectrum.

And what people call a compromise, I call a consensus because we are taking disparate ideas and moving the agenda forward. People can put the stake in the ground at either end and not move anything forward -- but you have to move the field forward because, at the end of the day, the people who benefit the most are the patients.

So in this slide, you can see the differences, as I mentioned, between a small molecule oncology drug like Paclitaxel, Filgrastim, and monoclonal antibody, just based on size in itself. And size does matter in this field and you have to actually show that you are actually deriving the benefit of biosimilarity based on these complex proteins.

So Hospira has done a lot of work in this area. We made a commitment very early on that we are not going to treat this as a generic field. And here

in this pyramid paradigm that first narrows down, just like everyone has shown you, but actually opens back up, we do have the responsibility of developing this in a responsible fashion. And biosimilars are compared at every step of the way to a precedent molecule. The originator, by being an originator, does not have to compare itself from a structural perspective to the originator molecule because they are the originator. We have to compare ourselves to the originator molecule.

So our science has to show at each and every step for the extensive molecular characterization to the preclinical data to the pre-registration studies, we are comparing ourselves to someone and that is the originator. And the rigor has to be there. And the registration studies are done for confirmation purposes so that one has confidence in this particular data.

And by the way, clinicians do ask for substantial data when we go visit them. They do ask for it. Not because it's not scientifically proven, it's just that clinicians take comfort of knowing that you have done the adequate tests. And we have done those in the case of epo here. And then our commitment to post-registration studies in the case of epo for Europe because there are rare events for epo that you

want to track in the post-market setting. All of this does cost money, but we made the commitment to do that when we joined into this particular field. And over time, the dialogue will change as more and more people get more comfortable with biosimilars, but also as the science continues to evolve more and more.

So this is the sample data, just to show you that, at the end of the day, the originator product and the biosimilar product are virtually identical. They are not exactly the same, but there is batch-to-batch variability with the originator product by itself. You take a lot of the originator product and you try to reproduce it exactly the same the next time, it's not going to happen.

So therefore, there is inherent variability when you actually make biologic products, whether you are the originator, making the same product or a biosimilar product making it as compared to the originator. There is going to be inherent variability in the manufacturing of this particular product.

But what is shown very clearly is that if you apply a substantial number of orthogonal tests, looking at the same product from multiple angles, you ensure that it is highly similar to this originator product and therefore meets the basis of biosimilarity to get

an approval by the regulatory health authority through a number of tests that include analytical similarity, pharmaco-bioequivalence, as well as clinical efficacy and safety.

But it's not enough to get a product registered and then disseminated to the health care providers and patients. There is a responsibility for post-market tracking. That is where you will pick-up signals that could be rare in nature or, as Mark has pointed out multiple times -- it can happen to a specific lot in a loading dock. So you can't pick that up unless you are doing very good pharmacovigilance.

And what we do in this particular model, just to take an example, is that you have to set what your normative baseline should be and then you trend around that. And using advanced statistical technologies, you should be able to pick-up events that occur with that particular product. And the good thing about being a biosimilar is that you have years and years of history from the originator product, because you are virtually similar to what they are. And you have to trend and track for those known events, but also be sensitive enough to pick up sentinel cases of brand new events that could occur in the marketplace. So a robust pharmacovigilant system is extremely important.

Now, regardless of what people have said, our data actually does match Sandoz data. We actually looked at our data base for our two products in Europe, filgrastim, which actually shares the INN, so we call it Nivestim, the brand name, as the original product and we have an epoetin product that has an epoetin zeta. It was based on the fact that our partner, when they applied for an INN a long time ago, WHO did not have guidelines at that point for INNs for biosimilars and it got a zeta instead of an alpha after it.

And in both cases, regardless of whether it was a distinguishable INN or the same INN, you see that the records are identifiable greater than 95 or 99 percent of the time and the identification is by brand name. So mucking around and trying to change the INN is not the solution of getting you to a higher pharmacovigilance in this particular setting. There are cases where a distinguishable INN could be allowed, but not in the case of biosimilars in general.

I will tell you the market effects -- thank you very much, five minutes, the market effects of the distinguishable INN. In Romania, they have not approved a new INN category for reimbursement since 2009. What does that mean for Hospira? It means that epoetin zeta cannot get reimbursed in that market. But

Binocrit, which is the epoetin alfa, which is like Retacrit, it is a biosimilar to epoetin alfa, the originator, has obtained reimbursement.

So there are actually unintended consequences to things as simple as names that we have to actually consider what the market consequences are.

In Italy, we have been excluded from tendering of epoetin alpha batches and have gone through a very lengthy and expensive legal challenge to remove this restriction. And it's been successful over time, but it has delayed the uptake of our product.

And in Spain, despite legal challenges, we continue to be excluded from epoetin alpha with tenders in some regions and that is obviously delaying the uptake of Retacrit.

So you have to also consider the unintended consequences of simple things, such as names. So what does that mean? In the market, despite all of those hurdles, biosimilar companies, because of the rigor of the science, have been able to show data as improved market uptake, but it is not showing the data by just getting approval and then handing it to a distribution channel or getting to the physician for a prescription. We have had to make calls to those physicians from the medical science perspective, or from a sales and

marketing perspective, because people have questions. And prescribing physicians, as well as pharmacists, need to know that they can trust the data of the drug that they are giving.

So here is an uptake of the various -- for epo uptake as well as G-CSF uptake. And the uptakes are very different, based on a number of factors including clinical factors as well as competitive factors in each of these particular markets, but the market is evolving. The number of biosimilars are going to -- companies are going to increase in the market and it is actually going to increase the uptake of biosimilars over time. Increased competition will come and I think the train has already left the station on biosimilars. The market is going to form, the question is what is the slope of the uptake of the market curves at this point. The dominant player at this point, in these two categories, is Sandoz with Hospira being second player, for both Epo as well as for filgrastim.

Now, I want to show you this chart because it shows you that each country in Europe is very, very different. And how perverse incentives in a place like Belgium, to prescribe for high cost drugs, can drive almost no biosimilar uptake and therefore no health

care savings.

Or a heavily bid tendered market, where the entire country switches over, like Hungary, where it can switch from brand to brand every couple of years, where they will have a massive biosimilar uptake. So policy does make an impact. And the work of policymakers is to ensure that it's a fair and balanced field, it doesn't tip one way or the other, but allows for the appropriate competition practices and open access for patients who really do need this drug.

And then people have asked me multiple times, well, what's your market? I mean, the originator company already established the market, there's really no money for you because you are not doing anything new.

I will tell you in this case example in the U.K., when filgrastim was introduced at a more competitive price with high quality, people switched over from peg-filgrastim dosing to filgrastim dosing. You started getting patients from more access and people who were not eligible before, from a cost perspective, started getting access to biosimilar filgrastim. That is the prize -- patient access with high quality medicines introduced by competition.

And what could be, for Europe, some of the

savings? As you can see in this chart, this was published by -- it was published in 2012 and it shows that there was a minimum, over this time period of 2007 to 2020, of 11 billion dollars but it can go up to 33 billion dollars. In my opinion, this is an under-estimate. It is going to go more than that. In the U.S. alone, it can be potentially 250 billion dollars of savings and that is going to make a huge difference in terms of over a long period of time, but a huge difference in terms of health care costs.

And then lastly, I just want to point out that we recently got infliximab approval in EMA -- they got approval for moderate to severe plaque psoriasis in adult patients, yet the NICE technology assessment from the National Institute of Health Care Excellence in the U.K., which was published in 2008, says that it is only approved for reimbursement if the condition is very severe.

So where is the market? The fact that reimbursement doesn't actually match the approval is the market. You suddenly have, in the U.K., a number of patients, because NICE will have to do a reassessment when the new pricing model comes out, where they will find that, regardless of whether it is the originator or us or someone else who drops the

price, when they do the technology assessment, more patients will get access. And that benefits the patients who actually need it.

So I am going to skip over the next slide, because Steve Miller and Sandoz have gone over it. I just want to make sure that we go over the lessons from our learning.

So our introduction actually of biosimilars led to better patient access. A high scientific bar does need to be set, because it leads to trust and greater acceptance of biosimilars amongst payers as well as providers. So you set the bar at the scientific level and all other things in the market will follow.

Shared INN names reduce the chance of health care provider confusion and does facilitate patient access. And providers who are educated, and education is key, on biosimilar safety and efficacy become comfortable prescribing biosimilars. Health authorities have a role in this, as well as do the sponsoring companies and other government authorities.

Biosimilar competition thrives in markets where government policies set fair and even playing fields and fair rules need to support strong and early market formation and recognize the difference between

biosimilars and small molecule generics, not to incentivize higher-priced products and not to drive to extremely low products. That's important.

To reduce the cost of development and bring better access, extrapolation must be accepted. I can't emphasize this enough. Without extrapolation, this market becomes financially untenable in many ways, because then you have to do every single study every single time. So health authorities have a very key role, as well as do sponsor companies.

And stakeholder information campaigns must provide unbiased biosimilar education.

The reason I brought up the two points before is that we need to get to some middle ground on certain topics because there is a lot more to discuss on biosimilars. This is just the tip of the iceberg. If we get stuck in our extreme cases, we are not going to move the agenda forward, which is better access to high quality medicines.

Thank you very much.

LOOKING INTO THE FUTURE BIOSIMILAR LANDSCAPE:
A CASE STUDY

DR. HARTMAN: Good afternoon. My name is Helen Hartman and I'd like to thank the coordinators for this opportunity to share our views on naming.

Pfizer is a manufacturer of both innovator biologic drugs as well as biosimilars, and so we are committed to the development of both types of products. In fact, we have five biosimilars in the pipeline and active INDs. Therefore, Pfizer has previously called for a balanced, science-based approach to biosimilar naming and labeling.

Specifically, each subsequent entry biological product should have a distinguishable identifier. For example, either the USAN or INN name, followed by the manufacturer's name and/or trade name. In addition, it is important that the biosimilar have its own label containing a prominent statement regarding its biosimilarity or interchangeability status with regard to each indication. A distinguishable identifier, either a different nonproprietary name or a trade name, is essential to safeguard patient safety and is really supported by the regulatory science.

