FTC Follow-on Biologics Workshop
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Segment 4
Transcript

ELIZABETH: So good afternoon again. I'm Elizabeth Jackson, 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 US 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 non-proprietary 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 non-proprietary names that differentiate them from the reference biologics' non-proprietary 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 pharmacovigilant 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 non-proprietary names for biosimilars and interchangeables could affect how incidents involving biologics, biosimilars, or pharmacovigilant would be reported.

By way of background, the term "pharmacovigilance" is derived from the Greek word "pharmakon" 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 US through a voluntary drug safety program overseen by the US FDA. 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 products' manufacturers. If a manufacturer receives an adverse event report, it is required to send that report to the FDA as specified under regulations. The FDA's adverse event reporting system collects these reports in a database.

Our speakers this afternoon will describe how non-proprietary names have been used to date for generic drugs, and their views on whether unique or distinguishable non-proprietary names should be used for a biosimilars and interchangeables. We're 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 Secretariat Council of Experts for the US Pharmacopoeia. Tina Morris is Vice President, Biologics and Biotechnology in the Global Science and Standards Division at the US Pharmacopoeia, which she joined in 2003.

Next, Mark McCamish, Global Head of Biopharmaceutical Development for Sanders 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 the 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 a biosimilar market. Hospira's a leading provider of 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 its spin-off from Abbott. Emily is the Director of US Regulatory Affairs in the Biologic Strategic Development Group at AbbVie. We will then hear from Alan Lotvin, an Executive Vice President of Specialty Pharmacy for CVS Caremark. Alan will discuss whether the pharmacovigilant 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 specialty pharmaceuticals and naming. Harry is Vice President and General Manager for Aetna Specialty and Home Delivery Pharmacy.

Following these presentations, we'll have a short 10-minute break, and following that we'll have a one-hour moderated panel discussion on naming and pharmacovigilance. To introduce that panel, we'll 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 US and abroad on antitrust law and policy.

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

ANGELA: 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 US. 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 USP's role in naming, but that's something that maybe not all of you do you 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 USP's new chief executive officer. He joined yesterday, otherwise he would have been here, and 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 US Pharmacopoeia is that USP is a non-government, standards-setting organization. Most other pharmacopoeias in the world are within the Ministries of Health. USP is not. There's only one other pharmacopoeia, and that's Chile, and they modeled themselves after us. So being a non-government pharmacopoeia has its pluses and minuses.

I'm going to give the primer on nomenclature, and then Tina's 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, the drug label. And we're talking about not the brand name that you see in the middle there, but the non-proprietary name that you see there and, 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 the innovation, there's 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 INN 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 Non-proprietary Names, it's sponsored by World Health Organization. And they're obviously facilitating those names and identification of substancess, and so it's drug substances that they're naming. And they are unique names, and they're recognized to varying extents globally, so a regulatory authority has to take up an INN. And it's important to note that the US does not follow INN, and it doesn't have a role in federal law.

But you'll see that we do follow the US Adopted Names, USAN, and 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 and again focusing on drug substances only.

Because so many drugs go to USAN and INN early in the pipeline, some of them do not emergent from the pipeline. So 75% 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 non-proprietary naming authorities like INN, or British Applied Authoritative Names, and Japanese Names as well.

And to go back to my example, here is 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 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-- 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 USP's role in naming, and so that comes through the federal Food, Drug, and Cosmetic Act. And it's very, very important to note that this role is grounded in law. And I have some slides later that show you the provisions that those are in. But if there is an already applicable standard in USP and when a drug is approved, then it is important that that drug meet the monograph characteristics and also have that same official title. And 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 when USP creates a monograph.

Now, USAN creates names for drug substances, but USP's 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 same misbranding and adulteration provisions do apply to the Public Health Service Act.

So the FDA and USP have been working closely on these naming activities. But it's important to note that USP's role in naming does not really come about until there is the monograph elaborated in the USP. And that is what USP's doing primarily. It's in our general notices that we indicate that. So here are the details of USP and the law. And they're in your slides in your packet.

