

And so obviously you have to use judgment in the magnitude of the clinical trials that are required to understand the safety and efficacy profile. But if we use therapeutic equivalence as the benchmark to patients and clinicians, then we're, I think, obligated to really fully understand what really happens in the real world.

DR. SCOTT: That's a very interesting example that you presented because what you showed is that a PK that looked even favorable for a product did not predict the clinical outcome. At least I understand that you had two different studies to compare and I was wondering two things.

One is what do you think the explanation for that is? And the second is how does this effect your thinking about reliance on PK superiority versus clinical outcomes and the overall concept of how to approach follow-on biologics?

DR. BARRON: Well, I think the first question is, what do I think of the clinical data? I think it's really hard when you don't do head-to-head comparisons to really make much of any data. I think it's interesting. It certainly went in the opposite direction one might expect to see.

But I think it's very possibly either due to chance alone or differences in the populations of the trials. That having been said, it might be real.

And I think it was really shown to demonstrate the fact that you really just don't know all the things that effect efficacy and safety.

I think it's comforting to see the safety signals were virtually identical. So that, I think, is extremely important to understand. And we had a very large safety package at the time of filing.

But you certainly can't rely on these things to predict things when you certainly don't understand the mechanism clearly. And even when you think you understand the mechanism clearly, you're probably going to be found out to be wrong five or ten years down the road.

So I think it's just very challenging. And that's why, again, it requires clinical studies.

DR. KOZLOWSKI: Okay. Thank you very much.

DR. BARRON: Thank you.

DR. BAKER: Good morning. My name is Don Baker, and I'm a Vice President for Post Market Quality Management for Baxter Healthcare. However,

today I am representing the PPTA.

PPTA is the industry advocate organization for the manufacturers of plasma protein therapeutics and the recombinant analogues. And the perspective that I'm going to give today is that of an industry association in which we produce biologics on a very, very large scale. Our output is measured in metric tons.

We have both materials derived from human source material, human plasma, as well as recombinant proteins. And our patient population that we treat are by and large they receive our therapeutics chronically and they are a relatively small patient base. And the remarks that I'm going to be making today on the concept of FOPPs is within the context of these products.

This is going to be a brief industry-wide consensus. As you can imagine, when you're trying to represent one company's perspective, it's difficult enough. When you're trying to represent multiple companies' perspectives, it gets very complicated. And we will present more elaborate remarks to the written presentation.

The major theme I found in developing this

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presentation is case by case. It depends. Yes and no. All of these questions receive about the same kind of answer. And it seems to be that every question is responded to very much in the context of a particular therapeutic.

However, we would also, as an industry, very much encourage the FDA to take into consideration the European authorities and their biosimilar legislation. I think this was discussed at some length yesterday and as a global company, we just would very much hope that whatever steps that are taken with respect to follow-on products, that these take into account global considerations.

With respect to manufacturing issues, and again I'm going to try and frame my remarks in the perspective of clinical and preclinical studies, it is our perspective that all aspects of the process must be considered. For our products in particular, which are chronic use products and many of which are derived from human source materials, the safety of the product in terms of the viral inactivation is very, very important.

This is obviously less of a concern with recombinant products but certainly all aspects of the

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manufacturing process from the nature of the source material to the final product testing is important and needs to be thoroughly considered.

In terms of our products, what's likely to effect performance or preclinical or clinical safety very much, as I mentioned, the viral inactivation. That's a key component. Formulation can be very key.

We had a recent, for our own company, a recent experience in which we had a five percent immunoglobulin product. We were making what we thought was a relatively small change in formulation.

The analytical differences between the precursor product and the reformulated product were what we thought were insignificant.

And yet this product failed in its clinical evaluation. It showed an unacceptable level of allergic-type reactions. And I think this is indicative of the kind of minor changes that you can make which are only identified later on in clinical trials.

In terms of the capability of the current assays, it is our perspective that the assays that are available now are adequate in terms of looking at the -- from the primary to the quaternary in very fine

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structural details. However, our ability to understand the significance of small changes, it is our perspective that we can characterize better than we can understand.

Certainly there will be new technological advances but realistically I do not see within the near term that we will be able to fully understand for all products relatively small differences that we can see by characterization.

And has been mentioned by numerous people today, hindsight is 20/20. And when you know there is a difference and then you can go back at the molecule and take a look for it, you can frequently find it. However, understanding that that difference is important prospectively is a large challenge.

There has been a lot of discussion on immunogenicity. Our products, particularly the Factor VIII products, are virtual poster childs (sic) for immunogenicity and we have in our history many examples of manufacturers who made what they thought, again, were small process changes and had unexpected and unfortunate surprises in the clinics.

So, again, I think that we would recommend that clinical trials would be necessary to fully

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understand the safety of a product.