To inform Pfizer's current position on the

INN debate, we conducted our own internal research on two case studies that provide insight into the world of AE reporting and the traceability of manufacturer information in the U.S. Unlike previous studies that looked at spontaneous reporting systems, such as FAERS and the EV, which is really looking at the end of the reporting process, we concentrated our research at the beginning of the reporting process and really looked at the reports coming in to our internal database.

The first case study that we looked at was for a biologic in which there are multiple branded products with the same INN. These are not interchangeable, nor subject to pharmacy substitution, and are administered by the physician or they are self-administered. This case is very much analogous to a future biosimilar landscape in which you have multiple branded biosimilar products with the same INN.

A second case study that we looked at was for a small molecule in which there is a branded product, as well as multiple generics on the market, all of them having the same INN. Again, this case study would be more analogous to a situation where you have a future biosimilar landscape, where some of the biosimilars are branded and some of them are not, but they all share the same INN.

The primary objective of our analysis was to determine the frequency of cases containing identifiable manufacturer information in Pfizer's global safety database. A secondary objective was to determine the frequency of cases, which specifically included the national drug code information.

We started by analyzing all U.S. spontaneous cases. In other words, we excluded non-U.S. cases and we excluded cases that originated from the literature or post-marketing studies. And then we looked to see how many of these cases actually had identifiable manufacturer information, in order to be able to group it into either a Pfizer-identified product, a product that is identified by another manufacturer, or products that have no identifying information other than the INN or the generic name.

We further went on to look to see how many of these cases actually included the NDC number. Again, this data is a little bit different from what you've seen in other cases, simply because we are looking at the primary reports coming in. Thus, it is very much reflective of the reporting practices by physicians and patients.

When we look at the data for a small molecule, what we found was that, roughly 83 percent of

the time, we were actually able to correctly identify that it was a Pfizer product or were able to identify the manufacturer. However, that still left about 14 percent of the time when there was no manufacturer identified and we simply had to group it by its generic name.

Interestingly, when you look at these cases, and we looked to see if NDC numbers were provided, we found them less than 2 percent of the time. And when we looked further, one-sixth of those names -- those NDC numbers that were actually provided were inaccurate.

So really this goes to show that, irrespective of whether the NDC is recorded at the pharmacy level, it is not being captured and actually reported as part of an AE case.

Next, we looked at the data for a biologic and what we saw was dramatically different. In fact, what we saw was that, in about 99 percent of the cases, there was identification of the trade name. And just to remind you, this is a case where you have multiple branded products on the market, all of them sharing the same INN. Less than 1 percent of the time did we not -- were we unable to identify the manufacturer.

Despite this, again, we did the same research

and we looked to see if we could find the NDC code. Less than 10 percent of the time was there actually an NDC code provider and of those, about 30 percent of those were inaccurate.

So in reviewing the data from the small molecule, we find that 14 percent of reported cases have no identifiable manufacturer information. From this, we conclude that the use of non-distinct INN in the absence of distinguishable trade names does not really allow for AE reports to be accurately linked to the manufacturer. Therefore, a distinguishable identifier, either a trade name or an INN, is critical.

In contrast, when we looked at the biologic case study, we saw that less than 1 percent of the AE cases had no identifiable manufacturer information. Therefore, distinct trade names or brand names do allow for more accurate reporting to the appropriate manufacturer, irrespective of the INN in a setting in which all similar products have a distinct invested trade name. And that's a very important distinction to make because, at this point, it's not clear that global agencies would actually require a manufacturer to have a distinct invented trade name.

Given that pharmacovigilance is global and the naming system should also be global, there are

issues of practicality and enforceability of a system in which some products are branded, some products will choose not to be branded, may have unique INNs or may share the same INN.

Therefore, in the absence of a specific requirement for a trade name, dual identifiers are critical. And really, the necessity for this dual product-specific identifier is reflected even in the revised pharmacovigilance directive, which mandates that reporting information include two identifiers, a trade name and a batch number.

So one of the questions that -- one of the issues that has been brought to bear on this topic is whether the NDC number can function as this additional product-specific identifier in the U.S. Based on our data, we would say no. Our preliminary data showed that NDC numbers are rarely reported and may be inaccurate. It may be possible that the NDC numbers are somewhere in the system, but it is not getting to the level of AE reporting. And that's critical to understand.

Therefore, a distinguishable INN-based identifier, in addition to a distinct invented tradename, would help ensure accurate AE reporting.

So in summary, a balanced, science-based

approach to biosimilar naming and labeling is needed. Any naming policy for biosimilar products must be a viable, long-term solution that adequately addresses safety issues and also anticipates the future biosimilar landscape. This future biosimilar landscape will include some products that are biosimilar, some that are not biosimilar, some that may have invented trade names, and others that choose not to have invented trade names, and may share the same INN or have different INNs.

More importantly, in the absence of a requirement that all biosimilars and all follow-on biologics adopt unique trade names, then it is very likely that the identification of manufacturers in AE reporting will be hindered if the products share the same INN.

In other words, the debate really isn't whether trade names are effective for AE reporting, they are effective. The problem arises if all of the companies don't -- if everybody doesn't have an invented trade name. In that situation, where you have some companies that have invented trade names and some who don't, and all of them share the same INN, we are really left back at the same situation as the small molecule case, where you will have a pool of AE reports

with no identifiable manufacturer information. Therefore, a distinguishable INN plus a specific brand name would increase the accuracy of AE reporting.

Thank you.

REFERENCE BIOLOGIC PERSPECTIVES ON NAMING

MS. ALEXANDER: Good afternoon. I'm Emily Alexander and I'm the Director of U.S. Regulatory Affairs within the Biologic Strategic Development Group at AbbVie. AbbVie is a global leader in biopharmaceutical innovation and we are supportive of the entry of biosimilars in the United States, as they will present safe and effective options for patients.

We are very much appreciative of the efforts that both FDA and FTC have made in seeking public input on some of these regulatory issues related to biosimilars over the past several years.

My presentation today will focus on the complex topic of how nonproprietary names can affect spontaneous adverse event reports, reports of suspected product side effects that are submitted to the FDA after a product is initially approved and reaches the market.

Spontaneous adverse event reporting is a key part of the overall pharmacovigilance process. Effective pharmacovigilance is critical for all biologics, including biosimilars. All new prescription medicines come to market with the safety database that is limited to the extent of the pre-approval clinical trial program. In some cases, for all products, rare

but potentially serious side effects may be missed. In addition, the manufacturing process for all biologics is very complex and sensitive to even the smallest variations in materials, processes, and conditions.

Although these changes are very tightly regulated in the United States, it is not always possible to fully predict the potential effects of a post-approval manufacturing change.

Finally, some biologics are biologic device combination products, which means that device malfunctions or unexpected interactions between the biologic and the device component may occur and these need to be identified in the marketplace and reported as well.

The key to effective pharmacovigilance is being able to link a specific adverse event or trend in adverse events with the responsible product. Without this ability, we might fail to notice a new adverse event or, even more likely, a new trend in adverse events that is associated with a specific product and that can pose real threats to patient safety.

We know from our research at AbbVie that attributing adverse events to the responsible product, meaning the product that the patient actually took, can be especially challenging when products share the same

nonproprietary name. The research that I am about to describe was published in 2013 by the Food and Drug Law Institute and has been referenced in general in some earlier presentations today.

AbbVie worked with a third-party consultant to look at adverse event reporting trends for eight small molecule branded products, both before and after the entry of generic competition. The adverse event reports were pulled from the adverse event reporting database which is known as FAERS.

Just some quick background on FAERS. It collects spontaneous reports that are send to FDA by manufacturers, most of the time, but also patients, pharmacists, physicians and others. FDA may contact a company if it believes that an income adverse event report represents a new or serious side effect that could change the overall safety profile of the product, but FDA does not generally review incoming adverse event reports to gather additional product identifying information, to confirm that the adverse event was attributed to the correct product, or to correct any errors that might exist in the product identifying information.

So as you know, generics and brand name drugs in the United States share the same nonproprietary

name. We know that, after a generic enters the market, the number of patients taking the brand name product drops dramatically. So you would expect that the number of adverse events attributed to the brand name product would drop at least in rough proportion, but for six of the eight products that we've looked at, this was not the case. The number of adverse events reported for the brand name product remained roughly the same, or even trended upward, after generic entry. This means that the adverse event was being reported as being caused by the brand name product, when in reality the patient was most likely taking a generic version.

Let's look at a specific example. You can see that the number of prescriptions for branded Zocor drops dramatically after a generic enters the market in 2006, that's the orange line. But the number of adverse event reports, the blue line, remains roughly the same even many years after initial generic entry. This misattribution of the adverse events results effectively in the pooling of adverse event data for products that share the same nonproprietary name.

Our research also established that product name, whether brand or nonproprietary, is often the only information in an adverse event report that meaningfully identifies the product that the patient

took. For example, 90 percent of all FAERS reports across drugs and biologics do not have lot numbers. Although there is a slot on both the voluntary and mandatory adverse event reporting forms for the NDC number, National Drug code, that number is not included in FAERS reports that come out of the FAERS database.

However, we know that NDC and lot number are mixed up in some cases, and so a very, very small portion of the FAERS reports actually do include the NDC number, although it is reported as the lot number.

This is why relying on other types of product-identifying information, such as NDC or lot number, may not be sufficient to support pharmacovigilance. And again, to echo what we heard earlier today, simply because NDCs may be prevalent in the pharmacy systems does not mean that they are reaching the reporters, who are primarily patients and health care professionals, physicians.

To be clear, our research on the misattribution is from the generic drug context, because there are no approved biosimilars on the market in the United States. But the FDA has repeatedly recognized the risk of misattribution of adverse events in the biologic context as well.

