FTC Follow-on Biologics Workshop
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Segment 5
Transcript

Presentation by Neal Hannan. And then we'll begin our panel discussion on Naming and Pharmaco Vigilance.

NEAL HANNAN: Good afternoon, I'm just going to give a brief couple of slides which are more to provoke discussion amongst the panel. And it's going to focus on drug safety and Pharmaco vigilance. I think everybody in this room is committed to a robust Pharmaco vigilance system so that we can record, report, and monitor adverse events. Some of today's speakers have questioned the current FDA adverse event reporting system's capacity to serve the goals of Pharmaco vigilance if follow-on biologics have the same non-proprietary name as their respective reference biologics. In particular, people have argued that adverse events will be incorrectly attributed to reference biologic when they might belong with the follow-on biologic.

But most of the concerns, or not most, but not all, of the concerns raised by today speakers are unique to biologics. There may be special considerations appropriate for biologics, but the problems pointed to in today's presentations arise in the context of existing drugs. If the current system is inadequate can we identify solutions that would address it shortcomings in a way that would also address the Pharmaco vigilance concerns for follow-on biologics.

Let's start by looking at an example of an existing drug. The low molecular weight heparin enoxaparin sodium comes in a branded form known as Lovenox, an authorized generic that does not carry a brand name, and two other generic forms that also omit a brand name. Each form of the drug bares the active ingredient name on its respective label. If an adverse event were to occur and a doctor records just the active substance name, or the INN, it would be impossible to identify which particular enoxaparin product was involved in the event. I think many would contend that reporting the active substance is a start but is a long way from providing the kind of data needed for a robust Pharmaco vigilance system.

So is the solution to this problem to require each generic version of this product to have a unique non-proprietary name? Or does the problem go beyond the distinction between reference drug and follow-on versions? If we were to remove follow-on versions of a drug from consideration, would reporting an adverse event by drug branding be sufficient? We go back to our example of an adverse event were to occur with the branded Lovenox product would it be adequate for a doctor to record only the drug's name and report? Would that serve the goals of a robust Pharmaco vigilance system?

Well if we look at the branded Lovenox, at just one dosage and one delivery mechanism there are five different labeled versions. And those five labeled versions are not even manufactured in the same country. So if we have complex drugs like low molecular weight heparins, would it help to know where a drug associated with an adverse event was manufactured? Who the labeler or was? If so, does reporting just a drug name provide the right level of detail?

In the case of biologics as it stands now without follow-on competition, does a branded or non-proprietary name capture enough of the story for robust adverse event reporting? Or, as I think Jeff suggested this morning, are there other attributes of a dispense biologic product that provide important information for Pharmaco vigilance purposes? For instance, last year the FDA published guidance saying that interactions between therapeutic protein products and the container closure itself may negatively affect product quality and immunogenicity.

These interactions are more likely with prefilled syringes of therapeutic protein products. Yet under the proposals we've heard today about naming, none of the data that would be submitted would capture the type of delivery mechanism provided with the biologic product. In the US if you look at the product Humira it is marketed under nine different labels. Among the nine are three different methods of delivery in a varieties of dosages. Humira come in prefilled syringes, the one that the FDA says can lead to an increase in immunogenicity, prefilled pens, and vials. If the FDA is correct that the container closure for therapeutic protein can play significant role in product quality in immunogenicity, is relying just on brand name or an INN for adverse event reporting adequate to further the goals of vigilance?

Now, right now there are a variety other unique identifiers associated with drugs. One is a National Drug Code, also known as NDC codes. NDC codes are printed, bar coded, and are on nearly every drug label in the United States. NDC codes are unique to particular formulations and product labelers. If a doctor will record just an NDC code they would know, for example, if an adverse event rose in a patient using a prefilled syringe versus a prefilled pen. If you combine that with lot information you would have a pretty robust picture for biologics.

Now the idea of using NDC codes for adverse event reports is already firmly planted on the reporting forms. Now it's our understanding, or my understanding as a former programmer, when I looked at the FDA database specification that it's actually impossible to upload in a batch an NDC code for an adverse event report. So it's no surprise that on the back end when you look at the database data, you're not going to find any in NDC codes. It's amusing-- well not amusing given the severity of the problem-- that someone was trying so hard to supply the NDC code that in some instances it ended up in the lot field. It might be helpful if we had an adverse event reporting system that even took in the data that we provide on the forms to doctors. Moreover, we've heard from a number of pharmacy specialist today that the pharmacies due record NDC data, they do record batch and lot information, and they record this for every patient. So it's not this information isn't available. It's just not being transported over the last hurdle, which is to the adverse event report.

Some have argued that NDC codes are not a good way to record adverse events, because they're concerned that doctors prefer just to use a drug name when reporting an adverse event. What we've heard today that we were told this morning that if a particular batch or a particular lot sits on a dock for too long we need to know what a lot that was. Well the same data showed the NDC codes were under-reported also showed that lot information is missing in 90% of adverse event reports. So if the reality is that we just prefer to go with drug names, rather than a more robust set of data, is the consumer safety best preferred by deferring to that preference? Or would it be possible to get doctors to report NDC codes? In the context of Medicaid reimbursement we have

seen instances where Medicaid has required doctors to supply NDC codes on common forms and in common software in order to receive Medicaid rebates.