In terms of the characterization of the immunogenicity studies, this is, again, difficult in terms of whether one is going to do head-to-head studies or use historical controls.

Our perspective is that head-to-head studies are necessary because the changes in medical practice and changes in our ability to understand what we're seeing in the clinic do change with time. And so head-to-head studies are certainly the most definitive.

In terms of streamlining human and animal studies, first off we very much want to indicate that we believe that the innovator information must be absolutely protected. Our companies have decades of experience in many cases with the production of our products and this proprietary information represents a substantive asset to the corporation. And so we believe that these should be properly protected.

However, where appropriate animal models exist, it is our perspective that follow-on products could conceivably have a shortened clinical trial. And, again, this becomes very much a case-by-case situation.

Certainly, for example from our perspectives, a follow-on manufacturer that was producing a human serum albumin, a relatively simple and low molecular weight protein, could have a very much abbreviated clinical course relative to a follow-on manufacturer that was producing say a Factor VIII.

However, given that, we still believe that it will be impossible to avoid doing some form of clinical trial.

Potency assays, again this is very much of a case-by-case situation. With respect to intravenous immunoglobulins, the potency is a very difficult issue to address simplistically.

The utilization of these products, they are utilized for many very diverse clinical situations, and so it is, again, difficult for us to make a simple statement with respect to how potency for follow-on products ought to be addressed.

However, for some products in general there can be at least an approximation of an assessment of potency in-vitro. However in-vitro studies are generally not appropriate for safety testing.

In-vivo studies with respect to animal studies, it is our perspective that these can be used

for perhaps acute toxicity but not immunogenicity. And we've had lengthy discussions on immunogenicity today so I won't get into that.

What we are looking for, though, in follow-on products is that there is a balance between the innovator's experience and the burden placed on the innovator and the burden placed on the follow-on.

We certainly would like to achieve a, if you like, a natural justice in this situation.

Finally with respect to terminology, our companies found that the second generation definition appears to be satisfactory. We had no particular comments on that.

However on the follow-on protein product, here we had, in essence, in our industry, very little consensus. And we found the words similar version or copy to have different flavors in the meaning. And we will get into this in more discussion in our written comments.

Thank you.

(Applause.)

DR. DAVID GREEN: You've talked about viral inactivation. Could you expand on that in terms of the degree of testing that might be appropriate

regarding chemical versus mechanical means of viral inactivation? And the degree of testing that you foresee with the structural changes in terms of whether CMC or physico-chemical determination would be enough? Or additional studies, let's say non-clinical and clinical studies, would be appropriate?

DR. BAKER: That's a very extended question. However, I'll try to make a few remarks on that.

I would divide viral inactivation studies into -- or viral elimination studies into two buckets.

One, a bucket in which you are truly inactivating the virus. And another bucket in which you are partitioning the virus.

In our experience, we found that both of these can be effective for viral elimination. However, partition experiments are extraordinarily -- and partition processes are extraordinarily sensitive to the nuances in the production process.

And so I would require a very high burden of demonstration of efficacy for a partition process in which you are just separating the virus from the process stream.

On the other hand, an inactivation process

such as say solvent detergent inactivation for lipid envelope viruses, this is a very robust process. It is one in which if you achieve the appropriate concentration of the materials, and there is a very wide effective range, I would require perhaps somewhat less of a demonstration. But I would require very, very substantive validation to show that, in fact, you did achieve the concentration of inactivation materials.

So that's sort of a brief response to your question. And with that I forgot what the follow-up questions for that. But I'm sure you will remind me.

DR. DAVID GREEN: What was the degree of testing that would be required, whether the physico-chemical characterization would be adequate or going on to other standards?

DR. BAKER: The extent of testing in the context of viral inactivation? Yes, we are very much supportive of a small but perhaps five to six model viruses that encompass the range of known pathogens in that the inactivation or elimination process should be subjected to utilization of this full range of viruses to capture the known pathogens.

If you get into some of the -- well, the

CJD, the prion-type pathogens, this gets to be a somewhat more complicated area. And much more difficult to discuss in a short period of time.

DR. WALTON: In your comments, you indicated that you felt that for safety assessment, particularly the longer term safety assessment and immunogenicity, that clinical testing was important for that.

Can you comment on with regards to the assessment of efficacy whether you -- there are circumstances when you feel that the clinical testing for efficacy would be necessary? And how you would go about assessing the extent to which that's needed.

DR. BAKER: Yes. And in that regard, I'd want to frame the response particularly in the context of our products because we have typically a very small patient base in which we can address. An 80-patient clinical trial is a big trial for our products.

So with respect to efficacy in say a Factor VIII product or coagulation factor which has a very well understood, well defined biological role and you can address this relatively straightforwardly, I think an efficacy study there could be very much abbreviated.