As many of you know, within the last two

years, FDA has approved three originator biologics that were in some way related to a previously-approved originator biologic. And in each case, FDA gave the later originator a related but distinguishable nonproprietary name. And in each case, FDA reasoned that that was necessary in order to facilitate pharmacovigilance and reduce the risk of medication errors.

For example, in the case of tbo-filgrastim, FDA concluded, "Unique nonproprietary names will facilitate post-marketing safety monitoring by providing a clear means of determining which filgrastim product is dispensed to patients."

We've also heard a little bit today that the focus on naming and pharmacovigilance for biosimilars is a new, made-up topic that all of the sudden we've come up with. And I'm here to tell you that that's not true.

Just a brief example, in 2007 and in 2008, when biosimilar legislation was being debated in the United States, the Department of Health and Human Services and the FDA wrote letters to Congress saying that biosimilars should be assigned distinguishable, nonproprietary names in order to facilitate pharmacovigilance, so this is not a new topic.

One of the main areas of focus of the naming debate, if you will, both here today and more broadly, is whether distinct brand or trade or product names, however you want to say it, will help to facilitate pharmacovigilance. And unique brand names for biologics will help with accurate identification and traceability.

But there are at least three potential limitations to relying on distinguishable brand names as the primary means for assuring accurate attribution. First, as we've heard today, FDA does not have explicit statutory authority to require that products use a brand name in the first place. This is in contrast with the situation in Europe, where regulatory authorities have authority to do that and have exercised that authority. In addition, FDA has recognized that adverse event reports often do not include meaningful product-identifying information beyond a product's nonproprietary name. And it cited this issue, again, in the process of assigning distinguishable nonproprietary names to both ziv-aflibercept and tbo-filgrastim.

The third potential limitation is that prescribing practices are regulated by states in the United States. And we're not aware of any state that

requires that a physician prescribe a biologic by brand name. This means that prescribing can occur by nonproprietary name, though admittedly it is less common in certain contexts.

If two biologics share the same nonproprietary name and a prescription is written using the nonproprietary name, then a patient could receive any one of a number of products. And we heard this confirmed by one of our pharmacy representatives earlier today. If the physician doesn't know which product the patient ultimately receives, it becomes more challenging to accurately attribute any adverse event that that patient might experience back to the responsible product.

Although our focus has been the U.S., and appropriately so today, we wanted to provide a brief global perspective. The role of distinguishable nonproprietary names is critical outside of the United States. There are countries where brand names are prohibited, or strongly discouraged. China is a great example. Some products are not even permitted to have a brand name in the first place, so of course you could not prescribe by brand name.

And these practices outside of the United States are relevant in the U.S. Each year, FDA

receives a significant portion of adverse event reports that are from foreign-based reporters.

We are running out of time, so I just thought I will skip ahead. All of these considerations, and others that we don't even have time to address today, have led to AbbVie's support for the use of related but distinguishable nonproprietary names for biosimilars and indeed distinguishable nonproprietary names for all biologics.

A distinguishing portion of the nonproprietary name will help to facilitate pharmacovigilance by helping to improve the likelihood of that accurate attribution that I talked about earlier. But if a core portion of the nonproprietary name is the same, this will allow adverse events to be pooled across a product class, if that is appropriate in a given case.

Related names would also signal to health care providers and patients that these products are indeed related, which is appropriate to do. I don't think you'll hear anyone, certainly not today, but hopefully not in the broader conversation, suggest that a biosimilar should have a fundamentally different nonproprietary name than its reference product.

Importantly, distinct nonproprietary names

will not prevent patients from having access to biosimilars. Just one quick example, because I know we are running out of time. In Japan, where biosimilars must use both a distinguishable, nonproprietary name and a distinguishable product or brand name if you will, the biosimilar version of epo alpha now has over 40 percent of the market based on sales volume. That's just in three years post-launch and in the absence of an interchangeability designation.

I think we can all agree on two things today. Patients deserve to have access to these life-changing therapies, including biosimilars. But the second thing is that every adverse event matters and every adverse event needs to be counted. The benefit of a policy of distinct, nonproprietary names is that both of these things can happen, we don't need to choose.

Thank you.

CUSTOMER PERSPECTIVE ON CONSUMER SAFETY, ACCESS, AND INTERCHANGEABLE BIOSIMILAR COMPETITION

DR. LOTVIN: Hello and thank you. My name is Alan Lotvin and I am a cardiologist by training and I currently run CVS Caremark Specialty Pharmacy.

I just want to -- I would like to put this in context a little bit, why we are so passionate about this. What our industry exists to do is really to create a marketplace, or one of the things we exist to do, is to create a marketplace among manufacturers to create the access to the best products at the lowest possible costs. And we do that by minimizing the differentiation among products that are not that important.

So I'm going to give you our perspective. And our first perspective is that, you know, biologic agents are incredibly important. No one is going to deny or debate the impact these have had on human health, on patient quality and length of life. That is -- and the industry deserves a tremendous amount of appreciation from any of us in this room who might have, at one point, become ill.

Having said that, we have to be sure that these products become available to all people at all times. And my group has direct responsibility for over

700,000 patients who receive these products. I can tell you, a substantial part of the time that the 3,000 or 4,000 people I have who work on this do is trying to assess and help patients get coverage, get copay assistance, get through the financial barriers associated with this, with these products.

If you look at what has happened in the market in the U.S. over time, the blue bar represents the trend, the spending year over year, associated with traditional pills, tablets and capsules. And you can see the tremendous generic wave that has just crested and run through 2012, 2013, and 2014, has resulted in pharmacy trend rates being negative to low single digits. This is not driven by a reduction in utilization.

When you think about costs, it's pretty simple, right? It's price per unit times the number of units. This is not driven by the change in the number of units, this is driven by the price related to the significant amount of generics that have been introduced into the marketplace.

Now, the orange is a different bar. The orange bar is speciality products. And you'll see a variety of numbers for the trend rates for specialty, it really depends on what your particular definition

is. But if you think of specialty as biologics, we think of trend rates in the 14 to 25 percent range. There is no entity, government, business, that can absorb a 20 percent year over year increase and any input costs for any significant amount of time. That doubles your costs every three-and-a-half years. Not sustainable.

So what's our perspective? Our perspective is how do we create and balance the needs for patient safety, because obviously that's critically important, with the desire to create a robust market on behalf of patients and ultimately payers of these services?

So there are two things that, you know, have come to light a lot and that we are focused on at CVS Caremark and I'll get to those a little later. Naming, which we've heard a lot about in the last few minutes, and the impact of naming on the safety and pharmacovigilance, and can some of the states direct activity to talk to physicians.

First, I want to put the opportunity up there. There is a substantial amount of biologic agents that are losing patent exclusivity over the next several years. And if we approach this market correctly, we can correct the same sort of economics for the ultimate payer of health care that we have done

in the last five to six years for our traditional pills, tablets, and capsules.

And one of the people who I am sort of fond of quoting is a guy named Per Lofberg. And Per used to make the point that for innovative pharmaceutical manufacturers, the only way to continue to be able to pay for innovation is to enable generics to come to market, and biosimilars to come to market, when appropriate. That creates the headroom in the budget. Because again, no input cost goes up forever.

There is a tremendous opportunity in front of us and it is really dependent upon everyone represented -- or all of the entities represented in this room to execute on it.

So obviously, as an organization we support the development of a market. So I'm going to focus a couple of my comments around names. There's been a lot of discussion in the last -- you know, the hard part about coming last in a presentation like this is saying something that's reasonably interesting. The good part is you get to refute whatever you please.

But I think it's really important and I don't think we should underestimate the importance of pharmacovigilance. Well, let's decide -- we can all agree, based on the last two presentations, and I would

agree, that we have a problem with effective reporting of adverse events. I would put to you that the solution to that problem is not adding yet another data field that needs to be accurately collected and distributed. As I said, my role is running the entire organization for CVS Caremark and Specialty. There are 2,500 people who work to dispense these drugs every single day to patients and I can assure you that, not only do we know every NDC that goes out the door and to whom it went to, we know the lot number that it went to.

So as we start thinking about creating this concept that if we don't have -- if we don't have a unique INN so that we can determine -- we can address the variability and response between originator products and biosimilars, I would ask you the question, how do we handle the variability between individual lots from an individual manufacturer. Again, we have that data captured now.

The fact that we don't accurately put it all together, clearly in this system we don't do a good job of putting all information together. But it exists and the system can be fixed without having an additional name with which to burden data capture, data reporting, physicians, and to create artificial

distinctions among products that may only be related to who they are made by, versus what is truly an important clinical variability among different lots. Again, the data is captured today.

So if we don't -- let's look at the downside. If we agree that we can -- if we want to create a better pharmacovigilance system and we agree that it requires better data, let's fix that problem. What's the downside of creating different names? The downside of creating different names is that names have power and people get used to writing things. And I'm a physician and I'm totally guilty of it.

I can go back and tell you, where I trained in New York, if you tell what beta-blocker someone prescribed, I can tell you where they trained and I'll be right 90-plus percent of the time. So names have power and that's why it is really important.

So again, think about do we want the name because we want to be able to track? And if that's what we really want to do, I would tell you that we don't really want a different name. What we want is a better ability to track at the lot level, at the NDC level.

I'm not saying anything that hasn't been clearly said here. I think putting -- you know,

creating proprietary or individual nonproprietary names is really going to create a barrier to effectively creating competition among the manufacturers, to get the sort of economics that I think the payer community and patients are looking for.

And I think it's important to remember, one of the big changes going on in health care, as many of you know, are high deductible health plans. That puts patients at the forefront of that first 6,000 dollars of coverage. That's an incredible barrier to access. So to the extent that the overall price comes down, the overall challenge in meeting those early high copays goes down.

Let's talk a little bit about some of the state-level activities. And I think one of the important things here is some of the discussions around requiring notification of the physicians because of a biosimilar change in dispensing.

On a number of levels, again, why would we want to do this? The hypothesis is the physician wants to know which lot, which drug, which manufacturer is dispensing the product. That's the hypothesis, right? Today, with -- I don't even know how many manufacturers of simvastatin and atorvastatin, no one would suggest that we should call every prescriber of simvastatin or

atorvastatin to let them know which particular brand happened to be carried in the pharmacy that day. And while granted, we can talk about the differences in science, it is still a burden.