I just want to add one more question. The biggest example we've heard today of adverse event report problems with biologics came up in the context of Eprex. . And in that example at least the common conclusion has been that there was a particular delivery mechanism that was at fault. And if that's the case, none of the solutions that focus on naming would have solved that problem any faster. But if an NDC code were used you would have known exactly which delivery mechanism and which manufacturer had supplied that biologic in that case. So with that I'd just like to turn it over to Elizabeth and Susan.

SUSAN DESANTI: Thank you, Neal. Elizabeth has prevailed on me to moderate again since her voice is going, and she claims that because I taught elementary school 30 years ago I much better at sort of wrangling people together and getting things moving along. So at any rate, I think Neal, you've done a fine job of starting out with some provoking questions.

And I'd like us to begin by asking the initial question we have on our slide, which is-- the first question really seems to be, how would they use of either unique or distinguishable non-proprietary names for a biosimilars and interchangeables either reduce or increase confusion. And we'll get to competitive effects next. But there are some people who claim that it would increase confusion not to have distinguishable non-proprietary names. And then there are people who are argue to the contrary, it would increase confusion to have distinguishable non-proprietary names. So I'd like to get that debate out on the record.

Oh I'm sorry, I need to explain to you all that if you want to speak please put your table tent up. I also need to explain-- Don't touch it Neal. Do not touch your mic. OK? This button down here puts it on mute and that apparently was the problem we had this morning. All right so now I go back to my question which is, where would the confusion come from if we went with either kind of strategy. OK. Gino.

GINO GRAMPP: Yes, I'd like to turn the question around to say that-- well I'm going to address confusion that there's a long history of distinguishable non-proprietary names for biologics. So in fact in Europe I believe there are seven different ESA's that drug substances with six different non-proprietary names. Five of those are short acting, so they all have similar doses and indications et cetera. And I don't think there's any evidence of confusion among prescribers for that. They're used to this idea of a common core INN indistinguishable root. We believe that distinguishable names will increased transparency, and also help with Pharmaco vigilance which will actually reduce confusion in the market.

SUSAN DESANTI: I'm gonna go side to side. Sumant?

SUMANT RAMACHANDRA: From our perspective I just showed data and I think from an INN prospective, I don't think we want to sit there and changed the INN. There are two things. One is that we have seen, and I've shown you data, it's real data, that there are unintended consequences of having a distinguishable name. It's very important. Maybe there's not a confusion at the

prescriber level. I believe there is. As a prescriber, first of all prefixes are unacceptable from my perspective, OK. Far more palatable, but still not ideal, are suffixes.

SUSAN DESANTI: OK, can you explain why a suffixes would be preferable to prefixes?

SUMANT RAMACHANDRA: So what happens is as a prescriber I look at a drug name. And when I look at the drug name, I say to myself, do I recognize that name? If there's a prefix to that and there's something proceeding what I would normally recognize I may mentally just take that out of the system and say that's something I don't recognize and therefore is not equivalent in my mind to what the originator was. So prefixes are something that could be problematic.

Suffixes on the other hand that follow a name, even though not ideal, are palatable. The only reason I say that is that if there is a scientific rationale that it will make a difference, then a suffix can be put in place that is not appended to the INN. It's not an INN, but we've talked about this whole qualifier aspect which needs to be thought through carefully. And the reason it needs to be thought through carefully, the only stakeholder here is not the physician. They are peer systems in place, there are a number of other systems in place that have to be thought through when it comes to name.

And the last point is that NDC codes, which are very, very important in the US, are a US centric issue. Now maybe we're just only trying to solve a US centric problem and that's fine. There are no NDC codes outside the US. OK. So I think we have to look for an appropriate solution and a lot has been talked about batch number and another recordable items. But I don't see from our data that adding something or changing the INN or USAN is going to solve this issue to a major extent.

SUSAN DESANTI: Bruce.

BRUCE LEICHER: So let me say that I think this is more than confusion, I think it's actually disinformation to be asking for separate names. If you think about it, for an interchangeable biologic which is demonstrated to be switchable and substitutable, there's no basis whatsoever for distinguishable name. So the only purpose of having a different name is to inform physicians that it's somehow different. And the whole point is that the NDC code as we discussed this briefly before is really the best means for telling the difference between all biologics at the lot level when there are manufacturing changes and when there's a different product. So it's the way to level the playing field and open it up for competition.

SUSAN DESANTI: Emily.

EMILY ALEXANDER: One important thing to keep in mind here is that there's not any biosimilars approved in the United States. And I know that sounds obvious to a lot of us in the room, but that means that there is a real opportunity for FDA to come out and say this is how we're doing it for all biologics going forward including biosimilars. This is going to be our naming policy. It doesn't mean that some are better than others, or some are worse than others, or that it affects interchangeability or substitution. It just means we want to improve on the adverse event miss attribution that can occur improve transparency. So we think it's an opportunity for

FDA to come out with a clear, consistent policy and that can reduce a lot of confusion that could otherwise occur with physicians or payers for things like that. Another thing that we've talked a lot about today is the need to improve the Pharmaco vigilance system across the board for all products. And we absolutely agree with this. We need to have a better quantity of product identifying information and better quality meaning it's actually accurate. And that's true for all biologics. And this improves these improvements in the Pharmaco vigilance system could come through better education, better electronic interoperability at many other means. But some of those will be long term improvements. And that means in the short term when biosimilar are reaching the market we need to work within what reporters are already using. And right now we know that names.

