

DRUG INFORMATION ASSOCIATION

FDA/DIA SCIENTIFIC WORKSHOP ON FOLLOW-ON
PROTEIN PHARMACEUTICALS

BREAKOUT SESSION A:
PHYSICAL CHEMICAL CHARACTERIZATION & IMPURITIES

Monday, February 14, 2005

3:35 p.m.

Marriott Crystal Gateway
1700 Jefferson Davis Highway
Arlington, Virginia

M O D E R A T O R S

BARRY CHERNEY, PhD [CHAIR], CDER/FDA

STEPHEN MOORE, PhD, CDER/FDA

ANDREW CHANG, PhD, CBER/FDA

CHARLES DILIBERTI, PhD
Barr Laboratories, Inc.

REED HARRIS, PhD

P R O C E E D I N G S

DR. MOORE: Good afternoon, everybody.

Welcome to the second session of "Physical Chemical Characterization and Impurities."

And there is a format that we're going to use this afternoon. There are going to be three moderator groups for this session: With FDA, Barry Cherney and myself, and Andrew Chang; and two industry people, one innovator group and one representing follow-on biologics. And they will introduce themselves as we go along here.

And FDA will be charting the discussion and will take notes, in addition to the visual transcriber who is here to my right. And she has the request that when you come to the mike, give your name and affiliation. And if you come back to join the discussion again, also give your name and affiliation. It would be very hard to remember and link those two events if you don't do that.

And also, give her your business card as soon as possible after you've spoken, so she can link the transcripts that she is going to make to

the speaker on the microphone.

In this format, the FDA moderator will present the first question. There are going to be three questions. And then industry moderators will provide a point-counterpoint each time we put a question up.

And important issues and points will be identified and recorded, including both where a consensus is reached, if we reach one, and where it's not, if we go to that point. And if we have other important topics or issues that are off the topic here, those will also be captured but parked somewhere.

The time limits for the questions are in order, 15, 30, and 40 minutes. Those can be extended as we go along, and adjusted as we go along. The moderators may present more specific questions to stimulate and focus the discussion as the discussion continues.

And here are some of the ground rules that we have for this session. The speakers should speak from the microphone. We have one here in the

middle of the room for people in the audience. Of course, we have some microphones up here. And as I mentioned, they identify themselves and their affiliation. And the statements that you make will be viewed as your own, and not necessarily your organization, unless you want to state so.

We ask that you focus the discussion on scientific issues, and not really delve into the legal or regulatory issues. Of course, there are many legal and regulatory ramifications of these things, but really we want to keep the discussion coming back to the science.

And the discussion should focus on the physical chemical characterization, since that's our session. It's been split out, as you can see in your program, into the other areas. And bioassays are another area, and then there will be PK/PD and clinical split out. Of course, we will cross-reference to those things, but not to dwell on them.

And we'd request that you'd start with protein products in your discussion that have

significant tertiary or quaternary structure. Of course, we start from the least complex, and then work our way up as the discussion goes.

To continue with some of the ground rules, we request that the persons from the audience speak to the issue for approximately two minutes, to keep this session rolling along. And moderators may ask questions from time to time, as I mentioned also.

And discussion on specific topics should be completed before moving to a new issue. That is, if someone is talking about something, and then what you have to say you're having in your mind something highly related, get up at that time and bring it up, and keep that discussion focused until we come to the completion of it. Not to say hold it back and then try to bring up the discussion again; not that that won't be permitted, it's just that it would help facilitate the discussion we're having today.

And the discussion should be data driven. Hard copies of data or references, if you have them, submit them to the docket. And this is the

docket number, which is open for the receipt of documents.

And we'll start off with question one: "Which product attributes should be evaluated?" That is, what should be looked at? And what we're going to do now is turn this to our industry colleagues. They're going to have a point-counterpoint; and also, introduce themselves before they give their talk.

DR. HARRIS: Thanks, Stephen. I'm Reed Harris. I'm the director of the Late State Analytical Development Group at Genentech. And I've been with Genentech--Sorry, just go on from here?

So I've been with Genentech for 21 years. And every clinical and commercial product that we've developed has come through my labs, to some extent. And I can assure you that every one of them has presented us with some unwelcome surprises.

It seems like a straightforward process to engineer cell lines and do purification and

recovery and the rest, but the fact is that there are unexpected events out there. We've seen extended and truncated forms. We've seen unexpected protein modifications. It's a complicated business. And so, though we have great confidence in our own analytical abilities, the fact is that we are humbled from time to time by experiences.

So when we look at a new molecule, what are listed here are some of the key characteristics that we try to evaluate. What is known about the characteristics that drive, for example, bioavailability? It's an important question. Also, potency. And the other point that's up there is safety. And especially, we want to look at those characteristics that have been linked to immunogenicity.

Let's see, what else? The other thing that we take a look at are the routes of degradation. What are the degraded forms? How did the different containers affect the route and the rate of degradation? We do a lot of this work so

that we can establish end-process hold times, and also so that we can do final product expirations. It's a key component of comparability, as well. This is a subject we didn't really discuss much in the first section. It is, how do you use stability data to establish comparability?

And then, the last part up there has to do with process-related impurities. We have invested a lot of money in whole-cell assays that are very specific for the products and the cell lines that we use. I don't know how a reviewer who would be looking at a different manufacturer could compare--for example, the whole-cell protein data would be generated by a different assay--and compare that to ours. And that's an issue that maybe needs to be discussed.

And then finally, the other aspect that we're spending more and more time on is looking at leachable compounds. These are things that come out of the glass or come out of rubber components. And here the concern is that those leachates might somehow either activate proteases, or modify the

protein directly, or perhaps serve as an adjuvant.

And I turn it over.

DR. DILIBERTI: I'm Charlie Diliberti,
Vice President of Scientific Affairs at Barr
Laboratories.

Next slide, please. The question is,
which product attributes should be evaluated? And
in a nutshell, I think the appropriate answer is:
All of them.

In the previous session, in retrospect, I
wish I had underscored the word "relevant," also,
because it was sort of taken to mean that we should
mindlessly throw everything in the analytical tool
box at the problem. That's not my intent. What
I'm trying to get across here is that through an
intelligent process of understanding the product,
we need to apply all of the relevant analytical
tools to that problem.

Also, it's important to remember that in
the context of this conference what's really
important is a comparative analysis. This is not
the issue of trying to predict toxicological and

pharmacological properties from a particular structure in the context of a new chemical entity, de novo. We're comparing side-by-side product "A" with product "B," and assessing how well our analytical tools can compare those two products.

The second issue is that, as we heard this morning, we need to perform redundant measurements of each aspect of structure impurity with multiple orthogonal methods. And my understanding and thought process here on orthogonal methods is that they rely on different physical principles, not just themes and variations on a given physical principle.

In the characterization process, obviously, we need to address the issues of identity, purity, and potency. And then, also, as we heard this morning, the analytical results should be not looked at in isolation test by test, but rather collectively. And we can apply various mathematical tools to evaluate the sum total of all the data and come up with a highly sensitive and selective fingerprint of the product. Thanks.

DR. MOORE: We will move now to open up the discussion for the audience to participate in addressing question one. And we're here to give

you our feedback.

DR. SCHENERMAN [In Audience]: This is Mark Schenerman, from MedImmune.