So looking at the physician's side, asking physicians to take that phone call is a burden on the physicians. I think if you talk to the physician community, their willingness to want to hear that data is going to be very low.

Then the perspective is the physicians are going to capture that data. And again, you are asking to create a different data capture system than one that exists very well today, that is automated, that handles literally billions of claims a year just by the companies represented in this room, and does it effectively and efficiently.

I just want to use this as a closing slide, just to emphasize the importance of creating the market. This is work from my colleague, Troy Brennan and what Troy did was look at quality-adjusted life years, cost per quality-adjusted life year for effective diabetes control. So you can see, prior to the introduction -- one introduction of generics, 49,000 dollars per quality-adjusted life year, which is quiet -- actually, it's a pretty good number. You

would absolutely go out and to this. After the introduction of generics, 1/50th of the price, 1/50th the price.

And not quite as dramatic, but similar results from the introduction of generic cholesterol-lowering agents.

So again, if we can create the same sort of market in the biosimilars, we may not get the same magnitude, but we will have substantial reductions in the cost per outcome or the value that is created for the dollar we pay in health care costs.

So you know, CVS Caremark is completely supportive of biosimilars, of developing a robust biosimilar market. We also understand the need to maintain appropriate incentives to create new and innovative new products. And we think the balance of creating a vibrant market actually does meet both of those needs, so I'll end there.

Thank you very much.

PRIVATE PAYER PERSPECTIVE ON GROWTH OF SPECIALTY MEDICINES AND NAMING

MR. TRAVIS: Good afternoon, my name is Harry Travis. I am the General Manager for Aetna's In-House Specialty Pharmacy and Mail Order Pharmacy. These pharmacies service approximately 10 million Aetna members. I like to refer to myself sometimes as a recovering pharmacist. I started practicing pharmacy here in the D.C. area in People's Drug Stores, those of you who will remember that, People's Drug Stores.

I want to take a moment and thank all of the prior speakers, for the vast amount of information that has been presented, and the FTC for organizing this event. It's been very educational.

I would also like to echo the speakers who have complimented the industry for bringing us these tremendously valuable medications that have brought great hope and improved lives to thousands and thousands of patients.

But with respect to the fact that I'm the last speaker today, I am going to keep my comments brief and my slides even briefer. I have only one slide.

As the final speaker, I'd like to make one point and that is that the elephant is still in the

room. And that is not a political metaphor for this town. The elephant is the rapidly rising cost and impact of biologic drugs, the economic impact of that cost.

We must create an environment that will allow for a vigorous, competitive market during the post-patent expiration period for these drugs. If we do not, in the very near future, we will face serious budget problems across many segments of the U.S. health care marketplace. And I stand here in support of Dr. McCamish, Dr. Miller, Dr. Lotvin's comments and others along the same theme with respect to naming and state regulations.

Let me share with you some of our concerns from Aetna. This is my slide. We are going to build on this. This pie chart represents our costs, or what we call our spend, for our fully-insured members. And this represents millions of lives and billions of dollars, that's billions with a B. Pretty straight-forward.

So far, last year our drug spend was actually split evenly between non-specialty and specialty medications for our fully-insured members. The classification, the specialty drug, is dominated by biologics, it's about 75 percent biologics is in that

specialty spend, which is driving that. The non-specialty category contains all of the small molecule drugs, either branded or generic.

Now, over the past five years, that total pie has been growing in kind of a mid to high single digits, manageable at that rate for the total pie. But we see the problem when we get inside that. Here, we see that the costs of non-specialty drugs has been growing at approximately 5 percent a year. And recently, it has been even lower. This is due primarily to the very beneficial effect of the introduction of generic medications, the patent expirations of brand name sole-source drugs, many of them billion dollar blockbusters, and the resulting dramatic price increase due to generic drug competition.

However, the majority of this beneficial effect will end in about two years. The pipeline of blockbuster drugs, high dollar volume drugs is about to run dry, so that benefit is pretty much over in about two years.

Now, let's look at specialty drugs. As many of the speakers before have said, this segment is growing at least 15 percent per year. And you can find reports of rates of growth much higher. This is due to three factors. One, the introduction of new biologic

drugs. Two, the expansion of approved indications and finally price increases. As patent-protected, sole-source products, the manufacturers of these products have had a fair amount of pricing power and have raised prices annually in the range of high single digit to low double-digit rates.

So to sum it up, on the left side, we have inexpensive medications, which in many therapeutic categories have gotten more affordable over time, versus on the right side, we have expensive medications, very expensive medications, getting more expensive every year.

And just to sharpen the comparison, on the right side, we are talking about biologics that cost, on average 100 dollars a day. The average is, out of our operation, which is serving millions of lives, is 100 dollars a day is the average. On the left side, it is a buck a day.

So I sometimes like to over simplify this when I speak to people and say that, in the future, there are only going to be two kinds of medicines. There are only going to be two kinds of drugs, real cheap and real expensive. And nothing in between.

Think of a patient who has rheumatoid arthritis consuming 30,000 to 40,000 worth of drug a

year, they are going to consume 1.5 million dollars worth of drug over their life.

And that right side of the pie, 50 percent of the dollars, is being spent on only 1 percent of the prescriptions. One percent of the prescriptions, by extension, 1 percent of the patients are driving 50 percent of the costs. And obviously the balance is on the other side, over here on the non-specialty side.

So I come back to my metaphor of the elephant in the room. If we cannot develop tools to create the competitive forces that gave us so much benefit from generic drugs, three things will happen. And I submit none of them are good. One, patients on these drugs will find it increasingly hard to afford them. Two, the 99 percent of the patients on non-specialty drugs will begin to feel the pressure, due to the fact that biologics will be eating up so much of a given drug benefit budget. They will feel it through their plan sponsor, that could be a private employer, it could be a union, it could be a state, a municipality, and of course CMS and ultimately the U.S. taxpayer. There are only so many dollars available to fund a drug benefit and this dramatic imbalance is causing and will cause major problems.

And finally, the third negative benefit. The

impact is not just on the drug benefit. My final point is that this 50 percent segment now represents 10 percent of total spending, our total health care spending at Aetna. So 10 cents on every dollar is going to specialty medicines. These are the dollars that used to pay physicians' bills, hospital bills, diagnostic bills.

So the rapid cost of biologics is not only going to create problems with everyone's drug benefit, they will quickly start to impact the overall medical benefit. Because right now, this 10 percent segment is the fastest growing segment of our health cost trend, our book of costs. I believe that this is the tip for the spear of the health care cost rate of growth in the U.S.

As I stated, we have benefited greatly from the introduction of generic drugs. We desperately need a similar tool and similar market for the time when each of these biologics goes off-patent.

Thank you.

MS. JEX: Thank you all. We are right on schedule. We will take a ten-minute -- well, we are a little ahead, but we will take a ten-minute break and we will come back at 3:45 for our final panel of the day.

And I just want to thank our panelists this afternoon. They were awesome and it was a pleasure to listen to all of them, so thank you very much.

(Whereupon, there was a brief recess.)

INTRODUCTION TO NAMING DISCUSSION

MS. JEX: Thank you again for coming back. Before our panel begins, we are going to have a very short presentation by Neal Hannan and then we will begin our panel discussion on naming and pharmacovigilance.

MR. HANNAN: Good afternoon. I'm just going to give a brief couple of slides which are more to provoke discussion amongst the panel and it is going to focus on drug safety and pharmacovigilance.

I think everybody in this room is committed to a robust pharmacovigilance system so that we can record, report, and monitor adverse events. Some of today's speakers have questioned the current FDA Adverse Event Reporting System's capacity to serve the goals of pharmacovigilance if follow-on biologics have the same nonproprietary name as their respective reference biologics. In particular, people have argued that adverse events will be incorrectly attributed to reference biologic when they might belong with the follow-on biologic.

But most of the concerns are -- not most, but not all of the concerns raised by today's speakers are unique to biologics. There may be special considerations appropriate for biologics, but the

problems pointed to in today's presentations arise in the context of existing drugs.

If the current system is inadequate, can we identify solutions that would address its short-comings in a way that would also address the pharmacovigilance concerns for follow-on biologics?

Let's start by looking at an example of an existing drug. The low molecular weight heparin, enoxaparin sodium, comes in a branded form known as Lovenox, an authorized generic that does not carry a brand name, and two other generic forms that also omit a brand name. Each form of the drug bears the active ingredient name on its respective label.

If an adverse event were to occur and the doctor records just the active substance name, or the INN, it would be impossible to identify which particular enoxaparin product was involved in the event. I think many would contend that reporting the active substance is a start, but is a long way from providing the kind of data needed for a robust pharmacovigilance system.

So is the solution to this problem to require each generic version of this product to have a unique, nonproprietary name or does the problem go beyond the distinction between reference drug and follow-on

versions?

If we were to remove follow-on versions of a drug from consideration, would reporting an adverse event by drug brand name be sufficient? If we go back to our example, if an adverse event were to occur with the branded Lovenox product, would it be adequate for a doctor to record only the drug's name in the report? Would that serve the goals of a robust pharmacovigilance system?

If we look at the branded Lovenox at just one dosage and one delivery mechanism, there are five different labeled versions. And these five labeled versions are not even manufactured in the same country.

So if we have complex drugs like low molecular weight heparins, would it help to know where the drug associated with an adverse event was manufactured? Who the labeler was? If so, does reporting just a drug name provide the right level of detail?

In the case of biologics as it stands now, without follow-on competition, does a branded or nonproprietary name capture enough of the story for robust adverse event reporting or, as I think Geoff suggested this morning, are there other attributes of a dispensed biologic product that provide important

information for pharmacovigilance purposes?

For instance, last year the FDA published guidance saying that interactions between therapeutic protein products and the container closure itself may negatively affect product quality and immunogenicity. These interactions are more likely with prefilled syringes of therapeutic protein products, yet under the proposals we heard today about naming, none of the data that would be submitted would capture the type of delivery mechanism provided with the biologic product.