SUSAN DESANTI: OK. Mark.

MARK MCCAMISH: Thanks Susan. Couple points to Emily's point just now, why shouldn't FDA do something different? Well they should do what's right and they should do what works. And right now we've shown that it works in Europe. So to do something totally different just for different sake is ludicrous. So they need to look at what works, what the data is, and then and go forward. Back to Gino's points in terms of EPO, yes there are different EPOs. But I just presented data where the INN was not used for reporting adverse events. So they reported the brand name. So again it doesn't give you support that a different INN would be helpful and it would be in fact more confusing.

And then on Australia we argued over this data. But if I look at your pie charts, your pie charts basically said that with the modify name you had about one fifth market penetration and with the not modified INN you had about one third market penetration. So I mean if I was there I'd rather have the one third market penetration one fifth. And then lastly it gets down to in terms of the just being disingenuous because the issue you mentioned in terms of naming if you go back to [INAUDIBLE] which I didn't go through but you guys can all look up the backup slides on [INAUDIBLE] when the manufacturing changes that happened if that was an issue and you wanted to track and trace there was a significant [INAUDIBLE] change with [INAUDIBLE]. And you had the chance at that point in time to have a different INN if you wanted to track if it's so important to tracking it yet it comes up 10 years later. So again the issue is those are all potentially very confusing issues for a physician and we know that and we're on different sides of the fences because we all have different motivations. But again this is data that really deals with the issue.

SUSAN DESANTI: Aaron.

AARON KESSELHEIM: Yeah. So I mean I think that my answer to this question is it depends. I think that one should just follow what the science is and what the drug is. And for a drug that is truly interchangeable and is the same drug it should have the same name. And if it has a different name, I can tell you as somebody who sees patients every weekend and talks to them about the names of their drugs, it will cause confusion. But if it's the same drug it should have the same name. If it's a different drug or even if it's a similar drug but not exactly the same drug then maybe there's an argument for it to have a different name and we already have experience with that. With [INAUDIBLE] you focused on takeovers.

So we already have experience in the marketplace with similar drugs, Omeprazole and Esomeprazole. And they have different, slightly different, prefixes as part of their full name it's because they work approximately the same way. In the case of Omeprazole and Omeprazole work exactly the same way, but they're slightly different. And therefore there's a difference in the name. But for a product that is truly interchangeable there is no scientific rationale for having a different name.

And then I also wanted to just make a point about the adverse event reporting system, which is a good thing to have and is our current system as a way of reporting adverse events. And it's pretty good for hypothesis generating exercises about potential adverse effects. But nobody has ever pulled a drug off the market simply on the basis of data from the adverse event reporting system. What they then do is they then go to the real data with the NDC codes and the large data sets by in the manufacturers, the CVS's and the Etna's of the world. And they use these larger data sets to do real Pharmaco epidemiological studies to evaluate the association between a drug and an outcome. So I don't think that focus on the [INAUDIBLE] systems necessarily should be the focus here.

SUSAN DESANTI: Marissa.

MARISSA SCHLAIFER: I think it was mentioned-- and we know that the majority of physicians or a large number of physicians do prescribe by the brand name. However I think as younger physicians, the uptake with younger physicians is to prescribe by the generic non-proprietary or INN name. And I think as you start adding prefixes and suffixes for a physician who just wants the drug. Doesn't have a preference between the various brands. To just write out the one name it becomes the equivalent of writing for a brand name if there are variations in the INN or in the non-proprietary name. So you end up with the physician having to remember the alphabet, which is just not going to happen. They're going to write for the non-proprietary basic, non-suffix, just because it's easy way to go. And I think by throwing that in it's putting extra burden on physicians rather than trying to make their life easier.

SUSAN DESANTI: OK. And I do agree that we are missing physician-- we obviously have some physicians on the panel-- but we could use more physicians. And we have been asking the AMA in particular to help us collect some reactions from different types of physicians that do use biologics. Gino, you've been waiting awhile.

GINO GRAMPP: I'd like to address a couple things. First Europe has put in place a solution. We've been hearing a little bit about it today. But it's a coherent policy proposal. It's a coherent policy proposal because it requires manufacturers to use a brand name or trade name. They have that authority. It also is a coherent policy proposal because there are legislative mechanisms that are rolling out to the member states to require prescribers to use those names that are going to be put on the packages, or at least encourage it. And certainly require that reporters of adverse events use those names in the event.

I am completely open minded to that type of a policy proposal for other parts of the world, including the United States. I haven't heard anybody proposing a coherent set of package proposals the FDA could implement, because they can't do that. You have to go to Congress and

the states to do that. And so that's why this non-proprietary naming policy is something FDA can consider and implement right now. And it will address these holes in the system that we've been discussing about.