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In the situation where you were looking at say an intravenous immunoglobulin, which has a much more complex immunomodulatory role and many very different clinical indications, an efficacy trial there is more complex.

And, again, this, I think, would depend in the situation where you have follow-on products, exactly what labeling the follow-on product was intended to achieve.

I think it would be difficult for me to imagine a situation in which a follow-on product could do an efficacy trial in one indication and thereby capture all of the indications for a product like IgIV. I just don't think we're there yet in our knowledge base.

DR. KOZLOWSKI: Plasma-derived products might have a broader range of values in their characterization than some of the recombinant products. Do you think that, in some sense, will play out in how one would make follow-ons to those products?

DR. BAKER: You know I think I would probably respectfully disagree with the assertion. In looking at, again, Factor VIII -- now Factor VIII,

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again I admit, is a poster child. It is the largest biologic therapeutic currently available. The heterogeneity that we see in the recombinant product is very large. And the closer you look, the more heterogeneity you see.

I am not convinced that the heterogeneity in the recombinant product is any less than that from the plasma-derived analogue.

DR. KOZLOWSKI: And that is true in other proteins, too? That, in fact, the endogenous heterogeneity is less than or equivalent to purified recombinants?

DR. BAKER: You know there aren't a lot of examples. Earlier in my career, I did look at -- I was working at tissue plasminogen activator. And there, it was my perspective at that time that that product did show the micro-heterogeneity. However, I can only speak with real confidence to the plasma derivatives.

DR. SCOTT: Don, a clarification and a question. You mentioned immunogenicity studies and that they should be head to head. And I wondered if you were speaking of preclinical studies or clinical studies in the case of --

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DR. BAKER: No, my personal bias for our products is that immunogenicity studies, preclinical animal studies are virtually worthless. And I'll take that as a point. So when I'm talking head-to-head studies, I'm talking head-to-head clinical studies in people.

I think these can be done more or less cleverly and with more or less numbers of patients. But again, this is a very product-specific discussion when you start looking at that.

And, again, you know, we have had a lot of focus on immunogenicity but there are other reactions.

And, for example, the intravenous immunoglobulin products, as you know, show many allergic-type reactions ranging up to and including anaphylaxis. So it is not just immunogenicity in terms of antibody formation that we need to be concerned with here.

DR. SCOTT: I'm glad you brought that up because just to point out that this has been a problem from time to time with immunoglobulin products of all sorts. And nobody has come up with a predictive test in-vitro to tell whether or not this is going to happen.

Going back and looking at particular lots

even that are more strongly associated with this adverse reaction, again extensive studies in animals and in-vitro have not revealed a cause.

I just also wanted to ask you about something that you seem to be alluding to. You were mentioning that the amount of clinical trials needed for plasma-derived products or their recombinant analogues might depend, to some extent, on the complexity of the molecule. And the one that you suggested was perhaps less complex was albumin.

And I think what you had also brought up was the complexity of the underlying patient population. And I wondered if you could expand upon that because we've heard a lot about the complexity of the molecules. But they interact with the recipients.

And I think that's a challenge perhaps you could speak to.

DR. BAKER: Well, certainly the indication -- and again for complexity of the patient population, I would turn to our intravenous immunoglobulins. They are used -- I'd better be careful here -- off label and on label for a whole host of indications.

And the exact modality, biological modality, of how they exert their influence in these

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different indications is different.

And so I think that for these products, the follow-on product in which you would have inherently less experience with all this variety of indications would probably need either much more restrictive labeling -- and I am concerned about how that would play out in the field -- or a much more involved clinical trial to explore all of these various indications.

DR. KOZLOWSKI: Okay. Thank you very much.

DR. DUCHARME: Good morning, ladies and gentlemen. It is certainly my pleasure to entertain you about what may be needed in terms of clinical studies to bring a follow-on protein product on the market.

My name is Murray Ducharme. I'm Vice President of PK/PD at MDS Pharma Services and a Professeur Associe at the University of Montreal. MDS Pharma Services is a contract research organization that does work for both innovators and generic drug companies.

This presentation will be broken up into three parts. Firstly, we will briefly review the

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background on what clinical studies are necessary to do from a scientific point of view to bring a small molecule on the market.

Then we will highlight some differences between small and large molecules that are important from a PK/PD point of view.

And then we will present what we think is a reasonable clinical program to undertake for a follow-on protein product.

So first of all, when one wants to bring a follow-on small molecule product on the market, so two formulations of the same active drug, one only needs to look at the -- do you have a pointer actually? No? No pointers? Okay. One only needs to prove that the concentration time profile in the plasma, whole blood, or serum -- thank you -- I'll get there -- is the same between the two formulations.