But I wanted to show you now kind of how that role plays out in applying to both drug substances and drug products. And you can see here, again my example, 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 publicly available product quality standards and tests and criteria. And that's probably the most important aspect of USP's naming role.

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. And 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 and are connected to patients and know what patients need when it comes to drug product names.

So our prospective 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 OK. And 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's 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, and that would certainly be a good idea. USP supports that. So with that, let me turn to Tina to take you to our scientific issues.

TINA: 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'm going to put a boundary assumption up there just to make it very clear what the role of USP standards are. And 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 they can be a helpful resource to the regulator in a licensing decision. And I think there are examples of that, where USP has monographs and then later on we know the 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 a monograph. So the monograph can never be this all-comprehensive thing, and so FDA may very well prescribe additional standards that are material to an article sameness.

Going back to what Angie already introduced to you that the key concept also that's very important to our naming is the compendial identity. And this is the direct quote on what identity means in the context of the compendium, and 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 monograph has two identity tests, chromatographic purity by a 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's an additional bioidentity test that speaks to the functionality of the product, which is very important as well. I also use the somatotropin example here for you, because it's an interesting course because there are seven products in the US market right now, and they have come onto 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 and microheterogeneity. 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 who process. It's much more complicated, and it's 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's glycosylated or not in terms of how the article behaves. And so it may or may not be a critical quality attribute.

And one important thing that I want to point out 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 microheterogeneity 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, not for the compendium.

And this is an example that's well known for EPO where via isoelectric focusing, for example, you cannot distinguish between EPOR, and alpha and beta. And so clearly in this particular analytical test, you would say, they're the same.

So what's USP's experience to date? We have a lot of experience with very complex biologics. You heard about enoxaparin this morning. We have a monograph for that and for many others, especially naturally derived biologics. In the recombinant therapeutic field, we have a couple of enzymes. But we have no monograph that actively addresses glycosylation, but we're currently considering one.

So what would our Expert Committee look at the next case like that? So obviously the Science Expert Committee, as Angie told you, would consult with the Nomenclature Committee. It would look at the existing use and naming precedent at other compendial standards that exist. They would consider the proposed tests, their specificity, and their resolving power in the context of the entire monograph. And they would also 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 the USP. Thank you.

Mark:I give my thanks to Elizabeth, Susan, and Erin as well in terms of organizing this twice for us. And it's a pleasure for me to be here.

So let me run through the 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 me 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's inadequate access. And I have family members that have not had access

and has had an impact on their lives and mine. And most of you have 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 that's familiar with biologic and drug development. Usually as you see with the upside triangle on the left, you will see that a original drug or a novel drug is based a lot on the clinical data. So you do do your characterization, your talks, your PK, your 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, talked about by Emily earlier-- where the base is an analytical characterization. PKPD is 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'll look at that and scratch their head and say, 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 of EMA, a very well-known individual-- just documenting the number of manufacturing changes in a normal biologic. These are not biosimilars; these 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 what these changes will in fact lead to some clinical effect. And they're only approved if the manufacturing change has no expectation of a clinical difference that's there. Scientifically, it's valid to do this. There's nothing wrong with it. We're 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 drug substance. So that's something to consider.

Now, EMA has a lot of experience in this area. And they've talked about similar but not identical, and that it's 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's been a regulatory determination that they're the "same," in quotes, as the original without any significant clinical effect.

And then the revised EMA Q&A that recently came out really validates the principles of biosimilarity in this. And 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's essentially the same biological substance, i.e., it's variability overlaps with the variability the originator. Why would you call it a different name?

There's also been, as Sumant will mention, a biosimilar mAb approved in Europe. And this is 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's not the active substance modified; it's the active substance called infliximab. So they're using the same terminology, and in Europe you use the same INN. There's no differences in INN with various products.

So the biosimilar concept works. 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's surpassed the originator. So the uptake is substantial in moving forward.