Another point though is regarding manufacturing changes. It's a good point. Mark mentioned that manufacturers do occasionally make changes that are significant. That may entail more scrutiny in the post approval phase of the product. As long as all the reports for that product come to that manufacturer, which was the case for darbepoetin when we made that change. The Manufacturer and the regulatory agencies can sort that out. They have signal detection, there's enhanced monitoring, et cetera. It's when you have multiple players in the mix, and not all the reports are going to the right place, where it becomes a systemic risk.

SUSAN DESANTI: Can I ask you a question and this is for other people as well. I just want to clarify on the record if you have a number of brand name biologics, do all of those brand name biologics have the same INN or USAN? What is the current convention?

SUMANT RAMACHANDRA: So I can speak at you from experience of what we are just seen in a recent approval with the multiple antibody called infliximab. We got approval of the trade name Inflectra, the Brand name Inflectra in Europe, and the brand name Inflectra in Canada just recently. And the INN in that situation is infliximab. So one of the very important points is that a drug has multiple distinguishable features. But it has one common feature. What happens when your common feature becomes a distinguishable feature. And it has to be a scientific or clinical discourse across the world because these medicines are use across the globe. You can't even speak a common language anymore because you have to write a paper that says we used infliximab AKA infliximab something in Canada AKA infliximab something in Australia.

So you have to qualify everything so that you have to actually spell out every single version of that. The common language of a drug is the INN. And everything else around it is distinguishable so it's important to least keep that core as understandable and as common as possible between biosimilars. EMA has told us flat out in a recent workshop in London that they have not had a problem. In fact, they're quite proud of the Pharmaco vigilance reporting of biosimilars and biologics, originator biologics, in Europe. That was the comment that they made right at the workshop. So they don't see it as a problem and our recent approval in Canada points out that the Canadians actually have given it also the word name infliximab.

SUSAN DESANTI: Mark McCamish.

MARK MCCAMISH: Thanks. Again in response on EU having this coherent program Gino, when you're referring to that. Again mixed messages because what you're saying is for the tracking appear it wasn't helpful. And so something needed to be done but now it's coherent and so it works. So a little challenge there but I think the point that you bring up is a good one and also I think was Helen from Pfizer brought this point up which EU uses. They mandate a unique proprietary name. And then a non proprietary name. And there is discussion where FDA feels they do not have the authority to mandate a unique proprietary name. So then they're using that a authority for the unique INN. Theoretically. Now an easy resolution of this, quite straightforward, is if the manufacturer does not select a unique proprietary name, that's their

choice. And FDA can then mandate a unique INN or USAN. So that takes care of the problem. And then it's up to manufacture to do that. But in this situation that's the issue where Europe did work.

On the other issue for the INN and you brought this up physicians prescribing by INN. Literature published medical journal of Australia suggests that, and they mandate prescribing by INN, and if you go in and then evaluate it only 50 percent of the docks prescribed by INN and what they decided was in their research that it's the number of letters for the INN. And if you get more than 15 letters they won't prescribe by the INN. And so by adding something else on to it is going to be more letters and it's going to be more challenging for them to utilize that. So let's go for what's easy, useful, scalable approach.

SUSAN DESANTI: Bruce.

BRUCE LEICHER: I just wanted to add one additional comment to what Mark was just saying which is the FDA does require every manufacturer to put their manufacturer name on the product. Which is just as distinguishable as any brand name. So the notion that there needs to be a brand name when there's a manufacture name is more than adequate to know whose product it is.

SUSAN DESANTI: Emily. Emily Shacter? I'm sorry. You had a comment about the issue with lots being left on a loading dock out in the heat, and I just wanted to get your perspective on that.

EMILY SHACTER: Well the comment was made earlier today that, what if a lot gets it's left on a hot tarmac? How you going to know if a patient was prescribed material from that lot? And I was just commenting in a break room that I think that this is a decoy comment because all manufacturers have to have shipping validation studies in order to determine that their product actually can sit on a tarmac for a certain period of time and incur whatever heat and have boxes or containers that can control the product during that time. So I don't get the hot tarmac comment because this has to be controlled for all products, biosimilars as well as other protein products and other drug products. So, I don't thank that this takes out of control the ability to track one product verses another or has really anything to do with product quality biosimilars compared to innovated products.

SUSAN DESANTI: OK and then I would just like to follow up on the presentation in terms of likely competitive effect. I think we heard and please correct me if I'm wrong. I think we heard Sandoz and Hospira-- "huh-SPEE-ruh" excuse me, finally, finally she says it correctly-- that they have data that shows that using different names will reduce the uptake, is likely to reduce the uptake, of biosimilars. And I believe Gino you had data from Australia that you maintain shows that there is no effect. And I just wanted to give you all a chance to have a dialogue about the data and then we can move on to the next question. But to the extent that we can sort it out.