And basically if you do that, then all the concentration time profile, the site of efficacy, and toxicity that is driven by there will be the same between the two products.

And as most of you know, a clinical pharmacology principle is that the concentration of a drug at the site of efficacy is always related to

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efficacy. And concentrations of a drug at the sites of toxicity are always related with toxicity.

Now there is one assumption for this thing to work is that the drug product has to be bioavailable first and then goes to the systemic site of efficacy and toxicity. So, for example, if a drug is locally active, then one would need to do a clinical study in addition to this study.

If one wants to bring a supergeneric on the market, so basically a non-switchable product that is usually have some improvement over the original one, then one needs to do still the bioequivalence study but one also needs to do other studies that would be necessary to ensure that the product is safe and effective to give in patients.

But what is important -- and I should go back -- what is important is that actually there is no need to reinvent the wheel, meaning that what is known about the drug product is known. And we don't need to redo things.

And so for those types of products, you're going to have an abridged application from the preclinical and clinical point of view. And that should be kept in mind for follow-on biologics because

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it should be the same.

Now obviously there is a whole continuum of biologic products available out there so this presentation is not meant to be a one size fits all scenario.

Now some differences between large and small molecule products that have been alluded to already over the last two days or that some small differences in the structure of the drug or in the molecule, if you will, can lead to significant changes in the PK of the drug.

But also is that even though the PK of the drug would be the same, the PD may not be necessarily the same. And that is simply based on the assumption that it is not completely possible to characterize two different protein products and say that they are completely identical.

I realize that this is controversial with all the new technology that we have. We heard the talk from Charles DiLiberti yesterday and that should be kept in mind absolutely. But this presentation is more from a conservative standpoint and assumes that it is not possible to prove that two products are completely similar.

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One thing that does not change, however, is that the efficacy and toxicity of the drug are still related to its concentration at the site of efficacy/toxicity. This table summarizes what we've just mentioned.

And what is important from a PK/PD point of view, again, is that comparing PK of two different products is not enough. Comparing PD is not enough. One needs to compare PK and PD.

So we are bringing forward two different approaches. One we call it a clinical approach and the other one is what we call the bioequivalence approach so in line with clinical pharmacology principles that are well known.

So let's look at each of these approaches one by one. So first the clinical approach. In Phase I, what we think would be the objective is really to decide what is the equivalent dosage of the follow-on protein product compared to the reference one.

And so for this we would need to do a single dose PK/PD study but also we have to remember that for some biologics, there is some well known time dependence, non-linearity, for example, EPO, G-CSF, and others. So for those biologics, one would also

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need to do a steady state PK/PD study.

And depending on the results, then one would decide what is the equivalent dosage between the follow-on product and the reference product that is to be used for the pivotal Phase III study.

In that study we would compare head-to-head the reference and the follow-on product. There is an example presented on this slide. The example is for EPO. We would enroll, for example, 600 subjects. They would be on a regimen of EPO. Then they would be randomized to either receive the follow-on or continue on EPO.

And at the end of certain times, so, for example a minimum of 20 weeks, then one would look at two things. First of all, confirmation of equivalence so both products have to be shown that they can, for example, maintain hemoglobin level within a certain target. That is quite easy to do in a way because patients are titrated.

What is much more difficult to do is the equivalence in terms of dosage. And for this to be proven, one would need to study a minimum of 258 subjects per group.

In the BE approach, we would do the same

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Phase I studies but this time we would need to prove that the two formulations are behaving exactly in a similar fashion from both a PK and PD point of view. This means that we would have to pass 90 percent confidence interval for all the PK and all the PD metrics that are important.

So because we know that the clinical pharmacology principles still holds for biologics and so if we know that the PK and the PD are exactly the same, then we know that the efficacy will be the same.

So the Phase III, what is important to do in the Phase III is really to look at safety and immunogenicity.

So for the Phase III we believe that, for example from a scientific point of view, 300 to 500 subjects could be a reasonable number. We would think also that from a scientific point of view, what could be done is in a subset of those patients, for example 100, you could switch them over from one formulation to the other and then prove in patients from a PK/PD point of view that the two formulations are behaving exactly in the same manner.

And the next two slides are basically summary for two examples of what could be necessary to

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do. So for EPO and for G-CSF, so first of all for the clinical approach and secondly for the bioequivalence approach.

And I would like to conclude this presentation by thanking some of my collaborators at MDS, Paul Chamberlain, Ian Dews, and Diane Potvin. And welcoming any questions that you may have. Thank you.

(Applause.)

DR. KOZLOWSKI: It would seem to use the bioequivalence method, you'd be making the assumption that the PD really relates to efficacy. And I think what the measure of PD, certainly some of the ones we've seen, don't necessarily relate to efficacy.