In each of our products are the number one product in the world as biosimilars. And there's been 18 other products approved in Europe, and they all bear the same INN as the originator. And then I mentioned that Inflectra/Remsima already approved by the FDA. And even complex biosimilars can be developed successfully today for this.

So let me talk about naming. So USP presented this, basically just says these are the names. You see Genotropin and Omnitrope, just two examples of a somatrope. You see the label here having the branding, the INN, the manufacturer, 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, from either pharmacovigilance or for the physician to know what drug they're using. It's just not necessary.

And data to back that up, so here's our experience. If we talk about safety and adverse events, these are just our data up to 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 tracked 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 these, there's maybe one or two cases where the INN was used, and all the rest are with the brand name. And in the first category you see Binocrit, which is erythropoetin, only one was reported by epoetin alfa, which is the INN.

Omnitrope or somatropin, same; we received eight reports by the INN. But six of those were by the Health Care Authority, because everybody reports to the Health Care Authority of spontaneous events. Then they report to all the manufacturers of these, and they use the INN for that. And the same for Zarzio, very few in terms of reporting by INN. So modifying the INN will not have a significant impact on pharmacovigilance.

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

And you can see, compared to Enoxaparin, which is approved as an AB substitutable, complex product, we have about a 17% penetration. Now that may not sound that great, but that's the second-most prescribed growth hormone, because there are seven on the market. So we've had very good penetration with the same INN in competing with the remainder. And from a pharmacovigilance perspective, you heard from Steve earlier, no problem in terms of following pharmacovigilance there. So although not 50% penetration, same INN is helpful in terms of using the product.

Here is an example from Australia. And Australia has mandated that a biologic with a glycosylation requires an alternate INN. So here you can see the traditional generic penetration in Australia's about 50%. 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 TBA forced us to use a different INN.

And you can see the penetration difference, 25% down to 2%, of a tenfold decrease in penetration when you have to use a different INN. So data really shows that that's an issue. Same in Japan. Although the rates of generic penetration in Japan are very low, it still has an impact that our penetration for a biosimilar is really miserable. And you have to use a different INN or different name there as well. So again, data showing that there will be a difference.

In Europe, same INN. We've been able to have huge uptake. It's country-specific as was mentioned earlier by Ronny Gal. But overall, as I mentioned was G-CSF, we're 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% increase in the use of the drug by volume, because the cost has gone down. So we've accomplished that as well.

And I've got a couple of the 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's just saying what the active substance is. Different INN for biosimilars lead to confusion of physicians, discrimination of biosimilars, and it does impact affordability of patient and patient access. Current naming system for biologics works well; it should not be really dismantled.

So I had a couple of back-up slides. This one deals with the drift I want to quickly go over. We had a little talk about that 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 manufacturing change with Enbrel. And you can see in the far right top where the light blue dots are very, very consistent, and tell there's a manufacturing change, and then there's a shift in that glycosylation.

So there's two things you can see here, is 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 biological, and it's going to drift somewhere 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 back into the 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 with manufacturing changes, but not really drift in that sense.

And then two slides that basically this is from the Alliance for Safe Biological Medicine, makes me feel nice and comfy. But taken directly from their website-- and this is data regarding a survey they did-- key findings from the survey include 53% of surveyed physicians in Europe felt that an identical non-proprietary name implies identical structure, which will now be the case. 61% of surveyed physicians said that identical non-proprietary names imply that the medicines are approved for the same indications, which is not the case. 24% of reporting positions record only the non-proprietary name of biological products in their patient record. I'm not sure where that data comes from, because we showed you that it's the brand name that's used in terms of communicating.

And so all this says, that demonstrates the need for distinguishable non-proprietary names to be given for all biologics and then 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 as surveyed to produce a desired outcome. Naming does in fact of matter, and using a different non-proprietary name does communicate a different product, which it's not supposed to, and different non-proprietary names will cause doubt in health care providers, which is the desired outcome of some.

Thank you.