Just a question about the detailed characterization that's listed here in bullet point one. How would you go about doing that detailed characterization in the presence of the excipients in the drug product? And if you were going to reformulate the drug product, how do you know that that reformulation process wouldn't impair your ability to do detailed characterization?

DR. DILIBERTI: I guess sort of one aspect of that question is how often do the excipients in the formulation really pose a problem for the analysis of the finished product?

DR. NAKTINIS [In Audience]: Hello, again. Vytautas Naktinis.

We addressed actually the first hour these issues, really, I think in much detail. I just

simply summarize. If you cannot get rid of excipients with validated methods, testing, in which you did not damage or disturb picture of active ingredient you're looking at, simple approach is add those excipients to your material and analyze this.

And there are numerous ways around. And of course, you get access to API from innovator through compendium reference materials. In some cases--Again, we have to speak case-by-case basis; we can't generalize. Perhaps the short answer to your question.

DR. CHANG: I'd like to have a follow-up on that. As you said in the first part of this session A, you can add some excipient to your product. But the sum of the questions raised by the first part of this discussion is that once you formulate it, you lost the sensitivity of your assay. So when you spike the excipients in, then technically that may be problematic.

MR. SCHREITMUELLER [In Audience]: Thomas Schreitmuller, Hoffmann-La Roche.

I am just wondering, you know, looking at this first bullet, "Perform full physical chemical characterization using all available and relevant

comparability analytical tools." So for me, the question is how you define "relevant."

I think "relevant," in a way, this is related to the process you produce your product with. And "relevant" is also related in a way to the clinical experience you have with your product. When you now start off and establish a new process, what is your idea? How would you then define "relevant"?

DR. DILIBERTI: My thought process was that "relevant" relates more to the applicability to the particular protein material itself. There are some analytical methods that just won't yield any meaningful information on a given protein, but might be useful for other proteins. I'm not talking about relevance to the clinical effect.

MR. SCHREITMUELLER [In Audience]: Well, again, you know, I think protein properties, protein chemical properties, there are a huge

variety of these. And again, the definition, whether those properties are relevant for safety, for efficacy, and so on, you are going to test this--at least, this is what we as originator are doing--in clinical trials.

So I am really wondering how, let's say, from scratch you are able to define that. Of course, there is a lot of experience from the originator around; but this experience still is coupled with a certain process, with a certain product which was manufactured with a different cell line, you know, with a different purification process, and so on. So, well, for me, in a way, I think, without having this link to a clinical experience, you cannot define "relevant."

DR. DILIBERTI: I think that the clinical experience may allow you to reduce the testing later on in the product--in the product life cycle. But the initial characterization still, I think, has to be full.

DR. VAN DER PLAS [In Audience]: Martijn van der Plas, National Institute of Public Health,

from The Netherlands.

I think we need not try to define the word "relevant" for each and every protein in each and every case; because then we will be stuck, and we will be discussing this issue in 2030 still. But we need to look at this from a pragmatic viewpoint, I think. If we have a given product--for example, the single-chain FE [ph] fragment that we talked about this morning--if we have this given product with a given process, can we then define on a case-by-case basis--we like these words in Europe, "case-by-case"--define a pragmatic set of analytical tools? I think the answer is "Yes."

MR. GARNICK [In Audience]: So let me try that one for a second. So let's talk. I noticed in your slide you left off strength. You had done the potency, purity, but you left off strength. So let's try a basic technique.

So history has shown us that a good example of this was the international growth hormone reference standard. We had, I think, seven or eight important laboratories. The most

experienced laboratories in the world were sent samples by NIBS&C to determine the strength of the amount of growth hormone that was in the vials. And all seven of the laboratories reported back, and the differences were about 25 to 30 percent. So the laboratories couldn't figure out how much actual protein was in the vial.

Now, that translates. So how is a follow-on manufacturer going to determine how much drug--Even if they took the innovator's vial, tried to determine exactly how much drug is there, what basis are they going to use? And I should point out that there are a number of drugs--TPA is a good example--that if you get the dose wrong by 20 percent, you will kill people.

DR. VAN DER PLAS [In Audience]: Thank you. I'm Martijn van der Plas, again.

This point is to a certain extent not completely relevant, because what's happening is that we are looking at a comparative analysis. So even if there is a variability of, say, 10 to 20 percent between laboratories, the first question

is, can one laboratory of one manufacturer determine an original and a follow-on product with the same results? If the answer to that is "Yes, within a small margin of variability," then we at least have a basis to continue.

DR. DILIBERTI: Anyone who has a microphone--I'm sorry, anyone who has a question, please don't just raise your hand; go to the microphone. Thank you.

DR. VENKATARAMAN [In Audience]: Ganesh Venkataraman, from Momenta Pharmaceuticals.

I'd like to actually take a step up, and say, you know, it's not about adding more analytical techniques. You know, each of us has our own very favorite analytical technique, whether it's mass spec or NMR [ph]. But I think the product attributes, both this morning and in this session, I think the list of attributes like three-dimensional structure, immunogenicity, etcetera, I think those properties are becoming more and more clear, the list of those properties.

What kinds of techniques you use to

identify the actual parameters for those properties I think is something--You know, that's not really a question as to which is a better technique, whether mass spec is better or whether ESI is better, etcetera.

I would like to propose that one needs to make sure that you understand what that technique tells you, and really think about it from making sure that you're taking care of redundancies, looking at it from different angles. And that's really more important; rather than trying to argue as to how many more techniques, or how to relate whatever your structure is back to clinical activity. Because I think that whole relationship becomes an entire study in itself. Thanks.

DR. NAKTINIS [In Audience]: Vytautas Naktinis, Teva.

I would like to comment on a question raised by the person from Genentech. First, that was a negative example. Perhaps that was by assay evaluation, not HPLC. Yes, but [inaudible] is measured for potency by HPLC [inaudible] to

whatever cells. So I'm just very disappointed that this particular laboratory is so unlucky.

Let me tell you positive example. Our company participated in a collaborative study led by National Institute of Biological Standards and Control in the UK in establishing reference material for [inaudible]. And we were lucky, and the majority of laboratories were very lucky, to establish activity of this particular reference preparation exactly in the allowed limits of expected.

So if we will be hunting for negative examples to show and scare people away from follow-on proteins, perhaps it's not the best tactics. Perhaps I would be very much happy to hear what were the reasons that this particularly laboratory failed on such simple, just absolutely simple, methods. So that could be helpful for audience and follow-on product, to understand what we should be avoiding.

DR. DILIBERTI: Actually, I have a question on that growthhormone example. When did

that happen? Is that something that happened a long time ago with old technology, or is that very recent?

MR. GARNICK [In Audience]: I believe that happened about 1996, so it's relatively recent. And the methodologies for determining new anti-protein in a vial, for example, haven't changed a whole lot in about 20 years.

The reasons for the errors, there are various practices in various laboratories, many of which are not validated or well understood, by international reference laboratories, well established. And the results were that the protein concentration was off by about 30 percent.

And now, we can go through how this works, but that's the state of art. I would actually have to say that if we took a vial of any protein, gave it to any of the labs in this room, you would get almost a similar, or maybe larger degree of variation.

DR. MOORE: Can I just clarify that the 20 to 30 percent variation, are we speaking about the

HPLC assay? Or instead, is that the biological assay?

DR. DILIBERTI: I think he's talking about the mass of protein in the vial.