In the U.S., if you look at the product Humira, it is marketed under nine different labels. Among the nine are three different methods of delivery and a variety of dosages. Humira comes in pre-filled syringes, the one that the FDA says can lead to an increase in immunogenicity, prefilled pens, and vials.

If the FDA is correct that the container closure for a therapeutic protein can play a significant role in product quality and immunogenicity, is relying just on brand name or on INN for adverse event reporting adequate to further the goals of pharmacovigilance?

Right now there are a variety of other unique identifiers associated with drugs. One is a national drug code, also known as NDC codes. NDC codes are

printed, bar coded, and are on nearly every drug label in the United States. NDC codes are unique to particular formulations and product labelers. If a doctor were to record just an NDC code, they would know, for example, if an adverse event arose in a patient using a prefilled syringe versus a prefilled pen. If you combine that with lot information, you would have a pretty robust picture for biologics.

Now, the idea of using NDC codes for adverse event reports is already firmly planted on the reporting forms. It is our understanding, or my understanding as a former programmer, when I looked at the FDA database specification, that it is actually impossible to upload in a batch and NDC code for an adverse event report. So it's no surprise that, on the backend when you look at the database data, you're not going to find any NDC codes. It's amusing -- well, not amusing given the severity of the problem, that someone was trying to hard to supply the NDC code that, in some instances, it ended up in the lot field. It might be helpful if we had an adverse event reporting system that even took in the data that we provide on the forms to doctors.

Moreover, we've heard from a number of pharmacy specialists today that the pharmacies do record NDC data, they do record batch and lot

information, and they record this for every patient. So it's not that this information isn't available, it's just not being transported over the last hurdle, which is to the adverse event report.

Some have argued that NDC codes are not a good way to record adverse events because they are concerned that doctors prefer just to use a drug name when reporting an adverse event. We've heard today that -- you know, we were told this morning that if a particular batch or a particular lot sits on a dock for too long, we need to know what lot that was.

Well, the same data that showed that NDC codes were underreported also showed that lot information is missing in 90 percent of adverse event reports. So if the reality is that we just prefer to go with drug names, rather than a more robust set of data, is the consumer safety best preferred by deferring to that preference? Or would it be possible to get doctors to report NDC codes?

In the context of Medicaid reimbursement, we have seen instances where Medicaid has required doctors to supply NDC codes on common forms and in common software in order to receive Medicaid rebates.

I just want to add one more question. The biggest example we've heard today of adverse event

report problems with biologics came up in the context of Eprex. In that example, at least the common conclusion has been that there was a particular delivery mechanism that was at fault. And if that's the case, none of the solutions that focus on naming would have solved that problem any faster. But if an NDC code were used, you would have known exactly which delivery mechanism and which manufacturer had supplied that biologic in that case.

So with that, I'd like to turn it over to Elizabeth and Susan.

PANEL DISCUSSION - NAMING AND PHARMACOVIGILANCE

MS. DESANTI: Thank you, Neal. Elizabeth has prevailed on me to moderate again, since her voice is going. She claims that, because I taught elementary school 30 years ago, I am much better at sort of wrangling people together and getting things moving along.

So at any rate, I think, Neal, you've done a fine job of starting out with some provoking questions. And I'd like to begin by asking the initial question we have on our slide, which is -- the first question really seems to be, how would the use of either unique or distinguishable nonproprietary names for biosimilars and interchangeables either reduce or increase confusion? And we'll get to competitive effects next, but there are some people who claim that it would increase confusion not to have distinguishable nonproprietary names and then there are people who argue to the contrary, it would increase confusion to have distinguishable nonproprietary names. So I'd like to get that debate out on the record.

Oh, I'm sorry. I need to explain to you all that, if you want to speak, please put your table tent up. I also need to explain to -- don't touch it, Neal. Do not touch your mic, okay? This button down here

puts it on mute and that apparently was the problem we had this morning, so.

All right, so now I go back to my question which is, you know, where would the confusion come from if we went with either kind of strategy? Gino?

DR. GRAMPP: Yes. I'd like to turn the question around to say that -- well, I'm going to address confusion. There is a long history of distinguishable nonproprietary names for biologics. In fact, in Europe, I believe there are seven different ESAs, drug substances, with six different nonproprietary names, five of those are short-acting, so they all have similar doses and indications, et cetera, and I don't think there's any evidence of confusion among prescribers for that. They are used to this idea of a common core INN and distinguishable route.

We believe that distinguishable names will increase transparency and also help with pharmacovigilance, which we will actually reduce confusion in the market.

MS. DESANTI: Okay, I'm going to go from side-to-side. Sumant?

DR. RAMACHANDRA: From our perspective, I just showed data and I think, from an INN perspective,

I don't think we want to sit there and change the INN.

There are two things. One is that we have seen, and I've shown you data, it's real data, that there are unintended consequences of having a distinguishable name, it's very important. Maybe there is not a confusion at the prescriber level, I believe there is. As the prescriber -- first of all, prefixes are unacceptable from my perspective, okay? Far more palatable but still not ideal are suffixes, okay?

MS. DESANTI: Okay, can you explain why suffixes would be preferable to prefixes?

DR. RAMACHANDRA: Yes. So what happens in -- as a prescriber, I look at a drug name and when I look at the drug name, I say to myself, do I recognize that name. If there is a prefix to that and there is something proceeding what I would normally recognize, I may mentally just take that out of the system and say that's something I don't recognize and therefore it is not equivalent, in my mind, to what the originator was. So prefixes are something that could be problematic.

Suffixes, on the other hand, that follow a name, even though not ideal are palatable. The only reason that I say that is that, if there is a scientific rationale that it will make a difference, then a suffix can be put in place that is not appended

to the INN. It's not an INN, but we've talked about this whole qualifier aspect, which needs to be thought through carefully.

And the reason it needs to be thought through carefully, the only stakeholder here is not the physician. There are payer systems in place, there are a number of other systems in place that have to be thought through when it comes to name.

And the last point is that NDC codes, which are very, very important in the U.S., are a U.S.-centric issue. Now, maybe we are just only trying to solve a U.S.-centric problem and that's fine. There are no NDC codes outside of the U.S., okay?

So I think we have to look for an appropriate solution, and a lot has been talked about batch number and other recordable items, but I don't see, from our data, that adding something or changing the INN or USAN is going to solve this issue to a major extent.

MS. DESANTI: Bruce.

MR. LEICHER: Let me say that I think this is more than confusion, I think it's actually disinformation to be asking for separate names. If you think about it, for an interchangeable biologic, which is demonstrated to be switchable and substitutable, there is no basis whatsoever for a distinguishable

name. So the only purpose of having a different name is to inform physicians that it is somehow different.

And the whole point is that the NDC code, as was discussed just briefly before, is really the best means for telling the difference between all biologics, at the lot level, when there are manufacturing changes and when there is a different product. So it's the way to level the playing field and open it up for competition.

MS. DESANTI: Emily.

MS. ALEXANDER: One important thing to keep in mind here is that there is not any biosimilars approved in the United States. And I know that sounds obvious to a lot of us in the room, but that means that there is a real opportunity for FDA to come out and say, this is how we are doing it for all biologics going forward, including biosimilars. This is going to be our naming policy. It doesn't mean that some are better than others or some are worse than others or that it affects interchangeability or substitution, it just means that we want to improve on the adverse event misattribution that can occur and improve transparency.

So I think it's an opportunity for FDA to come out with a clear, consistent policy and that can reduce a lot of confusion that could otherwise occur

with physicians or payers or things like that.

Another thing that we've talked a lot about today is the need to improve the pharmacovigilance system across the board, for all products. And we absolutely agree with this. We need to have a better quantity of product-identifying information and better quality, meaning it is actually accurate. And that's true for all biologics. And these improvements in the pharmacovigilance system could come from better education, better electronic interoperability, many other means. But some of those will be long-term improvements and that means, in the short-term, when biosimilars are reaching the market, we need to work within what reporters are already using. And right now, we know that's names.

MS. DESANTI: Okay, Mark.

DR. MCCAMISH: Thanks, Susan. A couple of points. To Emily's point just now, I mean, why shouldn't FDA do something different? Well, they should do what's right and they should do what works. And right now, we've shown that it works in Europe, so to do something totally different just for different's sake is, you know, ludicrous. So they need to look at what works, what the data is, and go forward.

Back to Gino's points in terms of epo. Yes,

there are different epos, but I just presented data where the INN was not used for reporting adverse events. So, they reported the brand name.

So again, it doesn't give you support that a different INN would be helpful. It would be, in fact, more confusing.

And then on Australia, we argued over the data, but if I looked at your pie charts, your pie charts basically said that with the modified name, you had about one-fifth market penetration and with the non-modified INN you had about one-third market penetration. So I mean, if I was there, I'd rather have the one-third market penetration than the one-fifth.

And then lastly, it gets down to, in terms of just being disingenuous. Because the issue you mentioned, in terms of naming, if you go back to Aranesp, which I didn't go through but you guys can all look up the backup slides on Aranesp and the manufacturing changes that happened, if that was an issue and you wanted to track and trace -- there was a significant glycosylation change with Aranesp and you had the chance at that point in time to have a different INN, if you wanted to track it -- if it is so important to tracking it, yet it comes up ten years

later.

So again, the issue is those are all potentially very confusing issues for physicians and we know that. And we are on different sides of the fences because we all have different motivations that's there. But again, there is data that really deals with the issue.

MS. DESANTI: Aaron?

DR. KESSELHEIM: Yes, I think that my answer to this question is, it depends. It depends on -- and I think that one should just follow what the science is and what the drug is. And for a drug that is truly interchangeable and is the same drug, it should have the same name.