GUSTAVO: 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. And based on this collective experience, I know that biologics should not be treated like generic drugs for the purposes of naming, traceability, and manufacture accountability. So if you're looking for a 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 means they're distinguishable and they should be distinguished. Second, naming is important to the long-term traceability of these products, first, any biologic after it's approved, as well as long-term over its life cycle. And third, distinguishable naming does not necessarily impact market update.

So let's start with the science and the fundamental nature of the biologics. They're complex, they're large, they're sensitive to their conditions, they've made in living things, and they're variable. Now why does this matter for naming? As they're large and complex, that means it's difficult to define exactly their molecular structures. As they're made in living things, it means a scientist like myself can't always predict how processing conditions could affect their quality.

And as they are variable, which we just heard quite a bit about, they're variable because they're composed of multiple components. They're variable within batches and between batches. It's difficult to define precise boundaries for what is and what is not a given active ingredients. Instead, we have approximations.

So these three factors currently make it scientifically impossible to say that two active ingredients are the same. Say essentially the same, but can't say that they're the same. And also it's 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 manufacture, reflecting different glycosylation patterns, slight sequence variations, and other structural features. So these rules have been taken to account for years.

Oh, and I should mention we heard about glycosylation. So that's particularly important as we talk about biosimilars, because it is something that's 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 have applied these types of rules, have a common core to reflect common structure and function, so the prescribers and patients and others know about that with the distinguishable feature.

But this is not just about taxonomy. There's 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 a manufacturer-specific data.

But this is clear that policy makers in the United States, Europe, and elsewhere do not accept this paradigm for biologics. We heard a lot about this morning, about why you have special rules for biologics, but this is coming from the regulators that watch these products. They understand their complexity. So there may not be a consensus yet on the specific policy measures to achieve this policy remit, but there is consensus that biologics need to be tracked to the individual manufacturer.

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

care provider. Third, although brand names appear to be working very well in multi-sourced 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 biosimilars or interchangeables.

In fact, there's a trend towards increasing use of non-proprietary names for prescribing. It's being encouraged in medical schools, and because of computerized order-entry systems, prescribers are seeing drop-down menus with the drugs listed by the non-proprietary name, so 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 the all the information they need to identify the product, and that needs to account for all the different settings of use and all the different circumstances. So we think that means that you need brand names when they're available, that's the best identifier for a specific product; distinguishable non-proprietary names, when those may not be captured in a record; and other codes, especially for pharmacists that have good access to that.

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

So what are the consequences of that? We 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 these products just because they have a related structure.

So I've just described the situation at the time of biosimilar approval. When you consider the life cycle implications for multi-sourced biologics, it gets more complex. So as I mentioned, the products start in a place where there's already some structural diversity. It's not clinically meaningful, those differences, but they may not be interchangeable.

But now, over time, process changes can occur. And the history shows that that's occurred for reference products, for originator products. Those changes could be subtle. They may not affect the comparability of each product, 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's 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 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 a 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 will not be able to capture this product-specific information if there's a loss of information anywhere in the chain from prescribing through dispensing, record keeping, et cetera. So if a common, non-proprietary name is used for prescribing, there's already ambiguity from the beginning in the patient record about what medicine the patient will receive. If a pharmacist has discretion to dispense various medications and they're under the provisions of the institution or the pharmacy, there might be further ambiguity.

If those product identifiers are not captured in a medical record that's 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 multiple sources of specific and retrieval information. That means brand names when they're available, non-proprietary names that are distinguishable, and other codes when that's appropriate.

So I mentioned life cycle challenges, and I won't dwell on this slide. We already heard the example earlier today about the PRCA 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 non-proprietary names and brand names, and they were able to do that.

So be it, it was a rare event, but European policymakers took notice of that. As Jeff said earlier, the immediate policy response was to put warnings and precautions into the labels of all these erythropoietin products in Europe. It says, 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 Jeff also mentioned earlier, Europe has now codified that into law for all biosimilars and biologics that the brand name or trade name should be recorded in the prescription and track all the way through to adverse event report. So this shows that policymakers do take this seriously, that biologics need to be treated differently than generics.