DR. DUCHARME: That is very important. So for certain drugs, you will have a PD measure. So, for example, EPO you look at hemoglobin. That's exactly what you look at in the clinic so this is very clear. For G-CSF, it's clear also. You're going to look at absolute neutrophil counts.

But what happens with Interferon? What are you going to look at? There is no real PD measure for efficacy. And that throws out this method for that drug unless someone can think of a PD measure

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that would work. So you're completely correct.

DR. KOZLOWSKI: And you picked this safety number, 300 to 500. Would that vary from product to product? How would that number be generated?

DR. DUCHARME: Actually this is a good question again. This number comes out also from general experience when we bring, for example, a supergeneric on the market and your concern about safety.

You know one thing that reassured me in the presentation this morning was when it was talked about that in a Phase II trial a drug would still be - - because of immunogenicity, I think they had a problem in four or five patients out of 400 or 500. So I mean that's debatable. But --

DR. DAVID GREEN: Just a follow-on, you mentioned it may be difficult to understand in certain cases because there's no PD marker to have reliance on.

DR. DUCHARME: For efficacy, yes.

DR. DAVID GREEN: But there are some instances, for example, where the dosage strategy is saturation, where, for example, it might be very high levels of saturation. And there are other instances

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where it has gone beyond the dose response curve, which I think is an assumption in your consideration.

But my question is would you envision different standards or would you clarify what standards you would have for biologics which are aiming at a degree of, for example, exsaturation above which there is no benefit in terms of -- and no increase in toxicity? Would you have a standard of no less than rather than a higher and lower limit standard?

DR. DUCHARME: That's a good question. One thing I heard yesterday was that they was going to listen, right? And not ask difficult questions like this?

(Laughter.)

DR. KOZLOWSKI: I think it was just that we weren't going to answer questions. Not that we weren't going to ask questions.

(Laughter.)

DR. DUCHARME: I think that, you know, and it all depends, you know, in my presentation, I did not talk from a regulatory standpoint, just scientific. But one thing also that is important for you to consider is are you going to give a switchable

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status or a non-switchable.

Certainly I think if you were to give a switchable status and that you think that the product should be completely equivalent to the reference one, then I think you need to prove that the dose response curve is exactly the same. And that the saturation is going to be seen at the same point, et cetera.

Am I answering your question?

DR. DAVID GREEN: Well, it's important to

--

DR. DUCHARME: Kind of?

DR. DAVID GREEN: -- hear you discuss it.

(Laughter.)

DR. WALTON: In your comments, you sort of break things into the two approaches, the clinical approach and the bioequivalence approach based upon whether we can rely upon the pharmacokinetics and pharmacodynamics. Clearly that is an important question then in making that determination.

Do you have any comments on principles or criteria to take into consideration in or how to go about making the determination of which approach is the appropriate one in cases?

DR. DUCHARME: Okay, so I think from this

point of view that I'm going to have to talk a little bit about maybe a regulation point of view.

I think if you are to give a switchable status to a follow-on protein product, then absolutely you would need to look at the BE approach and, therefore, pass on 90 percent confidence interval for PK and PD. And obviously the PD has to be related to the mechanism of action. It has to be validated, et cetera. But it is for a lot of biologics.

If you were to use the clinical approach and again give a switchable status, then it would have to be a mix of the BE approach and the clinical meaning you would have to pass a 90 percent confidence interval for PK/PD also, meaning that if you look carefully in the presentation, in the clinical approach it gives you the opportunity to bring a follow-on protein product where you will have an equivalent dosage but not necessarily exactly the same.

Am I answering your question?

DR. WALTON: Again, it's interesting to hear more of your thoughts.

DR. DUCHARME: Okay, okay.

DR. KOZLOWSKI: Thank you very much.

DR. DUCHARME: Thank you.

(Applause.)

MR. GREENWOOD: Good afternoon, ladies and gentlemen. I'm glad to see that so many of you stayed to the very end.

I'd like to thank the GPhA for inviting me over to speak at this meeting and for the FDA for giving me a chance to speak.

Just as way of introduction, I'm Director of Regulatory Affairs at GeneMedix PLC, a UK-registered company involved in the manufacture of what, in Europe, in the European Union, are now being referred to as similar biological medicine or products. And I will go a bit more into that term a little bit later.

During my time with the company and due to my involvement within the European Generics Medicines Association and direct discussions with the EMEA and the CHMP, I've gained experience in the development of two of these products for subsequent registration in Europe.

And today will be addressing the considerations for an abbreviated preclinical and/or clinical development program based on the outcome of

in-vitro, physico-chemical, and in-vivo biological comparability testing.

