U.S. FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF PHARMACEUTICAL SCIENCE

SCIENTIFIC CONSIDERATIONS RELATED TO DEVELOPING FOLLOW-ON PROTEIN PRODUCTS

PUBLIC WORKSHOP

TUESDAY,
SEPTEMBER 14, 2004

The workshop was held at 8:30 a.m., in the Germantown Room of Building II, University of Maryland's Shady Grove Conference Center, 9360 Gudelsky Drive, Rockville, Maryland, Dr. Ajaz Hussain, Deputy Director, Office of Pharmaceutical Science, moderating.

PRESENT:

ROBERT ADAMSON, Ph.D

CAROLE BEN-MAIMON, M.D.

JOSEPH CARRADO, M.Sc., R.Ph.

ARNON CHAIT, Ph.D.

CHARLES DiLIBERTI

JOHN DINGERDISSEN

LINDA FRYKLUND, Ph.D.

ROBERT L. GARNICK, Ph.D.

JACOB R. HARTMAN, Ph.D.

WALTER W. HAUCK, Ph.D.

CHRISTOPHER J. HOLLOWAY, Ph.D.

PRESENT (Continued):

MATHIAS HUKKELHOVEN, Ph.D.

GORDON JOHNSTON

ANDREW J.S. JONES, D.Phil.

ART LeBLANC, M.S.

CAROLINE LOEW, Ph.D.

VYTAUTAS NAKTINIS, Ph.D.

SARA RADCLIFFE, MPH

SUZANNE M. SENSABAUGH, M.S., MBA

DORON SHINAR, Ph.D.

YAFIT STARK, Ph.D.

PATRICIA C. WEBER, Ph.D.

ROBERT ZEID

FDA REPRESENTATIVES:

JANICE BROWN, M.S.

DRUSILLA BURNS, Ph.D.

ANDREW CHANG, Ph.D.

WILLIAM EGAN, Ph.D.

BARRY CHERNEY, Ph.D.

BLAIR FRASER, Ph.D.

JESSE GOODMAN, M.D.

DAVID GREEN, Ph.D.

FRANK HOLCOMBE, Ph.D.

AJAZ HUSSAIN, Ph.D.

FDA REPRESENTATIVES (Continued):

CHRISTOPHER JONECKIS, Ph.D.

STEVEN KOZLOWSKI, M.D.

STEVEN MOORE, Ph.D.

DAVID ORLOFF, M.D.

AMY ROSENBERG, M.D.

PATRICK SWANN, Ph.D.

KEITH WEBBER, Ph.D.

JANE WOODCOCK, M.D.

LAWRENCE YU, Ph.D.

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P R O C E E D I N G S

(8:30 a.m.)

DR. HUSSAIN: Well, the audio visual system is a bit nervous. I think we'll correct that as we go on.

Well, good morning, and welcome to the public workshop on scientific considerations related to developing follow-on protein products.

I am Ajaz Hussain, and I'll be the moderator for this public workshop, and I'd like to say a few words before we get started.

This workshop is to provide the stakeholders, yourself, an opportunity to speak, and the role of FDA today is to listen and hear, to sort of absorb your thoughts, your issues, and your points of view. So please do not expect to hear from FDA. The directions are their thoughts on exactly where they stand. So we are here to listen today.

On day one we'll listen to your presentations on terminology, manufacturing issues, characterization, potency and surrogates for safety and efficacy.

And on day two, we'll discuss and hear from you on immunogenicity, preclinical and clinical

issues.

FDA staff members have been selected to serve on panels on these topics, and these FDA members will be on the stage, and they will ask questions to clarify certain points that they may have heard in your presentations, and the questions will be limited to clarification questions.

Time is limited. So it may not be possible to accommodate questions from the audience. We'll see how the workshop progresses, and then if there are opportunities, we'll create the opportunities for folks to ask questions from the audience also, but I cannot guarantee that right now.

The number of speakers, the topics, and allotted time should be in the agenda that's available to you. And so for the speakers, I'll request please restrict yourself to the time allotted, and as part of the introduction simply state your name and affiliation and move on to your presentation.

Following the presentations, you'll have to probably go back to the audience, and we will assemble the panel and ask questions for the entire set of presentations that have been given on each topic.

When we have the FDA panel assembled and the questions are being posed, please use the microphones, which should be in the aisles. I don't see those, but I think will make sure the microphones are in the aisles, and the presenters are requested to use the microphones to answer the questions because this is being recorded and also Webcasted.

If there are issues with respect to availability of microphones or time, the leads will adjust to that request. At the same time, remember I'm sitting right behind you. So you have to stick to your time.

(Laughter.)

DR. HUSSAIN: That's a strategic position.

A note about the FDA panel members and day one. We have a set of presentations which are not aligned with the topics, and a general panel has been developed for that purpose. This was to accommodate requests of travel restrictions or travel requests and religious holidays. So there are five presentations in the morning and a general panel, which includes members from all of the panels, for that purpose.