DR. MOORE: He was talking about that, but I wanted to clarify that. Because we did that--

MR. GARNICK [In Audience]: Okay. That was done by quantitative amino acid analysis. It was done by HPLC analyses by the laboratories that can conduct that. And it was done by UV spectrophotometric analysis, by the laboratories who then had to determine what the extinction coefficient was. So all three methods were used.

DR. NASHABEH [In Audience]: Wassim Nashabeh, from Genentech.

Just a quick change of topic, or going back to the primary question, I think it's important in doing a comparative analysis to understand what the critical attributes are. And it's very difficult, even for a class of a given type of proteins.

For example, I will take the case of the

monoclonal antibodies we manufacture, where we have multiple monoclonal antibodies for different indications. They are largely manufactured using similar processes overall. The critical attributes of what's relevant across these antibodies are not the same from one to another. I mean, each case we've found certain aspects of the molecules that are relevant for a given clinical indication that is not common to the other antibodies.

So without understanding what these parameters are, it's very difficult to do a comparison. Because eventually, otherwise what you'll end up having to do is to look at thousands and thousands of potential end points and try to compare them and match them all to each other, which becomes really an impossible task. You can't really define a subset of analytical methods that will give you a full picture unless you understand what are the critical things you need to look for.

DR. MOORE: I think we can go to the next question: "What are the capabilities and limitations of the available analytical tools to

evaluate those identified product attributes that we have just discussed?" I'll open it up to Reed.

DR. HARRIS: Thanks. Yes, as many people alluded to this morning, the limits are, to a certain extent, a function of the molecular size and the nature and the number of modification sites found on a protein, and also the number of polypeptide chains.

One of the issues we run into with therapeutic antibodies is that you only need one modification somewhere in one of the chains to drive it into a different profile. It may be a more acidic or more basic form. And then when you try and assign what the underlying characteristic is that makes it different, you always have to look for that altered form against a background that's generated by the unaltered form. And so these multimeric proteins really for us are among the most challenging that we've had to work with.

We also have to acknowledge that there are different approaches that have to be taken if you're looking for a single modification that may

be present at a large number of sites. An example of this is glycation, where maybe half a percent of ten or 20 sites are glycated. You would never see that in a peptide map, but you can see it when you analyze the intact material.

Conversely, if you're looking for a modification at a single site, like maybe a glycosylation site, then there are some opportunities to use peptide mapping and to analyze those in close detail and get some site-specific information. But as others have mentioned this morning, you really have to consider what is the end point that you're getting to, and make sure that the methods that you have will give you the necessary information.

I'm not going to talk much about higher-order structure methods; but certainly, an issue that we have to deal with on all of our proteins is deamidation. I think everything we've made has had some deamidation in it. And we have pretty good methods for assigning sites of deamidation.

One of the issues that we're dealing with with the newer therapeutic antibodies is we find that there's quite a bit of acidic material in

there that we can't assign. And this is a little bit frustrating. But it's one of those things where, when you have forms and you know they're there and you can't assign the underlying characteristics, then you do have to fall back to a certain extent on the knowledge that you have, that you're using the same cell line, you're using the same process, using the same control system. So there are times when you really just have to rely on the profile, and then back it up with your process information.

A bigger problem for us in some of the antibodies is the isomerization of aspartate residues. So this causes a shift in charge orientation that in a number of examples completely wipes out potency. But finding isoaspartate is really difficult, because it doesn't change the net charge, so you won't see it by iso-electric focusing, and it doesn't change the mass.

The other thing that has been alluded to this morning is glycosylation. And I think we could all agree that we have pretty good tools for looking at the N-linked oligosaccharides on our therapeutic proteins. Now, we have good enzymes and we have good analytical methods there. The

O-links, perhaps not quite as advanced as the N-links with respect to the tools that are available.

But generating the data isn't enough. I mean, you can generate reams and reams of data. But for each molecule you have to generate understanding, as well. So what is it that's important about glycosylation for that specific molecule?

For some of our molecules, it's site occupancy that's critical, and for others--I don't know if any of you were at the September meeting where Andy Jones talked about the lynerceptic [ph] experience, where it was the terminal carbohydrate groups that mediated PK. And now those of us that are working on cytotoxic antibodies, certainly,

we've gone away a little bit from looking at certain types of oligosaccharides. And now we're more interested in the potential role of fucosylation [ph]. Because it does appear that there is an inverse correlation between fucosylation and ADCC activity.

So it's kind of an iterative process. You know, you start out with an anticipated structure; you look for the usual sorts of modifications and degraded forms; and then perhaps most importantly, you look for all of the contrary data, because that's where the really important stories are that tell you you've got a mutation or an odd modification of some kind.

And in a number of experiences that we've had, we've gone all the way back to starting over with a new cell line or making modifications to the process to try and influence the extent of the modification that we have.

DR. DILIBERTI: Thanks, Reed. What are the capabilities and limitations? Basically, complete comparative characterization is both

possible and routine for most protein products. The reality is that comparative characterization is used routinely, all the time, to justify and support process changes. We don't have to reinvent the wheel here. It's not creating a new branch of science. It's been done many times before, and will be done going forward.

And this same process for comparative characterization, side-by-side, before and after a change, the same thought process and same kind of criteria can be applied to product comparisons between two manufacturers.

As we heard this morning, the analytical tools available have really blossomed over the last couple of decades, and they allow for complete elucidation of covalent structure in many cases. And also, we have very sensitive methods for comparing higher-order structure to assure that the three-dimensional structure is the same as a particular product. And likewise, we have sensitive methods for measuring impurities.

DR. MOORE: I would like to open back up

to the audience for discussion on question two.

Let's just go back to the question.

DR. CHANG: Well, just to stimulate discussion, let me just repeat some comments that Reed presented. It's that he stated generation of data, if I got that right, is not a goal. It's how you can learn from those data. So let me ask what type of information you should learn from those analytical methods, what data generated from those analytical methods?

And one of the earlier comments is some discussion on the relevant method. One gentleman pointed out that it should be linked to some kind of safety and efficacy. So let's have a discussion to say what we can learn from the physical chemical studies that can be related to the safety and efficacy. Is there any comment from the floor on this?

MR. GARNICK [In Audience]: I'll start the discussion, anyway. You know, I think the capabilities of analytical methods themselves have indeed improved significantly over the last 20

years. Nevertheless, we're really good at being able to find what we're looking for. We have really very few methodologies available to us that allow us to look at broad spectrum of these molecules in terms of things that we're not expecting.

Peptide maps, I mean, I did a lot of the early pioneering work in peptide mapping, in orthogonal peptide mapping with multiple enzymes, as well as mass spectrometry. And I can tell you, by coupling all these methods, you still are only able to find what you're looking for. It's the things that you're not necessarily looking for that come out in clinical trials, as well as in post-marketing surveillance of those products.

We weren't able to find the modifications of Epo that resulted in the pure rensylaplasia [ph] phenomenon. So despite all the best analytical tools available to man today, it's only when you know what to look for that you're able to find it.

The other problem with analytical methods is there are very few that are actually not

reference standard dependent. Those that are, are particularly valuable. I think mass spectrometry, [inaudible] for example, or even UV--Although the amount of information there is beyond what we can really deal with. Nevertheless, there are very few of those methods available. Most are determined against reference standards or other types of comparators.

And it's really interesting that the follow-on biologic doesn't have the advantage of being able to have effective reference materials, reference standards in most cases, and/or be able to compare.