GINO GRAMPP: A clarification to that, Hospira has-- we don't have data to say that a different name we'll reduce uptake. What we do have data for is to show that a unique INN is not needed because a brand name sufficed into two drugs that we've been marketing for several years. OK, what we also know is that when you do have different INN's, , you have a problem that occurs in

the country reimbursement systems in terms of getting the drug to be accepted. So I just want to make sure that it's very distinguished. One is a easily identifiable by brand name we're seeing that. In fact Pfizer's data, it was a joke at Pfizer, they said 99% in the biologics field are identifiable by brand name and that's exactly what we are seeing. Now the conclusion is different in our conclusion for the exactly the same type of numbers. But I think that's one set that we can actually identify by brand name. The other set is that there are unintended consequences.

Two things. The one thing that is common between originator and the biosimilar is going to be the INN. You start making that distinguished, there's nothing in common between the biosimilar and the INN. And maybe that is the intent at the end of day by some parties but to be honest with you that we have to have a common language of want drugs are used for. And that INN is that common language.

SUSAN DESANTI: OK, Helen.

HELEN HARTMAN: Actually, there's a couple of different things that I wanted to address. The question really isn't whether the packages have enough distinguishing information. It does have the manufacture information, it does have NDC. It has a brand name it has the INN. The problem is that's not actually getting into the reports. So it's really pointless when it comes to Pharmaco vigilance. And so really we need to work within the system that we have. We need to work within the parameters of the AE reporters. And the way physicians and hospitals actually report the data. And so it's for that reason where even though we came up with the same data where brand names really do work. The problem is when you have biosimilars out there without an actual trade name, an invented trade name. And then you have potentially a pool of AE where you have the same INN and there's no distinguishing information there.

SUSAN DESANTI: I think what you're proposing Mark, though, was that it would be up to the biosimilar or interchangeable manufacturer to decide whether they wanted to have a brand name. If they did that would be used. If they didn't then the FDA could assign a distinguishable INN. Was that what you were saying?

MARK MCCAMISH: Correct, I mean if that is driving the issue now I don't agree that it's driving the issue for AccraPharmaco vigilance. I think we have to improve the systems overall. And be able to track down to lot numbers, et cetera. And so let's talk about how we do that for all biologics that are there. But if that's the issue and you present it as the barrier then that's a simple resolution that FDA does have that authority mandate an INN. So that would be again pragmatic approach in terms of dealing with it. But Susan to get back to your other question which was in terms of competition. I mean I presented the data that's there from Sumant's prospective. What he presented really confirms that there is confusion. Confusion at a country level when you have a different INN. Now these aren't doctors, but they are policy makers that are making policies and they're confused. And they're not allowing us to compete in the tender and we've shown data from Australia and Gino showed the same data just a matter of interpretation where we have absolute evidence and we know we're trying to make it happen. But there is a difference. When you have a different name attached to that from an INN. And it goes back to the same thing, when you look at it really connotes different substance. I think Aaron's point was very good when you have something like pegfilgrastim, it's definitely different than [INAUDIBLE]. And

you should have a different INN that's there. And that communicates that to a clinician as well and so that's where it's pretty straightforward even the ABSM survey that I showed tells you that a name is important and it was suggests that the product is

Speaking from the perspective of someone who's running an organization that is processing thousands of these prescriptions a day, the $3, $4, $5,000 prescriptions a day across thousands of physicians offices, thousands of phone calls faxes and emails a day. Adding one more variable to that is a big lift. I would urge everybody to try to use the existing system you just said, that there's multiple pieces of information that are not going into the system now. How do we make that better? Adding the unintended consequences of adding another variable we just can't even quantify how much confusion that is going to put into the system.

SUSAN DESANTI: OK, I want to add in one more variable, which is the new track and trace legislation that has recently been passed, which is going to require serial numbers on pharmaceuticals and Elizabeth maybe you can explain a little better than I can.

ELIZABETH JEX: My understanding is-- and I believe the question from the audience identifies it as the drug quality and safety active 2013-- My understanding is that it identifies it establishes that there's a product identifier number that's to be assigned to each product and every pharmaceutical drugs sold in the United States will be-- and medical device-- will be tracked through the distribution system from the manufacturer through the wholesaler to that end retailer. And so the question is why can't that one-- are we right about that system? Can anyone elucidate us on that system and how that system can be married with adverse event reporting so that there is a robust and redundant system to determine whether or not the distribution of biologics among others has been penetrated by counterfeit adulterated miss branded or miss manufactured medicines.

EMILY ALEXANDER: If I may there's a few important nuances when we're talking about the track and trace legislation. One is the timelines for implementation are very long. So it will be many years before we had--

SUSAN DESANTI: 2017, is that correct?

EMILY ALEXANDER: Well there's I think there's multiple stages. It will be 10 years before we really have the full interoperability that's imagined ultimately in the statute. There's also exceptions for dispensers of products so that could be pharmacists or it could be physicians. The drug transaction history or the pedigree information can often remain at the wholesaler level. So it won't always translate down to the physician or the pharmacy. I also think one important thing when we're talking about integrating it with adverse event reporting is that there's no requirement in the act as it was passed that the pedigree, or drug transaction history information, be integrated into the patient's file. And so that's really where the gap would need to be assessed. And again, that may be a good long term policy goal that we should be striving towards for all products. But in the meantime that's not going to provide us much assistance.

SUSAN DESANTI: Gino?