And if it has a different name -- I can tell you, as somebody who sees patients every week and talks to them about the names of their drugs, it will cause confusion. But if it is the same drug, it should have the same name. If it is a different drug, or even if it is a similar drug but not exactly the same drug, then maybe there is an argument for it to have a different name. And we already have experience with that with, you know, erythropoietin and darbepoetin and we have filgrastim and pegfilgrastim. So we already have experience in the marketplace with similar drugs,

omeprazole and esomeprazole. And they have slightly different prefixes as part of their full name because they work approximately the same way. You know, in the case of omeprazole and esomeprazole, they work exactly the same way but they are slightly different and therefore there is a difference in the name.

But for a product that is truly interchangeable, there is no scientific rationale for having a different name.

And then I also just wanted to make a point about the Adverse Event Reporting System, which is a good thing to have and is our current system, you know, as a way of reporting adverse events. And it is pretty good for hypothesis-generating exercises about potential adverse effects, but you know, nobody has ever pulled a drug off of the market simply on the basis of data from the Adverse Event Reporting system. What they then do is they then go to the real data, with the NDC codes and the large data sets in their manufacturers -- in the CVSs and the Aetnas of the world, and they use these larger data sets to do real pharmaco-epidemiological studies to evaluate the association between a drug and an outcome. So I don't think that the focus on the AERS system is necessarily -- or should be the focus here.

MS. DESANTI: Marissa?

MS. SCHLAIFER: I think it was mentioned -- we know that the majority of physicians or a large number of physicians do prescribe by the brand name. However, I think younger physicians, the uptake with younger physicians is to prescribe by the generic, nonproprietary or INN name.

And I think as you start adding prefixes and suffixes, for a physician who just wants the drug, doesn't have a preference between the various brands, to just write out the one name, it becomes the equivalent of writing for a brand name if there are variations in the INN or in the nonproprietary name. So you end up with a physician having to, you know, remember the alpha -- which, it's not going to happen. They are going to write for the nonproprietary, basic, non-suffix, non -- just because it is the easy way to go. And I think by throwing that in, it is putting extra burden on physicians rather than trying to make their life easier.

MS. DESANTI: And I do agree that we are missing physician -- we obviously have some physicians on the panel, but we could use more physicians and we have been asking the AMA, in particular, to help us collect some reactions from different types of

physicians that do use biologics.

Gino, you've been waiting awhile.

DR. GRAMPP: I'd like to address a couple of things. First, Europe has put in place a solution. We've been hearing a little bit about it today, but it's a coherent policy proposal. It's a coherent policy proposal because it requires manufacturers to use a brand name or trade name, they have that authority. It also is a coherent policy proposal because there are legislative mechanisms that are rolling out to the member states to require prescribers to use those names that are going to be put on the packages, or at least encourage it, and certainly require that reporters of adverse events use those names in the event.

I am completely open-minded to that type of a policy proposal for other parts of the world, including the United States. I haven't heard anybody proposing a coherent set of package proposals that the FDA could implement, because they can't do that. You have to go to Congress and the states to do that, so that's why this nonproprietary naming policy is something the FDA can consider and implement right now and it will address these holes in the system that we've been discussing about.

Another point though is regarding manufacturing changes. It's a good point Mark mentioned that manufacturers do occasionally make changes that are significant and that may entail more scrutiny in the post-approval phase of the product.

As long as all of the reports for that product come to that manufacturer, which was the case for darbepoetin when we made that change, the manufacturer and the regulatory agencies can sort that out, they have signal detection, there is enhanced monitoring, et cetera. It's when you have multiple players in the mix, and not all of the reports are going to the right place, where it becomes a systemic risk.

MS. DESANTI: Can I ask you a question? And this is for other people as well. I just want to clarify on the record.

If you have a number of brand name biologics, do all of those brand name biologics have the same INN or USAN? What is the current convention?

DR. RAMACHANDRA: So I can speak at you from experience of what we are just seeing in a recent approval with a molecule antibody called infliximab. We got approval of the trade name Inflectra, the brand name Inflectra in Europe and the brand name Inflectra

in Canada just recently. And the INN in that situation is infliximab, okay?

So one of the very important points is that a drug has multiple distinguishable features, but it has one common feature. What happens when your common feature becomes a distinguishable feature and there has to be a scientific or clinical discourse across the world? Because these medicines are used across the globe. You can't even speak a common language anymore because you have to write a paper that says, we used infliximab a.k.a. infliximab-something in Canada, a.k.a. infliximab-something in Australia. So you have to like qualify everything so that you have to actually spell out every single version of that.

The common language of a drug is the INN and everything else around it is distinguishable. So it is important to at least keep that core as understandable and as common as possible between biosimilars.

The EMA has told us flat out, in a recent workshop in London, that they have not had a problem. In fact, they are quite proud of the pharmacovigilance reporting of biosimilars and biologics, originator biologics, in Europe. That was the comment that they made right at the workshop. So they don't see it as a problem.

And our recent approval in Canada points out that the Canadians actually have given it also the name infliximab.

MS. DESANTI: Mark McCamish.

DR. MCCAMISH: Thanks. Again in response on the EU having this coherent program, Gino, when you were referring to that. Again, mixed messages. Because what you were saying is, for the tracking of PRCA it wasn't helpful and so something needed to be done, but now it is coherent and it works. So a little challenge there.

But I think that the point that you bring up is a good one. And also, I think it was Helen from Pfizer that brought this point up which the EU uses a unique proprietary name and then a nonproprietary name. And there is discussion where the FDA feels they do not have the authority to mandate a unique proprietary name, so then they are using that authority for the unique INN, theoretically.

Now, an easy resolution of this, quite straight-forward, is if the manufacturer does not select a unique proprietary name, that's their choice and the FDA can then mandate a unique INN or USAN, so that takes care of the problem. And then it's up to the manufacturer to do that.

But in this situation, that's the issue where Europe did work. On the other issue for the INN, and you brought this up, physicians prescribing by INN, literature published in the Medical Journal of Australia suggests that -- and they mandate prescribing by INN. And if you go in and evaluate it, only 50 percent of the docs prescribe by INN.

And what they decided was, in their research, was that it's the number of letters for the INN. And if you get more than 15 letters, they won't prescribe by the INN. And so by adding something else on to it, there's going to be more letters and it is going to be more challenging for them to utilize that. So let's go for, you know, what's an easy, useful, scalable approach.

MS. DESANTI: Bruce.

MR. LICHTER: Yeah. I just wanted to add one additional comment to what Mark was just saying, which is the FDA does require every manufacturer to put their manufacturer name on the product, which is just as distinguishable as any brand name. So the notion that there needs to be a brand name when there is a manufacturer name, it is more than adequate to know whose product it is.

MS. DESANTI: Emily, Emily Shacter. I just

wanted -- you had a comment about the issue with lots being left on a loading dock out in the heat. And I just wanted to get your perspective on that.

DR. SHACTER: Well, the comment was made earlier today that, well, what if a lot gets left on a hot tarmac, how are you going to know if the patient was prescribed material from that lot. And I was just commenting in the break room that I think this is a decoy comment because all manufacturers have to have shipping validation studies in order to determine if their product actually can sit on a tarmac for a certain period of time and incur whatever heat and have boxes or containers that can control the product during that time.

So I don't get the hot tarmac comment because this has to be controlled for all products, biosimilars as well as other protein products and other drug products. So I don't think that this takes out of control the ability to track one product versus another or has really anything to do with product quality of biosimilars compared to innovative products.

MS. DESANTI: Okay. And then I would just like to follow-up on the presentations, in terms of likely competitive effect. I think we heard, and please correct me if I'm wrong, I think we heard from

Sandoz and Hospira, Hospira, excuse me, finally, finally she says it correctly, that they have data that show that using different names will reduce the uptake, or is likely to reduce the uptake of biosimilars.

And I believe, Gino, you had data from Australia that you maintain that shows that there is no effect. And I just wanted to give you all a chance to have a dialogue about the data and then we can move on to the next question. But to the extent that we can sort it out, that would be helpful.

DR. RAMACHANDRA: The clarification to that, Hospira has -- we don't have data to say that a different name will reduce intake, what we do have data for is to show that a unique INN is not needed because a brand name sufficed in the two drugs that we have been marketing for several years.

What we also know is that, when you do have different INNs, you have a problem that occurs in the country reimbursement systems, in terms of getting the drug to be accepted.

So I just wanted to make sure that it is very distinguished. One is easily identifiable by brand name. We are seeing that, in fact, Pfizer's data -- I was just joking with Pfizer, they are seeing 99 percent in the biologics field are identifiable by brand name

and that is exactly what we are seeing. Their conclusion is different than our conclusion for exactly the same type of numbers, but I think that's one set that we can actually identify by brand name.

The other set is that there are unintended consequences to things -- the one thing that is common between an originator and the biosimilar is going to be the INN. If you start making that distinguished, there's nothing common between the biosimilar and INN. And maybe that is the intent at the end of the day by some parties, but to be honest with you, we have to have a common language of what drugs are used for and that INN is that common language.

MS. DESANTI: Helen.

DR. HARTMAN: Actually, there are a couple of different things that I wanted to address. The question really isn't whether the packages have enough distinguishing information, it dose have the manufacturer information, it does have the NDC, it has a brand name, it has the INN. The problem is that's not actually getting into the reports. So it's really pointless when it comes to pharmacovigilance.

And so really, we need to work within the system that we have. We need to work within the parameters of the AE reporters and the way physicians

and hospitals actually report the data. And so it is for that reason where, even though we came up with the same data, where brand names really do work, the problem is when you have biosimilars out there without any actual trade name, an invented trade name, and then you have a pool, potentially a pool of AEs where you have the same INN and there is no distinguishing information there.

MS. DESANTI: I think what you were proposing, Mark, though was that it would be up to the biosimilar or interchangeable manufacturer to decide whether they wanted to have a brand name. If they did, that would used. If they didn't, then the FDA could assign a distinguishable INN. Was that what you were saying?

DR. MCCAMISH: Correct. I mean, if that is driving the issue -- now, I don't agree that it is driving the issue for accurate pharmacovigilance. I think we have to improve the systems overall and be able to track down to lot numbers, et cetera. And so let's talk about how we do that for all biologics that are there.