I mentioned earlier that for generic chemical drugs, there's been an aggregation of safety signals without regard to specific manufacturers. And what's the consequences of this? This is a figure from a recent publication showing the safety reports for a product with the loss of exclusivity. As we know, generic drugs are very successful with regard to 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 a loss of exclusivity. So that means the vast majority of reports went to the wrong manufacture.

We believe that there are data contradicting what Dr. McCamish said that distinguishable names have not impacted market uptake in similar markets overseas. And we'll be presenting more data than what 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 the non-proprietary name with the originator product, and EPO does not. And it's hard to distinguish that there's a meaningful difference in uptake between these product classes in Australia. So really 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 US show that 80% of those responding believe that there should not be this identical non-proprietary names for biosimilars.

Although some payers clearly oppose this policy, a survey of payers, 93% of those responding in the United States believe the same thing, that the non-proprietary names should not identical for biosimilars. And policymakers overseas have also implemented policies towards this end, including in Japan and Australia, where they have rules for non-proprietary names.

So in closing, we've shown that the nature of these complex medicines dictates 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 product life cycles, and this is best imported by distinguishable names.

So we believe that the US Biosimilars Program will thrive with these policies that encourage accountability and transparency and instill confidence in patients and prescribers.

SUMANT: Good afternoon, everyone. My name is Sumant Ramachandra. I'm the Chief Scientific Officer and Head of R&D for Hospira, which is an injectable company that founded its core actually out of generic injectables as well as infusion devices. We operate actually both in the technology space with integration to electronic medical records, as well as in the generic space.

It's 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 right for our entry.

Sorry about that. Great. Thank you.

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

So there's 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 drug 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 to the cost of 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 that the state of the science was there to make a product as similar as possible to the originator product and 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 compound annual growth rate of close to 9%. So there's no slow growth in this particular market, and obviously as originator companies come up with new innovative drugs, biosimilar companies will come with the options for the original drugs in the past.

It's important to note that biosimilars are not generics. I'm going to emphasize that multiple times. I said in the panel earlier-- I'm 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. And we're speaking from the experiences we have had in Europe, not just in a simple biosimilar called "Filgrastim," or a more complicated one called "erythropoetin," or an even more complicated one that we're 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 not to mimic a generic market, because that will kill the biosimilars market also. So you have to get even ground, where the access is given to patients, but not the prices go so low that there's a disincentive to actually participate in this market. Anti-competitive behavior can go to both extremes. So we have to be careful on both extremes to make sure that this is a viable market.

And I've 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 that we have compromised I call a consensus, because we are taking disparate ideas and moving the agenda forward. People could put the stake in the ground at either end and not move anything forward, which is maybe what the hope is, but you have to move the field forward, because in the end of the day, the people who benefit the most are the patients.

So in this slide, you can see the difference is, as I mentioned, between a small-molecule oncology drug like Paclitaxel, Filgrastim, and a molecule 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's done a lot of work in this area. We made a commitment very early on that we're 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 similar are compared in 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 an originator molecule, because they're the originator. We have to compare ourselves to the originator molecule. So our science has to show in each and every step from the extensive molecular characterization, through the pre-clinical data, through the pre-registration studies, we are comparing ourselves to someone, and that is the originator. And the rigor has to be there.

And then 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 where we have done those in the case of EPO here. And then there are a commitment to post-registration studies in the case of EPO for Europe, because there are rare events with EPO that you want to track in the post-market setting. All of this does cost money, but we made a 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 science continues to evolve more and more.

So this is the sample data, just to kind of 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're 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.

What is shown very clearly is that you have done a substantial number of orthogonal tests, so you're looking at the same product from multiple angles, to ensure that it is highly similar to this originator product and therefore meets the basis of biosimilarity to get 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's where you will pick up signals that could be rare in nature, or as Mark has pointed out multiple times, Dr. McCamish has said, anything can happen to a specific lot in a loading dock. So you can't pick that up unless you are doing a very good pharmacovigilance.