GINO GRAMPP: Yes, I'd like to make clear, Amgen fully supports comprehensive solutions to Pharmaco vigilance. And yes, we focus on biologics because that's what we make. It would be ideal to be able to improve Pharmaco vigilance for other classes of products that are more complex and require traceability. So yes we ought to find a way to get more batch numbers. Which already exists we don't need the track traced legislation to get batch numbers into the pharmacist hands. The challenge right now is to get the batch number into the adverse event report. How can we do that? Can that be captured in the new EHR meaningful use requirements. I don't think that's in there right now but could that be captured? Is there a way for that to be automatically uploaded into a midwatch form, which as you mentioned earlier Neal, doesn't happen right now same thing for NDC codes. So I think we need to be having these conversations, fully support them. I just don't know what the timeline for that is. It could be 10 years it could be more before such a thing is broad based and implemented. That's why we believe we need another solution to plug the gaps in the next 10 years.

SUSAN DESANTI: Marissa and then Mark.

MARISSA SCHLAIFER: I think, and maybe I'm just a little slow but, what keeps coming back at least what I've heard is the only place I've really heard that a suffix or prefix could really assist in confusion seems to be in the Pharmaco vigilance area, at least that seems to be where we keep coming back to. And today we have, if we need an additional piece of information, if we need a suffix, we have a manufacturer name. And everything we would accomplish by adding a suffix we could accomplish today by using the manufacturing name as a suffix. If the problem is that the manufacturer name is not being reported then what makes it so likely that the suffix-- I mean we've got the tool if we're not using it then let's use it. But I don't see-- so far no where today have I heard a reason for another tool it's just that we're not getting that manufacture name and we need it so let's create a system where we get it.

SUSAN DESANTI: Mark.

MARK MCCAMISH: I agree with Gino and with Marissa on this, where we just need to capture the information I think the new legislation which is designed to try to track down misbranded adulterated fake products is we'll provide the same information we need for track and trace down to the lot level, which I think would be nothing more than helpful here in this situation. And you can imagine if you're selling something for $5,000 a vial, people are going to try to make fake products and get it in the system. It just happens. So I think the legislation, however long it takes, is going to be helpful to bring more information and better tracking as we move forward.

SUSAN DESANTI: Bruce.

BRUCE LEICHER: So we-- I'm not going to repeat the comments made by others-- we agree that this creates confusion for biosimilars but just step back for a minute and think about the confusion having different non-proprietary names would have for an interchangeable biologic. Because if doctors are in fact moving to prescribing by established name and they write and there's a different established name for the product. How does the substitution going to occur? It just doesn't make sense. One of the frustrations I have with the discussion we're having as we're all assuming for the purpose of this question that there's a Pharmaco vigilance problem. And I

think we heard a lot of evidence today that there really are some opportunities for some real innovative solution. And if we're going to fix it we should fix it for all the manufacturing changes that Mark identified earlier, that if we're going to track stuff we should be able to track it would NDC number.

SUSAN DESANTI: Sumant.

SUMANT RAMACHANDRA: So even though there are no biosimilars actually approved in the US, there are biologics that have the same INN a different brands created by different companies by different processes. So for those who think that the US has zero precedence there are precedent in this country. So yes, it's a different pathway understand it's a 351A pathway or another pathway that got these biologic agents approved. But even in that situation the INN was kept the same and the brand was different. So those drugs were not even approved by what is a highly regulated high bar biosimilar pathway. And now we're seeing a new rule must come into place for biosimilars even though it's done in a highly regulated high scientific bar concept. And this is the US guys, I just want to make sure everyone knows it's already happening in the US, maybe not as a biosimilar, but as an original biologic with the same INN, different manufacturers, different trade names. So we have to be careful of creating a new rule in already precedented market. And I think there are going to be unintended consequences that companies will feel as a result of this.

SUSAN DESANTI: Emily.

EMILY SHACTER: So I want to comment on the how the name might change and the FDA has already indicated it's thinking on prefix versus suffix and the leanings are certainly towards prefix given the examples that Emily Alexander gave. What I would worry about this scientifically and from the patient safety perspective is to equate three letter prefix for something like ado-trastuzumab, which is an antibody drug conjugate, which is dosed very differently from trastuzumab, to an XYZ biosimilar that's dosed identically to the innovator product would suggest that there has to be concern around the dosing of the product and other areas of confusion. To have those equal each other in ado-trastuzumab to-- I mean tbo-filgrastim got a different name, most likely because it was not developed as a biosimilar. One could discuss the value of having that different name for product that is actually dosed the same as, for example, Neupogen, Amgen's product. But to equate ado-trastuzumab to an XYZ biosimilar seems to be off the cliff. Because they're so vastly different. So what's the message in that?

SUSAN DESANTI: Well and also Emily isn't there a large portfolio of antibody drug conjugates in the pharmaceutical pipeline? So we're going to look at more and more of these conjugates with a drug name in front of an antibody name.

EMILY: Very much so, that's very true. They're very promising drugs.

SUSAN DESANTI: Gino.