But if that's the issue and you present it as the barrier, then that's a simple resolution, that FDA does have that authority to mandate an INN. So that

would be, again, a pragmatic approach, in terms of dealing with it.

But Susan, to get back to your other question which was, in terms of competition. I mean, I presented the data that's there. From Sumant's perspective, what he presented really confirms that there is confusion. Confusion at a country level when you have a different INN. Now, these aren't doctors, but they are policymakers that are making policy and they are confused. And they are not allowing us to compete in the tender.

And we showed data from Australia and Gino showed the same data, it's just a matter of interpretation where we have absolute evidence and we know, because we are trying to make it happen, that there is a difference when you have a different name attached to that from an INN.

It goes back to the same thing, when you look at it, it really connotes a different substance. And I think Aaron's point was very good, when you have something like pegfilgrastim, it's definitely different than filgrastim and you should have a different INN that's there. And that communicates that to a clinician as well, and so that's where it is pretty straight-forward.

Even the ABSM survey that I showed tells you that a name is important and it suggests that the product is different.

MS. DESANTI: Go ahead.

MR. TRAVIS: Speaking from the perspective of someone who is running an organization that is processing thousands of these prescriptions a day, the 3,000, 4,000, 5,000 dollar prescriptions a day across thousands of physicians offices, thousands of phone calls, faxes and emails a day, adding one more variable to that is a big lift.

I would urge everybody to try to use the existing system. You just said there are multiple pieces of information that are not going into the system now. How do we make that better? Adding -- the unintended consequences of adding another variable, we just can't even quantify how much confusion that is going to put into the system.

MS. DESANTI: Okay. I want to add in one more variable, which is the new track and trace legislation which has recently been passed which is going to require serial numbers on pharmaceuticals. And Elizabeth, maybe you can explain a little better than I can.

MS. JEX: My understanding is -- and I

believe the question from the audience identifies it as the Drug Quality and Safety Act of 2013. My understanding is it identifies -- it establishes that there is a product identifier number that is to be assigned to each product and every pharmaceutical drug sold in the United States, and medical device, will be tracked through the distribution system from the manufacturer, through the wholesaler, to the end-retailer.

And so the question is, why can't that -- one, are we right about that system? Can anyone elucidate us on that system and how that system can be married with adverse event reporting so that there is a robust and redundant system to determine whether or not the distribution of biologics, among others, has been penetrated by counterfeit, adulterated, misbranded or mismanufactured medicines?

MS. ALEXANDER: If I may, there's a few important nuance when we are talking about the track and trace legislation. One is, the timelines for implementation are very long, so it will be many years before we --

MS. JEX: 2017, is that right?

MS. DESANTI: 2017, is that correct?

MS. ALEXANDER: Well, there's -- I think

there's multiple stages. It will be ten years before we really have the full interoperability that is imagined ultimately in the statute.

There's also exceptions for dispensers of products, so that could be pharmacists or it could be physicians. The drug transaction history or the pedigree information can often remain at the wholesaler level, so it won't always translate down to the physician or the pharmacy.

I also think, one important thing when we are talking about integrating it with adverse event reporting is that there's no requirement in the Act, as it was passed, that the pedigree or drug transaction history information be integrated into the patient's file, and so that's really where the gap would need to be assessed.

And again, that may be a good long-term policy goal that we should be striving towards for all products, but in the meantime, that is not going to provide us much assistance.

MS. DESANTI: Gino.

DR. GRAMPP: Yes, I'd like to make clear Amgen fully supports comprehensive solutions to pharmacovigilance. And yes we focus on biologics, because that's what we make. It would be ideal to be

able to improve pharmacovigilance for other classes of products that are more complex and require traceability.

So yes, we ought to find a way to get more batch numbers, which already exist. We don't need the track/trace legislation to get batch numbers into the pharmacist's hands. The challenge right now is to get the batch number into the adverse event report. How can we do that? Can that be captured in the new EHR essential -- I'm sorry, meaningful use requirements? I don't think that's in there right now, but could that be captured? Is there a way for that to be automatically uploaded into a med watch form, which as you mentioned earlier Neal, doesn't happen right now. Same thing for NDC codes.

So I think we need to be having these conversations, I fully support them. I just don't know what the timeline for that is. It could be ten years, it could be more, before such a thing is broad-based and implemented. That's why we believe we need another solution to plug the gaps in the next ten years.

MS. DESANTI: Marissa and then Mark.

MS. SCHLAIFER: I think -- and maybe I'm just a little slow, but what keeps coming back, at least what I've heard, is that the only place -- the only

place that I've really heard that a suffix or prefix could really assist in confusion seems to be in the pharmacovigilance area, at least that seems to be what we keep coming back to.

And today we have -- you know, if we need an additional piece of information, if we have a suffix, we have a manufacturer name. And everything we would accomplish by adding a suffix we could accomplish today by using the manufacturer name as a suffix. If the problem is that the manufacturer name is not being reported, then what makes it so likely that the suffix will -- I mean, we've got the tool. If we're not using it, then let's use it. But I don't see --

So far, nowhere today have I heard a reason for another tool, it's just that we're not getting that manufacturer name and we need it. So let's create a system where we get it.

MS. DESANTI: Mark.

DR. MCCAMISH: And I agree with Gino and Ms. Marissa on this where we just need to capture the information. I think the new legislation, which is designed to try to track down misbranded, adulterated, fake products, will provide the same information we need for track and trace down to the lot level, which I think would be nothing more than helpful here in this

situation.

You can imagine, if you are selling something for 5,000 dollars a vial, people are going to try to make fake product and get it in the system. It just happens. So I think the legislation, however long it takes, is going to be helpful to bring more information and better tracking as we move forward.

MS. DESANTI: Bruce.

MR. LICHTER: I'm not going to repeat comments made by others. We agree that this creates confusion for biosimilars, but just step back for a minute and think about the confusion, having different, nonproprietary names would have for an interchangeable biologic. Because if doctors are, in fact, moving to prescribing by established name, and there is a different established name for the product, how is the substitution going to occur? It just doesn't make sense.

And you know, really one of the frustrations that I have with the discussion we're having is that we're all assuming, for the purpose of this question, that there is a pharmacovigilance problem. And I think we heard a lot of evidence today that there really is, you know, there are some opportunities for some real innovative solution. And if we are going to fix it, we

should fix it for all the manufacturing changes that Mark identified earlier. If we are going to track stuff, we should be able to track it with the NDC number.

MS. DESANTI: Sumant.

DR. RAMACHANDRA: So even though there are no biosimilars actually approved in the U.S., there are biologics that have the same INN, different brands created by different companies by different processes.

So for those that think that the U.S. has zero precedence, there is precedence in this country. So yes, it's a different pathway. I understand it is a 351(a) pathway or another pathway that got these biologic agents approved, but even in that situation, the INN was kept the same and the brand was different.

So those drugs were not even approved by what is a highly regulated, high bar, biosimilar pathway. And now we are saying a new rule must come into play for biosimilars, even though it is done in a highly regulated, high scientific bar concept.

And this is the U.S. guys. I just want to make sure everyone knows, it's already happening in the U.S., maybe not as a biosimilar, but as an original biologic with the same INN, different manufacturers, different trade names.

So we have to be careful that we are creating

a new rule in an already precedented market. And I think there are going to be unintended consequences that companies will feel as a result of this.

MS. DESANTI: Emily.

DR. SHACTER: So I wanted to comment on how the name might change. And the FDA has already indicated its thinking on prefix versus suffix and the leanings are certainly towards prefix, given the samples that Emily Alexander gave.

What I would worry about this scientifically, and from the patient safety perspective is, to equate a three letter prefix for something like azo-trastuzumab, which is an antibody drug conjugate which is dosed very differently from trastuzumab, to an xyz-biosimilar that is dosed identically to the innovator product would suggest that there has to be concern around the dosing of the product and that there are other areas of confusion. To have those equal each other, azo-trastuzumab to -- I mean, tbo-filgrastim got a different name most likely because it was not developed as a biosimilar, one could discuss the value of having that different name for a product that was actually dosed the same as, for example, Neupogen, Amgen's product. But to equate an azo-trastuzumab to an xyz-biosimilar seems to be off the cliff, because they are

so vastly different. So what's the message in that?

MS. JEX: And also Emily, isn't there a large portfolio of antibody drug conjugates in the pharmaceutical pipeline? So we are going to look at more and more of these conjugates with a drug name in front of an antibody name.

DR. SHACTER: Very much so, that's very true.

MS. JEX: Right.

DR. SHACTER: They are very promising drugs.

MS. DESANTI: Gino.

DR. GRAMPP: Yes, I'd like to come back to Bruce's question, which I think is a good question, but what does this mean for interchangeability.

I think the first thing we might want to ask is will we expect interchangeable products to be branded. We've been talking about the past tense for biosimilars, which are not interchangeable in the U.S. sense of the word in other parts of the world. And they all have brands, or at least a tradename such as filgrastim hexal in Europe, for example. Fine. And the traceability to those brand names or trade names seems to be working to the 90 percent plus rate, as we heard earlier.

But when you go to interchangeability, will companies develop brand names? How are we going to

trace these products when it's interchangeable? Are we going to just hope that the NDC code makes it into the system? What is the mechanism? If the manufacturer named -- somebody else made that point. Yes, that would be great. That's what Europe has, essentially, for non-branded products. You put the manufacturer name with the INN and that must be captured in the medical record. There is no requirement, regulation or policy for that in the U.S. and there is no requirement for that at the state level.

MS. DESANTI: Tina.

DR. MORRIS: I just want to tack on to what Emily said and raise the scientific concern that, if you had something that has a prefix from a scientific point of view that, that from the substance identity is basically the same as something that does not have a prefix it is problematic.

For example, we would find out that teva filgrastim at the primary structure level passed the USP identity test for filgrastim we would have a real problem. And I don't see how that's helpful.

MS. JEX: Do you have a real problem with that?