And what they do in this particular model, 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 of 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 pharmacovigilance system is extremely important.

Now, regardless of what people have said, our data actually does match Sandoz's data. We actually looked at our database for our two products in Europe, filgrastim, which actually shares the INN, so we call it Nivestim as a brand name as the originator product. And we have an epoietin product that has an epoietin zeta. It was based on the fact that are partner when they applied for an INN a long time ago, WHO did not have guidelines at that point 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% of the time, and its identification is by brand name. So mucking around and trying to change the INN is not the solution of getting you to higher and better pharmacovigilance in this particular setting. There are cases where a distinguishable INN could be allowed, but not in the case of biosimilars in general.

And 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 reimbursements since 2009. What does that mean for Hospira? It means that epoetin zeta cannot get reimbursed in that market. But Binocrit-- which is epoetin alfa which is like Retacrit, it's 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've been excluded from tendering of epoetin alfa batches. And we've gone through a very lengthy and expensive legal challenge to remove this restriction, and its been successful over time, but it's delayed the uptake of our product. And in Spain, despite legal challenges, we continue to be excluded from epoetin alfa tenders in some regions, and that's 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 has improved market uptake. But it's not showing the data by just getting approval and then handing it to a distribution channel and giving to the physician for 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's 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 only companies that are going to increase in the market, and it's 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's 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 the 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 bidding tender market where the entire country switches over like Hungary, where it can switch from brand to brand every couple of years, it 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 a market. There's really no money for you, because you're not doing anything new.

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

And what could be for Europe some of the savings? As you can see in this art-- this was published by an ISA study, and it was published in 2012-- it shows that there's a minimum over this time period of 2010 to 2020 of about $11 billion but it can go up to $33 billion. In my opinion, this is an underestimate. It's going to go more than that. In the US alone, it can be potentially $250 billion 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, that we've got approval for moderate to severe plaque psoriasis an adult patients, yet the nice technology assessment and the National Institute of Health Care Excellence in UK published in 2008 says that it's only approved for reimbursement if their 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 UK a number of patients, because NIHCE will have to do a reassessment when the new pricing model comes out. And they will find regardless of whether it's the

originator or us or someone else who drops the price, that when they do the technology assessment, more patients will get access. And that, it benefits the patients who actually need it.

So I'm going to skip over the next slide, because Steve Miller has already gone over it, and I just want to make sure we go over to the lessons from our learnings. 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 thus 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 sponsoring companies and other government authorities. And biosimilar competition thrives in markets where government policies are set fair and even playing fields. And payer rules need to support strong and early market formation and recognize the difference between biosimilars and small-molecule generics, not to incentivize for higher priced products and not to drive to extremely low products, and that's important.

To reduce the cost of development and bring better access, extrapolation must be accepted. And 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, at 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's a lot more to discuss on biosimilars. This is just the tip of the iceberg. If we get stuck in our extreme cases, we're not going to move the agenda forward, which is better access with high-quality medicines. Thank you very much.

HELEN: 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's a manufacturer of both innovator biologic drugs as well as biosimilars, and so we're committed to the development of both types of products. And 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's 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 non-proprietary name or 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 US. Unlike previous studies that looked at spontaneous reporting systems such as FAERS and the EB, 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 into our internal database.

The first case study we looked at was for a biological, 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-ministered. 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 US spontaneous cases. In other words, we excluded non-US 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 manufacturing information, in order to be able to group it into either a Pfizer-identified product, a product that's 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 is a little bit different from what you've seen in other cases, simply because we are looking at the primary reports coming in. And thus, it's very much reflective of the reporting practices by physicians and patients.

When we looked at the data for a small molecule, what we found was that roughly 83% of the time, we were actually able to correctly identify that it was a Pfizer product or able to identify the manufacturer. However, that still left about 14% of the time when there was no manufacturer identified, and we simply had to group it by its generic name.