So for example, how would you know that your product is pure with respect to an e coli protein concentration, for example, without knowing what the innovator was using in their particular assay, which is usually proprietary to that particular process? Same thing holds true for CHO impurities.

The effects of these impurities and/or reagents that can affect the protein can have a

pretty dramatic effect on safety. And that's, I think, the important thing to think about.

Proteins are wonderful molecular amplifiers. If you think about the reaction of small molecular weight organic materials with a protein, you can get a very large amount of protein reacting completely with a very small amount of leachates or other species within the process. If you're not looking for those--if you're not looking for those--you won't find them. And that can have a tremendous effect on the safety of the product.

Until we have that kind of an ability to look broad spectrum against products, we're not going to be able to do anything more than essentially what we did 20 years ago, which was throw every copy of Leninger [ph], every method known in Leninger, against the characterization of the molecule.

You can do an okay job, but you can't do a perfect job that way. And I don't think it's actually adequate to do just characterization without a full spectrum of biological assays, human

PK, clinical trials, and potentially some expanded safety testing.

DR. DILIBERTI: Is the implication here that testing for attributes such as leachates or also, in the case of erythropoietin, aggregation, that those are unique, special tests that are not routinely applied across the board to every biopharmaceutical product?

MR. GARNICK [In Audience]: There are tests that are done. Everyone who has used the product container [inaudible] system looks for leachates and things like that. But are you looking for the right ones? Do you know what's really there?

Because if you don't have an idea of what's really there, you may not find it, unless you have a method specific for that. And that's the case of what happened in J&J.

DR. DILIBERTI: Shouldn't you know what leachates are there based on the composition of your closure materials?

MR. GARNICK [In Audience]: No. You

wouldn't have a clue. Unless you're a better organic chemist than I.

DR. NAKTINIS [In Audience]: Vytautas Naktinis, again, Teva.

I would like to pick up one thing of this avalanche of, let's say, negative dragons which could jump out of the bottle of follow-on proteins. So simple one, whole-cell protein, e coli. So, yes, in fact, we cannot tell how much, how many ppm in this particular example, growth hormone from Genentech. But once we develop follow-on proteins, we do not develop them in a vacuum, in the absence of public knowledge, in the absence of knowledge whereby pharmaceuticals are today.

So industry standards--I use this terminology--are well known to everyone in the audience. For example, we know that e coli whole-cell proteins currently in the majority of pharmaceutical approved preparations are below 5 ppm. And we know it is safe.

So with our product we developed the same technique. We developed mock cells, all this

stuff, you know perhaps as well as me. We developed our validated assay for whole-cell proteins. And we demonstrated that our process is capable to remove the whole-cell proteins to levels below 5 ppm.

So now the question. These e coli proteins which are present in Genentech, are they different from these 5 ppm which are present in our product? Of course, we generally will be different, yes; but does it matter? Of course not. Because we know experience--grovomon [ph], great example--that six products approved, coming from all different manufacturing processes. So we're having all different composition of whole-cell proteins. But all below some threshold level are safe.

So therefore, number seven product which comes with the threshold, with the level of ppm, e coli protein below threshold, also should be safe. Let's remain on scientific basis here, not on some emotional fear. Okay, two minutes passed.

DR. VAN DER PLAS [In Audience]: Martijn

van der Plas, again.

I'd like to take another part of the avalanche. The PRCA story in Eprex, this is not really a good example, by similar, in this respect. Because what happened with Eprex was that the manufacturer introduced a major change to the formulation and removed the serum albumin and put as a replacement some new excipients back. I do not know if this was supported by clinical data or not. But the old and the new product were not the same.

While I think that a follow-on manufacturer should aim to try to make its products--well, not identical, but at least as close to identical as possible. So that, yes, Eprex has been a burning case, but we should not be cramped by this, and see what's happened at Eprex and what is the difference between Eprex and follow-on biologics. Thank you.

DR. CHERNEY: Yes, I would just like to make one point with that. It is that part of the purpose of this discussion is to say what's the

capability of the analytical methods. In that case, there was a difference in the products. They changed things.

But part of the point is that the analytical methods that were used were unable to distinguish the differences in the product that clearly had a clinical effect. Obviously, there was something different about that product, but we didn't understand what that difference was. And it took years with the manufacturer, and now they've come up with a potential explanation. I don't know how strong that information is, but they have a link now to leachates.

But the point is that nobody would have expected it. And if you saw that low level of leachates, everybody would have said that was insignificant and it would never have produced an issue.

And we'll get to question three, which is how do you interpret differences. First, you have to look at the thing and see the differences, and then interpret it. And I think the Eprex thing

comes up in the context of both those things.

DR. DILIBERTI: But along those lines with Eprex, was the issue that the problems or the characteristics of the product were really undetectable, or that the appropriate set of methods was just not applied?

DR. CHERNEY: Well, I think the appropriate set of methods were used to look at it, in general. Now, one might argue that--And with the leachates that were used in the USP test now--Now, one might argue that those additional tests might be used.

But even if they used additional tests, they would have seen a slight difference in the leachates there. And perhaps would we require a clinical study? I don't know the answer to that. It wasn't our product. But one might have justified saying these are so low that they would not possibly affect the protein.

But I think what we have to realize is that proteins are exquisitely sensitive moieties; that even small amounts of contaminants can affect

the protein. And that's a lesson that I think we can take from that.

I don't think we should over-stress that, because Eprex had certain things. It was a low amount of protein for the Epo, and those types of things. And so a little bit of a contaminant can hurt a protein that's in low concentration, but if you have a higher concentration you might not alter the protein--Such a large percent, that might not affect things. So it's all in the context of case-by-case and the proteins themselves.

But I think there is concern about the analytical methods and the capability of them. I think after the fact it's easy to find, "Oh, yes, there is this difference." But I think I've stimulated a lot of conversation.

MR. SCHREITMUELLER [In Audience]: Thomas Schreitmueller, Hoffmann-La Roche, again.

I would like to elaborate very briefly also again on the wording "limitation." I think any analytical tool is as good as the sample you have to analyze. That means every kind of result

and interpretation you draw out of this.

So we are here not only talking about release analytics. This is a very limited set of methods. Establishing comparability--and, I would assume, at least this should also hold true for the establishment of biosimilarity--you need much more additional samples. That means you have to go through the whole process; you have to analyze it step by step; and then, based on the complete set of results, you can establish whether you have something similar or not.

But those samples for this data set have to be there available, in order to establish that. Without that, I do not think, even if you apply the highly sophisticated tools with the highest sensitivity and the highest resolution, that you really can establish similarity.

DR. DILIBERTI: Does anyone want to address that point?

PARTICIPANT [In Audience]: [Statement Inaudible.]

DR. DILIBERTI: Okay. We're trying to

finish discussion on a given point before proceeding to the next.

DR. NAKTINIS [In Audience]: Vytautas Naktinis.

We don't need in the sample from originator anything what is not present there. We need only that sample, and we have it from various means. And we analyze. We are not interested in your process, how you did it, what intermediates, and so on and so on. What we are interested to detect, within reasonable limits which we know from industry standards: Are there, or are there not, some materials which should be, from a regular biopharmaceutical process, present in the final product?

DR. SIEGEL [In Audience]: Rick Siegel, Centocor.

Just getting back to the Eprex argument, I'd just like to remind the audience that the PRCA result was something that affected approximately one in ten thousand patients, and was indeed a very rare event and not present in each and every vial.