DR. MORRIS: Yes, based on -- I'm looking at our lawyers, but I think, if I understand --

MS. JEX: Potentially?

DR. MORRIS: -- our rule correctly, teva filgrastim, if it is tested and complies with the USP identity test, the filgrastim is misbranded.

MS. DESANTI: Okay, Mark and then Sumant.

DR. MCCAMISH: I think, going back to interchangeability component and particularly U.S. FDA, there is another problem in that the FDA has made their preference known that they would rather have a two-stage approach, so approval of the biosimilar first and then, with some undefined experience in the market, then consideration of interchangeable biosimilar.

And if you follow the naming, you would then have this biosimilar with a unique INN that is then approved as interchangeable. And then what do you do? You've got this history that's there.

So just -- again, it doesn't make sense. We can go back and round and round and round. I think the consensus thus far, from a pharmacovigilance perspective, all of the data suggests that adding a different INN is not going to be that helpful. And in fact, for interchangeability, it will be really, really confusing.

MS. DESANTI: Okay, Sumant and then Marissa.

DR. RAMACHANDRA: So one of the things is

Hospira is an injectable company just by nature. We have a lot of devices and software, but an injectable company. So we deal with a lot of small molecule injectables. We have three biosimilars in Europe, one in Australia and now one in Canada.

So one of the things that we learned is that the intake of pharmacovigilance, when the spontaneous call comes in, is probably the number one important step. I would actually submit that it is the responsibility of the manufacturer to capture the right data as much as possible. And what we have put into place is a system to capture as much of the data as upfront as possible. There are gaps in all of our systems, and Harry said this correct, if you start messing around with an adding an appendage to an INN and then you actually think it is going to solve the problem, it's not going to happen.

We are dealing, as a company, with multiple sources of the same drug. We just happen to be one source of, let's say, paclitaxel. And we have to make every effort, because of our systems, to make sure that paclitaxel, Taxol the brand name from Bristol-Myers Squibb, actually is ours and not one of the nine or ten other people who make paclitaxel.

We have to, as an industry, commit to have

robust systems in place rather than thinking that the hammer approach or the blunt instrument approach of adding something to a name will suddenly magically things even disappear, in terms of issues of the pharmacovigilance system. We need more sophisticated solutions to this, not naming solutions to this. And we need to commit, as an industry, to better pharmacovigilance systems. I think that's where the problem lies.

MS. DESANTI: Marissa.

MS. SCHLAIFER: I think as I listen to this conversation, and as a pharmacist and not an expert in biosimilars, it's creating questions. You know, we've talked about pharmacovigilance and we've talked about med watch reporting and we've talked about the differences that happen when there's issues with one manufacturer's product and not other manufacturer's product.

But as we see drugs that have been out in the market for long periods of time, as things are out in wider use, it's more common that we see something that would be across the drug that we wouldn't see when there was just the originator product and the product has been out ten years and we start seeing problems that go across all manufacturers. It's a problem with

the actual drug itself, not the manufacturer's lot.

And if we start having prefixes and suffixes, and I think with this I'd be more concerned about prefixes than suffixes, but either -- we need to make sure that we realize that there's a problem with the drug. And I think the prefix/suffix issue could actually cause more confusion when we have a problem with a drug and not a problem with a specific manufacturer.

And I'm sure people who are more experts in this industry can probably speak to that, but I think that's something we need to -- and we will see problems with drugs, not problems with individual manufacturer's drugs.

MS. DESANTI: Emily.

MS. ALEXANDER: I disagree in the biologics context. I think you can have multiple sources of a similar or same molecule across products, but one manufacturer could, for example, scale up. And that scale up, although there is nothing fundamentally wrong with the underlying molecule, has caused some unexpected problem that will then later manifest in the market and we want to be able to track that.

So I think for drugs, that's absolutely the case, that you expect the safety profile to be related

to the underlying drug. But the difference between drugs and biologics means, for biologics, that sensitivity of the manufacturing process means it could not be related to the underlying molecule.

MS. SCHLAIFER: Can I just clarify? By no means do I think that there's not -- I'm not saying that there's not a potential for a manufacturer problem. But when a drug has been on the market for two years, we don't necessarily know all of the problems it has. Drugs that have been on the market for ten years is when we start seeing a large number of problems.

And so I think -- I'm not debating whether or not there could be a problem with an individual product, and I could debate that, but I think that's a different question. My question now is, what happens when we find a problem? There will be problems with drugs. Drugs have side effects, we need to have a way to track those side effects.

MS. DESANTI: Emily.

MS. ALEXANDER: Well, I think again, you know, the real compromise here may be a distinguishable but related name. I agree that, if you are getting into fundamentally different, nonproprietary names, it becomes harder to pool across products and really see

common trends, but the common core element of the nonproprietary name will better help us pool that type of data that you're talking about.

MS. DESANTI: Okay, Emily Shacter.

DR. SHACTER: So if I could respectfully make a counter argument to this concept of changing the manufacturing process and having a product go out on to the market with an unexpected adverse event profile. If a manufacturer makes a manufacturing change that is adequate to have a potential impact on clinical activity, safety or efficacy, they are required, through comparability standards to demonstrate, before that product goes out to market, that it is not going to have a different clinical profile. And that doesn't mean that things don't happen, and FDA has seen every adverse consequence of manufacturing changes that can happen and that's one of the reasons why the FDA is risk-averse. You know, they have seen it all.

But if that happens, (a) the company has not done its job and the FDA has not done its job. And I would posit that also with the argument on drift and products changing over time. If significant drift is happening in a product, then again, either the sponsor is not doing their job or the FDA is not doing their job. If that drift is controlled so that you

understand the impact on clinical activity, and there is no significant impact on clinical activity, fine, you can have an attribute change, it is not critical.

MS. DESANTI: Thank you. I think we have time for two more comments. Gino and then Mark.

DR. GRAMPP: Just quickly to Marissa's point, I think that it is possible to aggregate safety signals for classes with related names and distinguishable suffixes. It's been done in Europe for epoetins. As I mentioned earlier, there are a large number of different drug substances there.

And then with regard to the safety issue and the potential effects of manufacturing changes, I think we all agree, this is a very rare event that it would happen, because we have a capable regulatory system, capable manufacturers, and good quality systems. But pharmacovigilance is part of that capable system, so we shouldn't lose sight of that.

MS. DESANTI: Mark.

DR. MCCAMISH: My only comment is along the same, in terms of what Marissa was saying and then Emily Alexander. I think it can be done when you have different INNs, but pharmacovigilance is a challenge to do that.

And Emily, you mentioned, I think, I believe,

that we have to be data based. And you know the data suggests that it takes extra steps to consolidate that kind of information. And the more INNs you have, the more difficult it is to consolidate. It can be done, but it takes more effort.

MS. ALEXANDER: Sure. My lack of eloquence aside, we know there are examples of related but distinguishable nonproprietary names where there has been pooling of adverse events.

MS. SCHLAIFER: And I guess my question was, you know, we go back to individual physicians. And an individual physician seeing a pattern when they have three different drugs or supposedly "three different drugs" across their patient base, and they are seeing something. But they may see some in this drug, some in this drug, some in this drug, it's really all the same drug. And having physicians not identify a pattern that they would choose to report, the physicians don't always report when they see one thing and when they see one thing in one drug. But when they see the pattern, that they may not see across drugs that they perceive as being different but are actually the exact same drug, they may not choose to report it.

MS. DESANTI: Okay, Marissa, you have the last word.

I want to thank our panelists and invite Andy Gavil to please come up and share some concluding remarks with us.

CONCLUDING REMARKS

MR. GAVIL: What a terrific day. Thank you all for joining us and participating and listening in on today's very thought-provoking and high quality presentations. I am really delighted with the presentations and comments that everyone brought to the table today.

I especially want to thank our presenters and discussants who have provided us with so much food for thought, even though budgetary constraints prevent us from offering any food. We've had a very lively and informative discussion reflecting very varied perspectives and we will take all of that back and seek to digest it.

As you all know, it takes many people to conceive of and organize a workshop such as this and I'd like to single out some of our organizers for their enthusiasm, dedication and commitment and creativity in assembling today's program.

First, join me in acknowledging and thanking the team, and it was a big team. Erin Flynn, Chris Bryan, Chris Garmon, Meredyth Andrus, who is here, Karen Berg, Kelly Signs, Stephanie Wilkinson, Andrea Kelly, Cheryl Warner, Rich Custer, and Gail Kingsland.

Our OPP Deputy Directors, Tara Koslov and Suzanne Munck. There are also lots of FTC support staff that help with the event, too. The Office of Public Affairs, event planners, the media team, paralegals at the registration table. As I said, it takes a big team.

I'd like to especially single out Neal Hannan and our moderators today, Elizabeth Jex and my predecessor in OPP, Susan DeSanti. A special shout-out to Elizabeth. I know many of you have interacted with her. She's spent many, many months conceiving of and organizing the program, reaching out to speakers, and I think she is particularly owed a round of appreciation for her work.

Finally, I'd like to remind you all that the public comment period for today's workshop will remain open until March 1st. The details of the submission process can be found in the federal register notice or on our workshop website. We encourage and look forward to receiving and considering your comments.

So thank you all again and safe travels home. And we did it, we made it through a day without adverse weather conditions. Thank you all very much.

(Whereupon, the proceedings concluded at 5:05 p.m.)

C E R T I F I C A T I O N O F R E P O R T E R

MATTER NUMBER: P131208
CASE TITLE: FOLLOW-ON BIOLOGICS WORKSHOP
DATE: FEBRUARY 4, 2014

I HEREBY CERTIFY that the transcript contained herein is a full and accurate transcript of the notes taken by me at the hearing on the above cause before the FEDERAL TRADE COMMISSION to the best of my knowledge and belief.

DATED: FEBRUARY 19, 2014

STEPHANIE GILLEY

C E R T I F I C A T I O N O F P R O O F R E A D E R

I HEREBY CERTIFY that I proofread the transcript for accuracy in spelling, hyphenation, punctuation and format.

SARA J. VANCE