I think before I actually move on, I think it is very important -- it's obvious from all the speakers that have been on the platform today and especially from the questions coming from the FDA panels, that we're dealing here with an extremely wide range of products.

And nobody who stands here on this platform can have experience enough to cover all the products and all the questions that may come. So excuse me, if you do ask a question which I can't answer, I will tell you I can't answer it, okay?

I think we have to make a premise here that we're looking basically at can we show physico-chemical comparability to a degree that we can be reliant upon? And if so, how can we move on from that stage? Do we have to do preclinical? Do we have to do clinical work?

And I believe here that if we can show in-vitro and in-vivo biological potency are shown to be comparable with the innovator protein, there really should be no concerns with reference to efficacy. In many cases the physico-chemical structure of the

molecule dictates its potency so that any non-structural conformity may well effect this parameter.

However, as the product is manufactured, tested, and formulated using different cell lines, again we've heard all this, the prime concern of any regulatory agency will be in its safety. For this reason, in Europe, the requirement for additional studies over and above the characterization are considered on a case-by-case basis on the complexity of the molecule and its therapeutic use during discussions between the company and the CHMP.

I believe that as we are dealing with such a wide range of products here, that we must be able to have a system whereby we can determine, on a case-by-case basis, what class of product requires what sort of study. And this has been obviously discussed in great detail.

And I believe it varies from the far left with possible short-chain peptides, which are conjugated to some of the toxoids, insulin, through the longer chain non-glycosylated products, such as GM-CSF, through to long-chain glycosylated products, such as EPO, right through to the final righthand side, which is monoclonal antibodies.

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And the characterization of the molecule must be by the most up-to-date methodology to determine the full structure, primary, secondary, quaternary, and tertiary, plus any possible post-translational modifications and impurities either from product or from process.

And I also believe, and I think this is also a belief certainly within Europe, the further to the right, the more likely preclinical clinical data will be required. And the extent of that data may increase from no preclinical clinical requirements to possible preclinical toxicology safety studies and clinical studies in patients.

However, in all instances -- and I think this is very important to note this -- in all instances, it should not be the intent to duplicate the preclinical and clinical studies required for registration of the innovator product because if we have to do that as a generic industry, there will be no follow-on biological products.

I just put a slide up here very, very quickly on some of the techniques that are used. And these have obviously been described in more detail so I won't actually go into those.

The darker considerations preclinical, what I would like to do here is not to actually lay down what I believe will be the darker requirements because, as I explained earlier on, they are going to be tremendously varied dependent on product.

But I'd like to lay down something about the fears that the generic industry could well have, and certainly have in Europe, about the possible studies that we may be asked to do for specific products, which we don't necessarily agree with.

And we hope that certainly by these meetings with the industry from both sides of the house with the FDA, that you can actually come up with a scientifically valid program which can go into the ICH process. And at the end of the day, we have a harmonized view right across the industry. I mean that is the hope that we're all living with, okay?

In general, it's not believed that preclinical studies provide any data of scientific value. However, if deemed a regulatory requirement, and in Europe it is a regulatory requirement, clinical use of the product should be considered -- sorry, misread that.

If you have to do preclinical, which you

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have to do in Europe, then you're going to have to do it. But you have to decide on what you're going to have to do.

And in these cases, there seems no scientific rationale for exposing animals to large doses, e.g, 100 times the human dose equivalent, as the safety of these molecules has already be proven. In addition, due to the clinical usage, the possibility of large or even small overdoses is negated by the presentations.

It would also seem inappropriate to include two or more animal species in the studies, especially the use of higher order animals such as dogs and monkeys, unless there were a specific reason for doing so due to the pharmacodynamic action of the molecule.

Or, as reported earlier, they may have an incidence that the adverse reaction profile in a certain species of animal is proven in one product and you are doing a direct comparison so it would be advantageous to use that particular animal.

Again we come to the clinical usage, and we've heard lots of stories about and opinions today about whether we need to do clinical, do we need to do

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clinical, and again, I come back to the fact that it really is on a case-by-case basis. And you cannot lay down one single guideline.

But if you have to do clinical studies and if you've used the tiered system, which was explained earlier, and you have deemed that there is a reason and a scientific rationale for conducting a clinical study, all right, then the clinical study may well vary dependent on what the product is and what the product is used for.

For instance, small, short-term studies for rescue therapy products would only need short-term trials. Whereas longer-term studies for lifetime usage products would probably require much longer studies, much more complex studies.

The other thing to take into consideration is the patient population being treated. It should be remembered that the status of the patients to be treated for the different indications, if there are different indications, for any one product, if the mode of action is well understood and considered to be the same for all indications, there should be no requirement for clinical studies for each separate indication.