Interestingly, when we looked at these cases and we looked to see if NDC numbers were provided, we found them in less than 2% of the time. And when we looked further, 1/6 of 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's 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% 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. And less than 1% of the time 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, and less than 10% of the time was there actually an NDC code provided, and of those about 30% 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. And 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% 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 invented trade name. And that's a very important distinction to make, because at this point it's not clear that global agencies can 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 mixed 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 and 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 US. Based on our data, we would say, no. Our primary data show 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's 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 trade name 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's 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 the companies doesn't have an invented trade name. And 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're 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, both a distinguishable INN plus a specific brand name would increase the accuracy of AE reporting. Thank you.

EMILY: Good afternoon. I'm Emily Alexander, and I'm the Director of US 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 appreciate of the efforts that both FDA and FTC have made at 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 non-proprietary names can affect spontaneous adverse event reports, reports of suspected product side effects that are submitted to FDA after a product is initially approved and reaches the market. Spontaneous adverse event reporting is 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, to be especially challenging when products share the same non-proprietary name. The research that I'm 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 sent 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 incoming 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 airs that might exist in the product identifying information.

So as you know, generics and brand name drugs in the United States share the same non-proprietary 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 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 non-proprietary name.

Our research also established that product name, whether brand or non-proprietary, is often the only information in an adverse event report that meaningfully identifies the product that the patient took. For example, 90% 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 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's reported as the lot number. And 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 FDA has repeatedly recognized the risk of misattribution of adverse events in the biological 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 non-proprietary 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 quote, "Unique non-proprietary 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 a 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 FDA wrote letters to Congress saying that biosimilars should be assigned distinguishable non-proprietary names in order to facilitate pharmacovigilance. So this is not the 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 the 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 non-proprietary name. And it cited this issue, again, in the process of assigning distinguishable non-proprietary names to both Ziv-Aflivercept 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 non-proprietary name, though admittedly it is less common in certain contexts.

If two biologics share the same non-proprietary name and a prescription is written using the non-proprietary 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 US-- and appropriately so-- today, we wanted to provide a brief global perspective, the role of distinguishable non-proprietary names is critical outside the United States. There are countries where brand names are prohibited or strongly discouraged. I think 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

the United States are relevant in the US. Each year, FDA receives a significant portion of adverse event reports that are from foreign-based reporters.

We're 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 non-proprietary names for biosimilars and indeed distinguishable, non-proprietary names for all biologics. A distinguishing portion of the non-proprietary 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 non-proprietary name is the same, this will allow adverse events to be pooled across a product class, if that's appropriate in the 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 non-proprietary name than its reference product. Importantly, distinct non-proprietary names will not prevent patients from having access to biosimilars.

Just one quick example, because I know we're running out of time. In Japan, where biosimilars must use both a distinguishable non-proprietary name and a distinguishable product or brand name, if you will, the biosimilar version of EPO alfa now has over 40% 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 non-proprietary names is that both of these things can happen. We don't need to choose. Thank you.

ALAN: Hello, and thank you. My name is Alan Lotvin. I am a cardiologist by training, and I currently run CVS Caremark Specialty Pharmacy.

And I just would like to put this in context a little bit of why we're so passionate about this. What our industry exists to do is really to create a marketplace-- one of the things we exist to do-- is to create a marketplace among manufacturers to create access to the best products at the lowest possible cost. And we do that by minimizing the differentiations among products that are not that important.

So I'm going to give you our prospective, and our first perspective is that these biologic agents are incredibly important. And no one's going to deny or debate the impact these have had on human health, on patient quality, and length of life. And the industry deserves a tremendous amount of appreciation from any of us in this room who might 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 these products.

If you look at what's happened in the market in the US over time, the bar represents the trend, the spend increase year over year, associated with traditional pills, tablets, and capsules. You can see the tremendous generic wave that has just sort of crested and run through 2012, '13, and '14 has resulted in pharmacy trend rates being negative to low single digits. This is not driven by a reduction in utilization. If you think about cost, it's pretty simple. It's price per unit times number of units. This is not driven by the change in 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 specialty 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 we think especially as biologics, we think of trend rates in the 14% to 25% range.