GINO GRAMPP: Yes, I'd like to come back to Bruce's question which I think is a good question but what does this mean for interchangeability. So I think the first thing we might want to ask is

will we expect interchangeable products to be branded. We've been talking about the past tense for biosimilars which are not interchangeable in the US sense of the word in other parts of the world. And they all have brands, or at least a trade name such as filgrastim XL in Europe for example. Fine, in the traceability to those brand names or trade names seems to be working to the 90% plus rate as we heard earlier.

But when you go to interchangeability will companies develop brand names? So how are we going to trace these products when it's interchangeable? Are we going to just hope that the NDC code makes it into the system? What is the mechanism? The manufacturer name to somebody else made that point. Yes that would be great that's what Europe has essentially for nonbranded products. You put the manufacturer name with the INN and that must be captured in the medical record. There's no requirement regulation or policy for that in the US and no requirements for that at the state level.

SUSAN DESANTI: Tina.

TINA MORRIS: I just want to tack on to what Emily said and raise the scientific concern that if you had something that has a prefix from a scientific point of view that from the substance identity is basically the same as something that does not have a prefix it's problematic. For example, we would find out that tbo-filgrastim at the primary structure level passed the USP identity test for filgrastim we would have a real problem. And I don't see how that's helpful.

SUSAN DESANTI: Do you have a real problem with that?

TINA: Yes, based on-- I'm looking at our lawyers but I think if I understand--

SUSAN DESANTI: Potentially?

TINA MORRIS: If I understand our role correctly tbo-filgrastim would-- if it's tested and complies with the USP identity test for filgrastim is misbranded.

SUSAN DESANTI: OK, Mark and then Sumant.

MARK MCCAMISH: I think going back to interchangeability component and particularly USFDA, there's another problem in that the FDA has made their preferences known that they would rather have a two stage approach. So approval of the biosimilar first and then with some undefined experience on the market then consideration interchangeable biosimilar. And if you followed the naming you would then have this biosimilar with the unique INN that is then approved as interchangeable. Then what you do? You got this history that's there. So it just, it again it doesn't make sense and we go back round and round and round I think the consensus thus far from a Pharmaco vigilance perspective all the data suggest that adding a different INN is not going to be that helpful and in fact for interchangability be really, really confusing.

SUSAN DESANTI: OK, Sumant and then Marissa.

SUMANT RAMACHANDRA: So what one of the things is Hospira is an injectable company just by nature. We have a lot of devices and software but injectable company. So we deal with a lot of small molecule injectables and we deal we have three biosimilars in Europe, one Australia, and now one in Canada. So one of the things that we learned is that the intake of Pharmaco vigilance when the spontaneous call comes it's probably the number one important step. I would actually submit that it is the responsibility of the manufacturer to capture the right data as much as possible. And what we have put into place is a system to capture as much of the data as up front as possible. There are gaps in all of our systems and Harry said this correct if you start messing around with, and adding an appendage to an INN, and then you actually think it's going to solve the problem it's not going to happen. We are dealing as a company with multiple sources of the same drug. We just happen to be one source of, let's say, paclitaxel. And we have to make every effort because of our systems to make sure that paclitaxel-- Taxol, the brand name from Bristol-Myers Squibb-- actually is ours and not one of the nine or 10 other people who make paclitaxel. We have to as an industry commit to have robust systems in place rather than thinking that the hammer approach or the blunt instrument approach of adding something to a name will suddenly magically make things even disappear in terms of the issues of the Pharmaco vigilant system. We need more sophisticated solutions to this not naming solutions to this. And we need to commit as an industry to better Pharmaco vigilant system. I think that's where the problem lies.

SUSAN DESANTI: Marissa.

MARISSA SCHLAIFER: I think as I listen to this conversation, and as a pharmacist not an expert in biosimilars, it's creating questions. We've talked about Pharmaco vigilance we've talked about mid watch reporting and we talked about the differences that happens when there's issues with one manufacturer's product and not other manufactures product. But as we see drugs that have been out in the market for long periods of time as things are out in wider use it's more common that we see something that would be across the drug that we wouldn't see when there was just the originator product and the products been out 10 years. And we start seeing problems that go across all manufacturers. It's a problem with the actual drug itself not the manufacturers lot. And if we start having prefixes and suffixes, and I think with this I think more about prefixes than suffixes. But either we need to make sure that we realize there's a problem with the drug. And I think the prefix suffix issue could actually cause more confusion when we have a problem with the drug and not a problem with a specific manufacture drug. I'm sure people who are more experts in this industry can probably speak to that. But I think that's something we need to and we will see problems with drugs not products problems with individual manufacturers drugs.

SUSAN DESANTI: Emily.

EMILY ALEXANDER: I disagree in the biologics context. I think you can have multiple sources of a similar or same molecule cross product. But one manufacturer could, for example, scale up. And that scale up although there's nothing fundamentally wrong with the underlying molecule has caused some unexpected problem that will then later manifest in the market. And we want to be able to track that. So I think for drugs that's absolutely the case that you expect the safety profile to be related to the underlying drug. But the difference between drugs and

biologics means for biologics that sensitivity of the manufacturing process means it could not be related to the underlying molecule.