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The route of administration is important as both PK and PD studies in animals and the clinical setting. The products have different routes of administration for different indications or possibly different stages of treatment for the same indication. Additional studies may be conducted in animals and/or humans to demonstrate comparability.

And what I'm saying here is that it's obvious that all the way through the process, this must be a direct comparability study with everything, with using the reference product in the European Union.

Again, people have talked about numbers. And I think this is very deceptive to try and say we'll do 200, we'll do 300. I don't think you can pick whole numbers out of the air. You have to base your clinical studies on the stats, all right?

The ability to reduce the number of patients exposed to the follow-on product is paramount as in some instances, the patient numbers available will be limited. And even when available, may not agree to a change in their treatment to a previously untested product. You just may not have a patient population that you can treat.

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Patient numbers should be based on the known mode of action of the molecule, the ease of endpoint measurement, and the degree of difference to be allowed between the innovator and follow-on product in a comparative clinical study. These are the factors that determine the numbers, all right?

Now, again, the final word I'd like to say here is that it's essential that a company wishing to develop a follow-on protein consult with the agency at an early stage in their development program to determine if and what studies will be required to demonstrate comparability, physico-chemical, and biological. And if further study such as preclinical, safety, toxicology, and immunogenicity are required, the extent of those studies.

Now I just come back quickly to -- just to mention things we talked about very early on, which was the terminology.

And in Europe now, we do have an official terms for these products, similar biological medicinal products. You've heard the uneducated and the conference organizers calling them biosimilar and we are strongly discouraging that.

But what it leaves us, it leaves us with a

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means of determining comparability by any one of a number of methods. We're not saying their bioequivalent. We're not saying they're therapeutically equivalent.

We're saying they are similar. And the similarity is -- it allows you to determine similarity by either physico-chemical, by preclinical, or by clinical. So it doesn't tie you down to any one specific method of determining comparability.

Thank you very much.

(Applause.)

DR. KOZLOWSKI: One comment you made early in your talk was that you can determine efficacy solely by in-vivo and in-vitro studies.

So I think, again, this hinges on something that came up with the last speaker is that that clearly depends on a full understanding of the mechanism of action and efficacy.

MR. GREENWOOD: Yes.

DR. KOZLOWSKI: And that really may not be universally the same across all products.

MR. GREENWOOD: No, that is true.

DR. KOZLOWSKI: And furthermore, I'm just sort of curious, for instance, in dealing with the

European regulatory authorities, is there a concept they have of what is sufficient evidence for such a mechanism of action?

MR. GREENWOOD: Right. Let me just -- if we've got a bit more time, I'll just elaborate on exactly what happens in Europe at the moment because I think it's important to realize what's going on.

We, as individual companies -- is it okay?

DR. KOZLOWSKI: Go ahead.

MR. GREENWOOD: -- as individual companies and as members of the EGA, have for the last two years lobbied the European authorities, that being the European Commission, the EMEA, and the CPMP as it was, it's now the CHMP, to be able to get first of all recognition of the fact that these products could exist, a terminology which everybody could understand, all right, and some sort of data package that could be put forward that would allow registration of the products, okay?

We achieved two of those objectives and we have one little extra thrown in, which I'll mention, but we did actually get a regulatory pathway, defined regulatory pathway, we have a defined name, and we actually now have got a division which we never had

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before.

But we have not, to date, received any specific guidance documents on these particular products. We have guidance documents for changes that manufacturers may make with only very small reference to follow-on biologics or similar biological medicinal products. So we're really still in the dark.

So the only method that anybody approaching the European authorities has is to go forward to the CHMP for official scientific advice, all right? Now because there are no guidelines and because there were 13 members and there are now 25 members that sit on this team, all right, I believe that we're getting the worse case scenario presented to us.

And as Chris Holloway, if he's still here, alluded to yesterday, people have gone to, submitted their proposed data to the scientific advice committee.

And when they've received the fax or the e-mail back from them, they are all apt to go around the pub and try to have a few drinks to console themselves because from personal experience, we have been pushed far further than we really want to go.

And we really believe that the scientific aspects are not being addressed properly. And that is the situation in Europe.

DR. DAVID GREEN: I'm interested in the standards that are used to say something is similar or not. And that is if you have let's say a -- and I guess the question is what is -- is the standard the standard that is for the biologic as approved? Or does the standard apply to perhaps the additional and more extraordinary, more analytical insight that is applied to establish the sameness?

So if one discovers something unseen but it's not necessarily different and still falls within manufacturing specifications --

MR. GREENWOOD: Yes.

DR. DAVID GREEN: -- how is that handled, particularly if there is no attribution with regard to safety or efficacy?

MR. GREENWOOD: Yes. Well, the plan on this is that your characterization study, all right, will involve as many of the testing parameters that you can determine for the particular product that you are looking at.