It required a huge investigation to try and find out what was going on.

The second event has to do with whole-cell protein assays, relative just to a general argument. Now remember, these assays, at least in my view, were designed not to show safety, but to show consistency. They were designed to show that we can manufacture a product in a very consistent way, and the result of that is clinically validated. They aren't designed, per se, to show safety of a given product.

DR. ZHU [In Audience]: I'm Rong-Rong Zhu, from Abbott Bioresearch Center.

And I actually have a question about the analytical capability and the limitation. In every single heterogeneity about aggregates, we have multiple assays. Like you can have SEC, SDS page [ph], SDSCE, FIF technique, ultra-centrifugation [ph] methods. With chemicals we have new and better technology. But if the first drug was developed five, ten years ago, the credentials were set based on SDS page. Five years down the road,

we're based on FF [ph] system. The number will be not the same. Or try the heterogeneity, the same thing. Before was based on IEF; now it becomes ion exchange chromatography; then becomes CIEF. The number will not be the same again. The [inaudible] the same thing. You have ion exchange chemical detection. Now you go to [inaudible] labeling. Fluorescent labeling will be much better technique. The number will not be the same again.

So if the FDA has a set of rules like what kind of methodology you like to see for heterogeneity, for aggregates, or for oligosaccharides--Because they all have correlations, but they're not necessarily exactly the same number. Depends on which methodology you use.

DR. DILIBERTI: Does anyone have any comments on that?

[No Response.]

DR. DILIBERTI: If not, I'll offer a comment. I think that that's one of the motivations for using multiple orthogonal methods

to get at the same property; for example, aggregation. I don't think there's any set rule that you always have to use a particular method.

DR. ZHU [In Audience]: [Statement Inaudible--Speaker Away From Microphone.]

DR. DILIBERTI: That's right, but it's a comparative analysis. It's side-by-side.

DR. ZHU [In Audience]: [Statement Inaudible--Speaker Away From Microphone.]

DR. DILIBERTI: Well, I think if you're comparing the two products side-by-side, if you compare them with tool "A," you get a particular comparison; if you compare them with tool "B," you get a different comparison; and tool "C." And you look at the sum total of all your results to evaluate how well the two products stack up against each other.

DR. ZHU [In Audience]: Uh-huh. But do you have a--Like let's say for oligosaccharides, and you set up a credential. You have zero [inaudible], one [inaudible], two [inaudible]; has to be in certain percentage, in that range. And

then, if you use a different analytical technique, the range may be a little bit different. You know what I mean? And you may out the specification, and you may fail your whole production, depending on which methodology you use. Unless you're acceptable to change the credentials, the numbers.

DR. DILIBERTI: I don't think this is an issue of specifications. I think this is an issue of comparing one product to the other.

DR. ZHU [In Audience]: Uh-huh. Okay, let me think about it. Thank you.

DR. HARRIS: Can we reopen that question, then? Do the analytical chemists here believe that the available tools we have are in fact good enough to detect all of the molecular characteristics that you would want to see when you do a comparative analysis?

Personally, I don't think so. You know, for 20 years we've been submitting applications, and have been very proud of what we've put in our analytical packages. And then later on, as new techniques and new technologies become available,

we revisit those materials and find out that in fact we've missed something. And so I think it's perhaps a little too proud on our part to think that we're there now, when we really have never been there in the past. That's my opinion.

DR. NASHABEH [In Audience]: Wassim Nashabeh, from Genentech.

I just want to echo what Reed has just mentioned. I think the true limitation of the analytical technologies come not in assessing the primary structure, but in truly understanding the product mixture, and strictly the product related variance.

It is this profile, the combination of things that are relevant, that is really difficult to assess. Even in our own products that we spend years and years characterizing, we cannot fully identify all the variances that we see in a profile and account for 100 percent mass balance of what we have, for example, in the ion exchange profile.

So what then we rely on in comparability, we rely on the fixed conditions of a given

analytical methodology, with given conditions, with given standards, to ensure that as we make a change that that profile--not just a number--is consistent time and time again. And that profile is eventually our link to clinical safety and efficacy, because that is the same profile that we had when we did the clinical trials.

And definitely, that communication is more with complex proteins than it is, for example, in the case of insulin. But in the case of other monoclonal antibodies we have, it is very difficult, even in our hands, to fully characterize all of the variants that we have. And actually, we don't.

DR. SIEGEL [In Audience]: Yes, I'm Rick Siegel, Centocor.

Let me just echo Reed's comments. Many of us have been working on trying to describe the size and shape and chemical characteristics of proteins in solution for 20 years or more, and it is still a challenging field. We still see surprises that require us to go back and reformulate because we

saw something in the clinic that maybe we could work around by changing the formulation and getting away with--or changing interaction.

Proteins interact; they associate with one another; they repel one another. And sometimes this can be a bit challenging, to try and describe this in tremendous detail.

MR. GARNICK [In Audience]: Bob Garnick, Genentech.

I'm going to echo what the last three speakers have said. I think, to be clear, the analytical methods are not available. Whether they're done individually or in orthogonal methodology, they're simply not capable of fully characterizing these products today.

And particularly, it's closer with the simpler molecules, peptides perhaps. You can get to that point. I'm not sure we're actually there at that point. But for more complex molecules, as Reed said, every year we get new methodology; we look at our products; we find different things that we weren't particularly looking for before.

And there are surprises out there. And I do want to make the point that I think the Eprex thing is a shot across the bow. I think we

shouldn't be trying to cover it up and pretend it's a one-time-only thing.

At Genentech we have found periodically over the years adducts that have been formed both by process materials and by container closures. Sometimes when we weren't looking for them, we were able to find them; in others, when we looked very carefully, we were able to find them. So it's something, again, if you know what you're looking for, methodology can generally be found to find that. If you don't know what you're looking for, you won't find it. The methods aren't capable of finding them by themselves.

DR. VAN DER PLAS [In Audience]: Martijn van der Plas, again.

After this smooth Genentech show, I'd like to be somewhat provocative and to say that, well, should we really understand everything? Well, I don't think so. I think if we request that

manufacturers first understand each and every thing of their product, then no product will ever be approved. Because nobody understands everything about their products. And this is unreasonable.

But first, there should be a basic understanding. Second, this is all comparative data. We are not in a completely new, blind experiment. We are here trying to establish a link between an old product, a reference product, and a new product. And the basis is that there is science, and there is a comparison. And these two, even if understanding is incomplete, should be enough to answer the question: Do we believe that this product is safe and effective?

Well, this answer may be positive or negative, but this should be the basis of the assessment and of the product development. Because otherwise, we will never approve anything.

MS. MUNDKUR [In Audience]: Hi. Christine Mundkur, with Barr Laboratories.

I guess I just have two comments. One is then I don't know how everybody in this room is

making post-marketing changes, if the analytical methods are not there through comparability protocols, because I can't imagine everybody is doing safety and clinical studies for every change. So obviously, there must be some type, or otherwise, the quality regulatory people wouldn't be signing off on these changes for filing.

And my second point is, obviously, we also forgot that there is a spectrum of simple to more complex products. And I think that we need to keep that in mind.

MR. LUBINECKI [In Audience]: Tony Lubinecki, Centocor.

I'd like to address a concept that was implied by the last few speakers. And that's that similarity and comparability have a relationship to each other. But in order to do that, I'd like to show a slide, if that's okay.

DR. MOORE: If you have an overhead, we can do it.