MARISSA SCHLAIFER: By no means do I think that there's not. I'm not saying that there's not a potential for a manufacturer problem. But when a drug has been on the market for two years we don't necessarily know all the problems it has. Drugs that have been on the market for 10 years is when we start seeing a large number of problems. I'm not debating whether or not there could be a problem with an individual product. I could debate that but I think is different question my question now is, what happens when we find a problem. There will be problems with drugs. Drugs have side effects we need to have a way to track those side effects.

SUSAN DESANTI: Emily.

EMILY ALEXANDER: Well I think again, you know, the real compromise here may be a distinguishable but related name. I agree that if you are getting into fundamentally different non proprietary means it becomes harder to pool across products and really see common trends. But the common core element of the non-proprietary name will better help us pool that type of data that you're talking about.

SUSAN DESANTI: OK, Emily Shacter.

EMILY SHACTER: So if I could respectfully make a counterargument to this concept of change in the manufacturing process and having a product go out onto the market with an unexpected adverse event profile. If the manufacturer makes a manufacturing change that is adequate to have a potential impact on clinical activity, safety, or efficacy, they are required through comparability standards to demonstrate before that product goes out to market that it is not going to have a different clinical profile. That doesn't mean that things don't happen. And FDA has seen every adverse consequence of manufacturing changes that can happen. And that's one of the reasons why the FDA is risk averse. We, they, have seen it all. But if that happens A the company has not done its job and the FDA has not done its job. And I would posit that also with the argument on drifting and products changing over time, if significant drift is happening in the product then again either the sponsors not doing their job with the FDA is not doing their job. If that drift is controlled so they understand the impact on clinical activity and there's no significant impact in clinical activity, fine you can have an attribute change. It's not critical.

SUSAN DESANTI: Thank you. I think we have time for two more comments. Gino and then Mark. Gino?

GINO GRAMPP: Just quickly to Marissa's point I think that it is possible to aggregate safety signals for classes with related names in distinguishable suffixes. It's been done in Europe for epoetins, as I mentioned earlier the large number of different drug substances there. And then with regard to the safety issue in and potential effects of manufacturing changes. I think we all agree this is a very rare event that it would happen because we have a capable regulatory system, capable manufacturers, and good quality systems. But Pharmaco vigilance is part of that capable system and so we shouldn't lose sight of that.

SUSAN DESANTI: Mark.

MARK MCCAMISH: Now coming along the same in terms of what Marissa was saying and then Emily Alexander I think it can be done when you have different INN's. But Pharmaco vigilance is a challenge to do that. And Emily you mentioned I think I believe but in that would have to be databased. And the data suggests that it takes extra steps to consolidate that type of information. The more INN's you have the more difficult it is to consolidate. Can be done, but it takes more effort.

EMILY ALEXANDER: Sir my lack of eloquence aside we know there are examples of related but distinguishable non proprietary names where there has been pooling of adverse events.

MARISSA SCHLAIFER: And I guess-- I'm sorry.

SUSAN DESANTI: Marissa.

MARISSA SCHLAIFER: I guess my question was we go back to individual physicians and individual physicians seeing a pattern. When they have three different drugs or supposedly three quote unquote different drugs across their patient base. And they're seeing something that they may see some in this drug some in this drug some in this drug. It's really all the same drug. And having physicians not identify a pattern that they would choose to report. The physicians don't always report when they see one thing, and when they see one thing in one drug. But when they see the pattern that they may not see across drugs they perceive this as being different, but are actually the exact same drug they may not choose to report it.

SUSAN DESANTI: OK Marissa, you have the last word. I want to thank our panelists and invite Andy Gavel to please come up and share some concluding remarks with us.

ANDY GAVEL: What a terrific day. Thank you all for joining us and participating in listening in on today's very thought provoking and high quality presentations. I'm really delighted with the presentations and comments that everyone brought to the table today. I especially want to thank our presenters and discussants who have provided us with so much food for thought, even though budgetary constraints prevent us from offering any food. We've had a very lively and informative discussion reflecting very varied perspectives and we'll take all that back and seek to digest it.

As you all know it takes many people to conceive of and organized a workshop such as this and I'd like to single out some of our organizers for their enthusiasm, dedication, and commitment, and creativity in assembling today's program. First join me in acknowledging and thanking the team and it was a big team. Aaron Flynn, Chris Brian, Chris Garmin, Meredith Andres is here, Karen Bird, Kelly Signs, Stephanie Wilkenson, Andrea Kelly, Sheryl Warner, Rich Custer, and Gale Kingsland , our OPP deputy directors Tara Costloff and Susan Monk. There are also lots of FTC support staff that help with the event too The office of Public Affairs, event planners, the media team, paralegals at the registration table. As I said it takes a big team.

I'd like to especially single out Neal Hannan and our moderators today. Elizabeth Jackson, my predecessor in OPC Susan DeSanti. A special shout out to Elizabeth I know many of you have

interacted with her. She spent many, many months conceiving of and organizing the program. Reaching out to speakers. And I think she is particularly owed a little round of appreciation.

Finally I'd like to remind you all that the public comment period for today's workshop will remain open until March 1. The details of this mission process can be found in the Federal Register Notice or on our workshop website. We encourage and look forward to receiving and considering your comments. So thank you all again and safe travels home and we did it. We made it through a day without adverse weather conditions. Thank you all very much.