But in conjunction with that, running

along parallel, you have to test the innovator product as well, irrespective of where that actually originates from, all right? That way you can do a similarity -- comparability/similarity exercise.

The problem we have, and I've always asked this question every time I've gone to them, is how similar is similar?

And that has not been defined. So the only thing you can really say on that is that if you've measured the same parameter and you find that within the experimental limits, let's say, of the assay, are you still within those parameters, then you must be able to consider that similar. I don't know.

One of the other things that has been mentioned is the number of batches that you test. You don't just test one batch of yours and one batch of the innovator.

You take as many batches as you can get a hold of so that at the end of the day, you will find variation by your method of analysis in the innovator product.

So all you can do is say well, if that is the variation within the innovator product that's allowed, then surely I should be allowed that same

variation in my product and as long as I fall within those limits. But no definition of similarity has been given.

DR. KOZLOWSKI: And again to ask, and I guess you may not have defined rules is the way it's worked out in the EU yet, but say that there is a characterization of a follow-on product and a variety of parameters were looked at but the regulatory agency, knowing the innovator product, knew that there was a different assay looking for a certain deamidation, something very specific --

MR. GREENWOOD: Yes, yes.

DR. KOZLOWSKI: -- that was unique to the product. That might be a stability issue or you might not be overt from your looking at off-the-shelf samples.

MR. GREENWOOD: Yes.

DR. KOZLOWSKI: So does the EU then inform you that in order to really show biochemical comparability, you need to focus on this? How does that fit into innovator proprietary information?

MR. GREENWOOD: Well, this is an important issue obviously. I mean if you look at the actual legislation, if I can just quickly go on to

legislation, when you put your application in, it is a standalone application, all right?

You are not allowed to make any reference to any information on the innovator product even if it's in the public domain, all right?

So obviously there's still this aspect of protection of the innovator product. So in those sort of instances, I believe that you could well be in trouble if you're not aware, and has been said, what you don't know, you don't know. The only people who really know are the regulators.

DR. KOZLOWSKI: And so the communication might be that you've insufficiently characterized the molecule --

MR. GREENWOOD: Yes.

DR. KOZLOWSKI: -- without any additional information?

MR. GREENWOOD: Well, the scheme out is that when you go for scientific opinion, what you have to do is you have to submit a protocol for every single study that you're going to undertake. And it is a complete protocol.

You don't just say well, I'm going to do comparability. You actually enumerate every test that

you are going to do. And the limits that you are looking for and everything else.

So that is put into the CPMP, who then discuss it within their groups. They bring in their own experts. And they report back to you on the suitability of what you're doing.

And sometimes they will, you know, they will say well, you know, you really need to be looking at this. Or you need to be looking for that for this class of product.

So you get some feedback from them. But I still believe at the moment, because nothing is down in tablets of stone, that we are being asked to do more than is necessary.

Okay? Thank you very much.

DR. KOZLOWSKI: Okay. Are there any other questions?

(Applause.)

DR. KOZLOWSKI: Okay. Thank you.

DR. HUSSAIN: Well, we've come to an end of an exciting scientific discussion. And a lot of information gathered. But I think I'd like to share some quick remarks before we depart and close this session.

First of all, thank you for all the speakers and presenters who took effort to come here.

And all the audience members. And also the panel members.

And a number of the folks that have worked very hard. And you saw Ted, Mel, and Eileen outside.

And they have really done quite a tremendous job here. And my boss, Helen, actually put us through a lot of meetings to get to this stage so we have been through quite a bit of this.

But I do want to emphasize a few points. I think clearly this was a workshop to discuss science, not regulatory aspects, not regulatory pathway and so forth. And so the regulatory process and pathway is not within the scope of this discussion.

We'll address some of those concerns and questions through the aspects of citizen petitions that we are addressing right now. So I do want to emphasize that.

What's next?

I think next is our docket is still open.

And you are encouraged to submit further information to the docket.

We have a workshop planned in collaboration with DIA February 14 to 16. And this will again focus on science and technical aspects. And, I think, we hope to take the discussion further and more in depth at that workshop.

Keith Webber is a co-chair for that from the DS side. I'm not sure who the other co-chairs are. But I think it will be in Crystal City Gateway Marriott February 14th to 16th.

Transcripts of this discussion will be available maybe about three weeks from now.

What we will plan to do is once we have permission from the presenters to share the slides, they will go on our web site. On the CDER web site there will be a link to this meeting.

And hopefully by the end of this week, you will see many of the slides, presentation slides, up there.

And that, I think, again thank all of you for attending. And I think this was a good start for the discussion. But the challenge is great. So have a safe trip. Thank you.

(Applause.)

(Whereupon, above-entitled meeting was

concluded at 11:04 a.m.)

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