[Simultaneous Discussion.]

MR. LUBINECKI [In Audience]: Okay, so I

won't show this slide. I'll just describe what's on this slide that I couldn't show.

DR. DILIBERTI: Please submit it to the docket.

MR. LUBINECKI [In Audience]: We can do that. Basically, when a manufacturer assesses comparability of a product after a process change, it's pretty straightforward to gather up the in-process materials, the drug substance, the drug product, and to look at all the tests that can be run on those, to look at all the meaningful and relevant attributes.

It's also possible to look at, in a comparative way, the stability profiles, the degradation profiles; and to compare all that information with the clinical history, the non-clinical history, the manufacturing history; and to make a determination at the end whether those materials are in fact comparable before and after the process change.

That allows the manufacturer to, in essence, access the clinical and non-clinical

information available for the product from the earlier process, and transfer it to the later process.

But when one assesses the similarity of a follow-on to an innovator product, those materials, with the except of drug product, are not available. The assays used by the innovator are not available. The standards used by the innovator are not available. Much of the information used in comparability is not available.

And while I agree that modern chemical methods and physical methods and biological methods can be used to assess the similarity of the follow-on to the innovator product, drug product, it's not possible to assess all of the other things that go into making the assessment of comparability.

I therefore maintain that it's physically impossible for anyone to bridge to the clinical data of the innovator by the demonstration of similarity between a follow-on and an innovator product. Thank you.

DR. WOLFE [In Audience]: Rich Wolfe, Pfizer.

I just wanted to focus on the question and

the comment "capabilities and limitations of the available analytical tools." I think that's a critical point that we really haven't focused on.

We're talking about a heterogeneous mixture of molecules. We're basically being an innovator or a follow-on. You're basically going to throw all the analytical tools that you have available into the picture to assess what you have; what is your heterogeneity; which methods are useful, and which methods are not useful. You're going to develop a set of tools that's the best you have right now.

And I think the point that hasn't come out today is that years of experience with a particular molecule a particular set of heterogeneity allows you to develop and evolve your analytical tools. Thank you.

DR. WINDISCH [In Audience]: Joerg Windisch, from Novartis.

I think my comment is going kind of in the same direction. Because when listening to people, I got the feeling that because there will always be some limitations left, the capabilities don't really need to be utilized, or aren't really any good. And I think that's simply not true.

I think what we need to do is what was just said. We need to look at what experience is available, both in general, with proteins, with glycoproteins, and with the specific protein in question. And we need to do everything we can possibly do to cover those parameters which are already known to be critical, or non-critical. Any information you can gather, this needs to be done. If you don't do this, I think this would simply be unethical.

Then, I agree, you will still be left with some limitations. But the more you do them, the less limitations you will have. And those limitations will simply have to be addressed at other levels; be it pre-clinical, and eventually I think it will be clinical studies.

I think this is just the whole concept. And I think just because there are limitations, you should still utilize the capabilities as much as possible.

DR. NAKTINIS [In Audience]: Vytautas Naktinis again, Teva.

The previous two speakers actually addressed the majority of the comment I wanted to make on this particular time moment. I would like

now to concentrate on a very minute detail again, the previous question, which came from Johnson and Johnson.

We had this classic argument, which brand manufacturers telling that you have to know something in order to make comparability assessment once you did some change. But we very rarely hear any specific example. What is this something which we follow-on manufacturers cannot see because we don't know what to look at?

And this particular sample still has something, has to be visible by current analytical techniques which are used by brand manufacturers

today. Our analytical techniques, believe me, are the same. Maybe methods not the same; instruments the same, sensitivities the same; methods may be a little bit different.

So I would be very much happy to hear at least one example--practical, concrete example: What is this thing where brand manufacturers look back into their history and can judge that now, all right, this particular manufacturing change did not alternate that particular factor? I would be happy.

DR. MOORE: I think we've exhausted this question.

[Laughter.]

[Simultaneous Discussion.]

MS. TOUZOVA [In Audience]: My name is Tatyana Touzova, Biolex.

I don't want to speak for brand manufacturing. I just want to compare two systems that can produce the same protein. For example, [inaudible] cells protein and plant that can produce the same protein. They could be challenges

actually for manufacturing, innovator manufacturers who produce proteins using plant system; whether it's a plant culture system, whether it's whole plant or a root culture system.

We talk about industry standards for [inaudible] cells proteins. We talk about e coli proteins, industry standards. But sometimes there are no standards for host plant proteins that can exist and can be present in a drug substance. And this difference can make actually difference in the safety profile of the product, can make difference in the PK and the PD profile.

And of course, some challenges exist for the companies who produce proteins using plant system, because they would have to develop and utilize assay as well as sometimes develop reagents for their assay; for example, [inaudible] antibodies to detect those proteins. So these systems, it's challenges for the company. And there I can see some limitations and difference between the same proteins produced by different systems. Thank you.

DR. CHANG: Well, let me just say that actually FDA works with sister agencies on the transgenic plan for proteins that appear in

product. That is in the pipeline. Now, with the current system, if you change from [inaudible] cells to transgenic plant that is going to be--Your product manufactured from transgenic plant will be a new product; so that need for clinical evaluation from the current system.

DR. MOORE: I would like to thank the people, industries, who have brought forward these cases where they've had problems and performed the extensive investigations into them, and thank them for making this information public so we don't keep repeating these mistakes with other products; whether it be innovator or follow-on.

And with that, I'd like to turn to the last question: "What are the appropriate standards for the characterization of those identified attributes?" And here we're speaking to reference standards. I'll open it up to Reed again.

DR. HARRIS: Yes. The first issue that I

raised here has already been opened to some extent. How do you apply the comparability concepts for a follow-on biologics manufacturer who doesn't have access to the historical data set, nor to the sample set that was used over the course of development, and that was used to establish the safety and efficacy of that material? That's a link that I don't think a follow-on biologics manufacturer can ever establish.

And so you have to start looking at it. Is reverse engineering of a product perhaps as safe as the forward engineering that takes place at the innovator's company?

The second point that's up here is how to link the follow-on biologics manufacturer's lots to the innovator's clinical material. Again, without having the common reference or the necessary reagents to conduct equivalent tests.

To what extent does the follow-on biologics manufacturer have to recharacterize and assign impurities? Is it enough just to show that you get an equivalent profile, the same ion

exchange profile, the same peptide map? Or should the follow-on biologics manufacturers be expected to go back and reassign the structure characteristics that define the heterogeneity that's present?

And there are some limitations there because, again, if you want to define something as an impurity or not, you need some sort of a potency assay. And it's unlikely to be the same as the innovator's. And so you may wind up in a situation where the profiles look the same, but the definitions of the forms that are present somehow come out to be different.

And then, the last issue, which is really tricky, is that the innovators over the course of development can define what the critical quality attributes are and validate those with clinical studies. And how would a product reviewer then be able to look at a different application and make a determination that the critical quality attributes were also included in this newer application, without making reference to the proprietary

information that the innovator had submitted?

So those are some of the key questions that I wanted to bring up. I'll turn it over to Charlie.

DR. DILIBERTI: Thanks, Reed. In answering this question, I think there are really three main aspects. I don't have a bullet for the last, but I'll bring it up verbally.

The first one is: What's the appropriate comparator product or material? The second is: What are appropriate acceptance criteria? And third is: What action do you take if you do see a difference upon application of those acceptance criteria?