There is no entity, government, business that can absorb a 20% year-over-year increase in any input cost for any significant amount of time. That doubles your cost every 3 1/2 years. It's just not sustainable.

So what's our prospective? Our perspective is, how do we create and balance the needs for patient safety-- because obviously, it's critically important-- with the desire to create a robust market on behalf of patients and ultimately payers of these services.

So there's two things that have come to light a lot and that we're focused on at CVS Caremark, and I'll get to those a little bit later. Naming, which we've heard a lot about in the last few minutes and the impact of naming on safety and pharmacovigilance, and count some of the state-direct activities to talk to physicians.

First, I want to put the opportunity up there, there's 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 create the same sort of economics for the ultimate payer of health care that we have done in the last five to six years for untraditional pills, tablets, and capsules.

And one of the people who I'm 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 head room in the budget, because again no input cost goes up forever. So there's a tremendous opportunity in front of us, and it's really dependent upon everyone in all 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. So 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 else came before you.

But I think it's really important, and I don't think we should underestimate the importance of pharmacovigilance. But 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 and 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 unique INNs so that we can address the variability and response between originator products and biosimilars, I would ask 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-- well, 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're made by versus what truly is important clinical variability among different lots. And again, the data is captured today.

Let's look at the downside. If we agree that 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 name is, names have power, and people get used to writing things.

And I'm a physician, I'm totally guilty of it. And I can go back and tell you in where I trained in New York, if you tell me what beta blocker someone prescribes, I can tell you where they trained. And I'll be right 90% plus of the time. So names have power, and that's what's 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, we don't 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 here. I think creating individual non-proprietary names really will create a barrier to effectively creating competition among the manufacturers to get the sorts 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 in coverage. That's an incredible barrier to access. So the extent that the overall price comes down, the overall challenge in meeting those early high co-pays 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.

Today, with-- I don't even know how many manufacturers of simvastatin or 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 difference in science it's still a burden. So if I look 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're asking to create a different data capture system than one that exists very well today, that's 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 a market. So 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 broad introduction of generics, $49,000 per quality-adjusted life year, which is actually a pretty good number. You would absolutely go out and do this. After the introduction of generics, 1/50 the price. 1/50 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's created, for the dollar we pay in health care costs.

So CVS Caremark is completely supportive biosimilars. I'm developing a robust biosimilar market. We also understand the need to maintain appropriate incentives to create new and innovative products. 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.

HARRY: Good afternoon. My name's Harry Travis. I'm the General Manager for Aetna's In-house Specialty Pharmacy and Mail-order pharmacy. Now, these pharmacies service approximately 10 million Aetna members.

And I'd like to refer to myself sometimes as a recovering pharmacist. I started practicing pharmacy here in the DC area in Peoples Drug Stores. Those of you who are local, remember Peoples 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'd 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'm 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, 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 US 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 straightforward.

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% biologics 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 the 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 cost of non-specialty drugs has been growing at approximately 5% 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 all 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% 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're talking about biologics that cost on average $100 a day. The average is out of our operation, which is serving millions of lives, is $100 a day is the average. On the left side, it's a buck a day.

So I sometimes like to oversimplify 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, $40,000 worth of drugs a year. They're going to consume $1.5 million worth of drug over their life. And that right side of the pie, 50% of the dollars, is being spent on only 1% of the prescriptions. 1% of the prescriptions, by extension 1% of the patients, are driving 50% of the cost. 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% 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 planned sponsor, that could be a private employer, it could be a union, it could be a state municipality, and of course CMS and ultimately the US 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, this 50% percent segment now represents 10% of total spending, our total health care spending, at Aetna. So $0.10 on every dollar is going to specially medicines. These are the dollars that are 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% segment is the fastest-growing segment of our health cost trend, our book of costs.

I believe that this is the tip of the spear of the health care cost rate of growth in the US. 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.

ELIZABETH: Thank you, all. We're right on schedule, we'll take a 10-- well, we're a little ahead, but we'll take a 10-minute break. We'll 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.