For the first one, I believe that in most cases the brand product itself is the most appropriate comparator. Yes, there may be a few instances where there are reference standards, or possibly even some product monographs; but these are limited in scope. And generally speaking, I think the reference product itself is the most appropriate comparator.

The second point, acceptance criteria, these can be determined in a variety of ways. We heard this morning on the collective assimilation

of all of the product quality attributes that are assessed in a comparability study, and using advanced mathematical tools to assimilate them.

But I think in general, one main feature of this is going to be that the acceptance criteria should be based in part at least on the brand product variation. And in those cases where there are multiple brand products out on the market for essentially the same molecule, certainly I would look at the different manufacturer's products that are available.

DR. MOORE: Now I'll open this up to the audience.

[Laughter.]

PARTICIPANT: Now that they're all awake.

DR. MOORE: With that big thunder roll.

DR. CHERNEY: I'll make a comment anyway, that if you do set the acceptance criteria based on brand name variation, how many samples of the brand

name should you--If you do three and they're all of the same lot, that variation is going to be exceedingly small. And so there's an issue of how many lots are you going to look at to establish that variation?

And what do you do if you are outside that variation? You may even be within the innovator's release criteria still and his spec, because they're a little bit wider. You're only getting a small snapshot of that variation. And to just meet that would be difficult to consistently manufacture a product. So you have to base it on something else, and what are those other things, then, if you're going to do that? Or are we going to test the hundred lots of material?

DR. DILIBERTI: Are you going to address that particular question?

MS. YAMASHITA [In Audience]: I was going to add onto that.

DR. DILIBERTI: Okay. Go ahead.

MS. YAMASHITA [In Audience]: Elizabeth Yamashita, Bristol-Myers Squibb.

In addition to the number of what the standards are or reference materials, I think you have to figure out what the acceptance criteria is

[sic]. So if you do one lot, five lots, ten lots, a hundred lots, is it 80 to 125? Is it 90 to 110? How close is close enough? And I think that's something we really have to think about.

In addition, when you think about comparability or similarity, are you also looking at the stability profile? So think about when anybody does their comparability work. It's usually right after the product has been made, the API has been made. So are we considering the stability profile between the innovator and the follow-on? What if they diverge? What do we do then?

I think these are all different things that have to be thought about before you can say that something is truly comparable and similar.

DR. DILIBERTI: Just to address--Are you going to address Barry's question, also?

MR. LUBINECKI [In Audience]: No. Please,

go ahead.

DR. DILIBERTI: Okay. Before we change topic, I think part of the decision as to how many lots of the reference or brand product you want to be testing, depends on how pure the product is. You know, for some simple, non-glycosylated proteins that are very highly purified, you may not need to test quite as many lots. When you get involved with more complex glycosylated proteins, you may need to test more lots.

MS. YAMASHITA [In Audience]: Can I just finish up?

DR. DILIBERTI: Yes.

MS. YAMASHITA [In Audience]: Elizabeth Yamashita, Bristol-Myers Squibb.

I think one of the things that you have to think about in the number of lots is where that specific lot lands up within the specification range. Right?

DR. DILIBERTI: Uh-huh.

MS. YAMASHITA [In Audience]: So if that lot, for whatever reason, lands up at 110, then are

you really skewing all of your analytical--you know, the results, and accepting something that truly isn't representative of the total profile of the innovator product? So I think you have to have multiple lots, and you have to figure that out in some kind of statistical way.

MR. LUBINECKI [In Audience]: As a reaction to Dr. Diliberti's slides, in terms of how much information is enough to set an appropriate standard or acceptance criteria, I think that it's incumbent on all developers for all products to develop their assays, develop their process, develop their product, do clinical trials that link all of these together. And it is by linking all of that information together that one determines where the specification ought to be for that product.

Q6B, which is an ICH document which has been agreed by the major regulators of the three regions as well as the three industrial groups, attests very clearly to this fact, that you cannot take a specification from one product and apply it to a different product, because it's made by a

different process.

And hence, I would argue that the appropriate answer for your second question is what's appropriate for the follow-on product, based on the clinical studies with the follow-on product, using the validated systems and the validated assays for that product.

That's how risk is managed. And without those sorts of systems to manage risk, if there is less data or there are assumptions about what appears to be similar to what, there would just be less certainty about what is appropriate. Thank you.

DR. ZHU [In Audience]: I have a question. The thing is, if you're working with glycoprotein and if you use the same manufacturer process, lot to lot the variation is smaller. But if you have a process change, often we see huge change on the oligo-profiling. And that means if you do a follow-on pharmaceutical comparison with the brand product, typically you have a huge--I would expect you will see a large variation on the

oligosaccharide profiling.

So are you going to have to set a much wider acceptance credential? Or you have to retest all the--make sure to the safety, toxicity study on all the oligo-forms, make sure it's safe?

DR. NAKTINIS [In Audience]: Vytautas Naktinis, Teva.

I'd like to address one point again from the previous question. So how many lots of original manufacture we have to have access to in order to build up our specification? I would like to remind again that no follow-on protein is being developed in space, in a vacuum, without knowledge about biopharmaceuticals specification principles, how should they be built. So what is measured routinely?

And there's a second point. We are beneficial because we are developing these products usually significantly later than the originator. So the process improvements are here. Analytical improvements are here. And we are targeting our quality parameters, a priori, to be superior to

that what is currently available on the market.

So assume we have criteria--Okay, range of some certain criteria, like this. And let's say Dimer [ph], for example. All right? So we always will be targeting our process with our Dimer. A worst-case scenario would be below the lowest possible detectible non-published specification to that, compared to the innovator. So that's one of the approaches.

Again, in this short time you cannot describe all the tricks or all this knowledge which are done in order to build specifications of follow-on proteins based on limited access to different lots of originator.

DR. MOORE: In the previous session, one issue was brought up that someone who wanted to develop a follow-on product would not know whether the lots of drug product they were picking up were actually made from three different lots of drugs, or three different batches of drug substance. And that issue hadn't been addressed in this session yet, and I wondered if there was someone who wanted

to speak to that issue.

DR. VAN DER PLAS [In Audience]: Well, I can immediately react to get the following thoughts. In the end, not only the manufacturer has to know whether it's good, but he also has to convince the FDA--or in Europe, the EMEA--that it's good. So if he makes a mess out of his development and does not take enough lots, and his variation is too big or too small or just plain wrong, well, then his product does not get approved. So even if the manufacturer makes a mess, then the competent authorities can resolve this problem.

The other point which I wanted to react to is that Charles said in most cases the brand product is the appropriate comparator. If you look into the European law as it stands now, in fact, the brand product is the only allowed comparator. Because what you have to do, at least in Europe, is to show comparability or biosimilarity, or something, to a marketed reference product. And if you show this biosimilarity, then you are eligible basically for marketing authorization. Previously,

you had to extend this most of the times with supporting scientific data. But the comparison to the reference product is the basis of getting a marketing authorization.

DR. HARRIS: So how would the product reviewer make a determination that the proposed specifications, let's say, for the follow-on product were inappropriate, without making reference to the innovator's file?

DR. VAN DER PLAS [In Audience]: Well, good question.

[Laughter.]

DR. HARRIS: Got an answer to that one?

DR. DILIBERTI: They can either say "Yes, it is appropriate," or "No."

DR. CHERNEY: What would be the basis for a range? What's the basis for a range if it's not linked to clinical data?

DR. DILIBERTI: Well, it doesn't necessarily have to be the same range as the brand product manufacturer has. It can be based on the cumulative data across even multiple products.

DR. CHERNEY: We didn't talk about this, but part of the things, looking at all these lots, traditionally innovators will look at their

historical data and do statistical analysis to set the acceptance criteria. But here I see a problem with doing any statistical analysis on the data you collect, because you don't know how many came from this lot, how many came from this. And you have an imbalance in the data, and the statistical analysis will be difficult to interpret.

DR. DILIBERTI: You bring up a good point, Barry. How are those specifications typically set in the brand industry? Okay, is it set by the limits of the product that was actually introduced into a clinical study? Or do they take the variability in those clinical batches and expand upon that, beyond the clinically tested range?

DR. CHERNEY: Well, I think they take that within reason and within scientifically justifiable--where we have some instance of comfort level, that those changes are not going to have an impact. But we also rely on the clinical data or

dose escalation studies, which says that the range of those parameters when they were in a dose escalation did not impact. So there is some clinical tie to that level of data now.

One might argue about the amount of that data, because those clinical studies are small. And as we all have seen in these earlier things, it is that the amount of clinical information--that sensitivity to changes in clinical studies is difficult to interpret. But that gives us some basis, I think. But I think we'd better let the audience talk a little.

DR. SCHENERMAN [In Audience]: Okay. Mark Schenerman, from MedImmune.

I also just wanted to comment on Stephen's question earlier, which is: How does the follow-on company know how many lots make up the drug product samples that they're taking? And I'm not sure there would be any way of knowing. It really depends on the volume of the product that's being manufactured. It depends on the scale of the process. For a particular process, there could be

hundreds of lots run per year; but another process could be very large-scale and only a few lots are manufactured.

Then again, there are drug substance lots that are manufactured which could end up in multiple drug product lots. So I think it would be very difficult for someone to sort that out if they didn't have the innovator information.

But I wanted to raise a slightly different question, and it is relevant to this question three. How do you determine what range is acceptable for the comparison? And it might be useful to look at a hypothetical example.

So let's say we had a monoclonal antibody that had 1 percent oxidation in the active site, in the binding site. The innovator had shown through clinical studies that a range of 0.5 percent to 5 percent was acceptable for this particular oxidation. The follow-on company obviously doesn't know that. So they come along; they'll do their studies. They show, for example, that there's 8 percent oxidation in the active site. Well, how do

they know whether or not this is acceptable?

DR. SIEGEL [In Audience]: Rick Siegel,
Centocor.

Just getting back to Stephen's question, I think one manufacturing process also that might be very, very difficult to justify by product testing is with some recombinant methods or processes that utilize refolding, and where a final product is actually a blending process, where different lots with different activities are blended to give a uniform specific activity. And without having knowledge of the bulk drug substance, there could be a very, very different distribution of products in the drug product; that's if just by analyzing drug product without knowledge of the drug substance that went in it.

MR. GARNICK [In Audience]: Rob Garnick,
Genentech.

Just to put it in perspective--and we also covered this in the previous session--while it's probably okay for small molecules to obtain or isolate the active drug--which is a material of

very high purity, typically 90 to greater than 90 percent--and then use that as a reference standard--which is the practice for multiple batches of small molecules, where you can do it irregardless of variations in drug substance or the number of batches produced--that's not the case for a complicated mixture for more complex biological molecules.

There are two factors. One, as someone pointed out, the number of lots for a year of that actual final product that are available may represent one batch of drugs that was manufactured two years earlier. You have no way of knowing. Some of the larger production lots, bulk lots, will result in many, many final product lots, and we wouldn't have--or the follow-on manufacturer wouldn't have a clue as to which ones to combine or not. Which does raise the question of the validity of any statistical evaluation of various batches.

The other thing to consider is that these products aren't stable and that, with time and given the shelf life of these products, there are

degradations that occur in the actual product final vial that, if you isolated those and used that as a reference, could lead to very erroneous conclusions.

So basically, the final product is not, in the case of a biologic, the appropriate reference to use. It's the actual bulk substance, which is not available to the follow-on biologic manufacturer. So you have a built-in conundrum, in terms of what to use as a reference material.

MS. MUNDKUR [In Audience]: Ultimately, it's the finished product that goes into the human. So the comparator should be the correct one of what's actually being dosed to the human. So I really think that you don't have to have the API to get the correct comparator.

And I guess if the products are not very stable, they're still in the marketplace. So if they are stable to a certain point of whatever the clinical--whatever I'm dosing at whatever point of time it is, that should be what the comparator is. You don't have to have a fresh batch to make a

comparison.

The second point is the number of batches that are out in the marketplace. That's something we have to overcome. So does it have to be one lot, or 15 lots? That's going to depend on what my specs are. So if I can match yours every single time, fine. But we have to figure out what it is.

I think it's kind of crazy that we're sitting here talking about how many lots it needs to be. It's really: What is the appropriate standard? And we say that the comparator is the reference product of the brand.

DR. WINDISCH [In Audience]: Joerg Windisch, from Novartis, again.

I'm a little confused about the variability discussion here and the multiple lot testing. Because I think it must be clearly stated, the goal of testing multiple lots is not to find the widest possible window for your follow-on. It's to see where the bar is. I mean, you really have to do your best to meet the tightest specifications that you can possibly achieve.

That's one thing. So that's not the goal here.

The second thing is: Where do your specifications really come from? And I agree, to a certain degree, with the notion that they eventually are confirmed in your clinical trials. But wouldn't you feel much better if you had a product going into your clinical trials that is, according to all the methods available, at least as good as what's out there already on the market for years?

Honestly, I would. And of course, you might be missing something talking about limitations. But I would rather look at everything that I can actually look at, at this point.

DR. HARRIS: Can I just briefly raise one other issue? And it's perhaps a little bit afield. But I wonder how forthcoming the innovator companies are going to be about their methods and the characteristics that they have identified.

You know, I worry that, as it becomes apparent that more and more of the follow-on biologics manufacturers are going to use published

studies to set up their own control systems and resolve their own issues, that the speakers are going to be harder and harder to come by for the well characterized meetings and similar forums.

And I worry a little bit that the industry standards that may be apparent at this time are going to become more and more invisible as we go along. I don't know if anybody else has similar concerns about that.

DR. CHERNEY: Well, I just wanted to say, before we close, I think part of the discussion on the number of vials and lots that you look at is based on the assumption that no matter what analytical--When you do a whole battery of analytical tests, you're likely to see differences between a limited number of lots from the innovator, versus the lots that you compare as a follow-on. And the issue then is, how do we deal with this? Because I think you're going to see differences. I'd be expecting to see them.

It's great if your process capability is well within the process capability of the

innovator. But I don't know if that's really going to happen. The innovators are continuously improving their process. Process capability increases. What they release to the market over the years gets better and better--at least, for some of our products. And so, you know, the bar is setting higher and higher for a follow-on, then, in those terms. And, you know, what do we do with differences?

DR. MOORE: Well, that almost speaks to that the follow-on would continue to have to match the innovator after a possible approval of a follow-on.

DR. DILIBERTI: I think that's outside the scope of this discussion.

DR. MOORE: Yes. On that note, I want to thank everybody for attending this session. It's been a very lively one, from both the panel and the audience. Thank you again.

[Applause.]

[Whereupon, at 5:05 p.m., the session was concluded.]