With that and still since I see our AV system is still nervous, like me probably -- maybe if

I sit down it will not -- with that I will sort of invite Dr. Woodcock to give her opening remarks, and hopefully while we are going through this thing, the AV system will stabilize.

Janet.

DR. WOODCOCK: Thanks, Ajaz.

Good morning, everyone. We have a great turnout today, and I think we should be getting a lot of very good information on this topic.

Almost a year ago, FDA announced we were beginning work on a guidance on the scientific issues involving comparing two similar proteins, and this effort was stimulated by numerous inquiries we had received, particularly around certain approved drugs, such as insulin and human growth hormone.

Needless to say, this is history now. This announcement caused a great deal of consternation in the community, and it was followed up by filing of citizen petitions to the agency and a number of other activities. We received much input from stakeholders that this might be premature for us to go ahead and issue a draft guidance, and many people asked for a public process prior to issuance of such guidance.

And this is the kickoff of such a public

process. And it was probably good that the community did ask for this. As we have looked into this issue over the summer, we see that there are many complicating factors. There have been many routes of approval of proteins over the last four to five decades within the United States, and there are many issues that have been raised by the filings that have been submitted to the agency and that are available in the public dockets. And so these things are quite worthwhile to, have a public process around, and we do look forward to getting input in this meeting, which is in response to these concerns.

Today we're going to talk about the science issues or you are going to talk about the science issues. These proceedings are about the science issues related to comparison of proteins, not to other regulatory or legal issues that also might arise.

I think one thing we all must agree upon is that it is up to the scientific community to get the state of the science right first and to have a common and clear understanding of what that state is.

Now, one thing we have reached agreement on, I'm happy to announce, is that we need to define

terminology so that we're talking to each other about the same things, and in our notice of this meeting, we actually proposed a couple of definitions, and we're open to input on those definitions because there are so many terms flying around in this area that I think people are really talking past one another.

In Europe, they have settled on some defined terms, but they have a different structure for their regulation of these products, and so I think we need input on what to call these different products. What are we talking about here?

And we'll have a brief presentation of terms, definitions or perhaps proposed definitions that hopefully will be food for thought and discussion, but we haven't settled on any final definitions. That's something else we need input on.

We expect today, as I said, to get extensive and substantive input on the state of the science circa 2004 and what we should be able to expect over the next several years. Our panels of experts are assembled and are very eager to listen to the input that we get over the next day and a half.

I thank you for your attention and your efforts, and we look forward to hearing from everyone.

(Applause.)

DR. HUSSAIN: Dr. Jesse Goodman, Director, CBER.

DR. GOODMAN: Well, I'll just join Janet in welcoming you here and thank you for this opportunity to get your input.

I really don't have much to add to that except to say that I think it is really very important that you and your colleagues share your experience with respect to some of the issues in manufacturing, safety, and efficacy of biologic products so that we can move forward to hopefully a bright and optimistic and continuing successful future.

So, again, we really welcome your input here today. Thanks a lot.

(Applause.)

DR. HUSSAIN: As the AV system is being worked on, I had a few jokes to say. No, just kidding.

I think we'll take a few minutes' pause to make sure the AV system is working properly, and then Keith Webber, Acting Director of Office of Biotechnology Products, will share some thoughts on terminology.

(Whereupon, the foregoing matter went off the record at 8:39 a.m. and went back on the record at 8:42 a.m.)

DR. HUSSAIN: Well, it seems to be working, though a big smaller in size. I hope you can still see that. I think it should be okay.

Keith.

DR. WEBBER: Okay. Thanks, and welcome to everyone.

This is actually great because we're a little bit ahead of schedule now, and I'm sure we're going to have a tight schedule as the day goes on. So I will certainly try to be brief.

Before we get started really on the day's presentations, I wanted to go over some I guess what I call relevant terminology. The relevance, I guess, will be determined as we go on with this process.

But in general, as Gary Buehler once said, we understand the word by the words we use to describe it, and so I think it's good to have a starting point from which we move forward and try to use common terminology as best we can with consistent meanings.

And that brings me to the complex use of terminology. There are many words that have common

meanings, and common meanings are great, except that they may not be common to everybody. The meanings of words oftentimes are what we learned early on, but they are learned in different manners by different groups. And often they are not as precise as we would actually need to be using.

There is also, for many terms, legal meanings, and the advantage of legal meanings -- can everybody hear me, as well? Should have announced that first off -- legal meanings have the advantage that they are usually quite a bit more precise, as well as being documented somewhere so that you can always refer back to a standard meaning, and one of the topics today is new terms.

New terms, the importance of developing new terms is for new ideas, but also as we develop those, we have to be sure that those terms are consistent with the terminology that we already have as best we can, or at least maybe not consistent, but not contradictory.

And then, as well, they have to be precise and accurate for their intended purpose, much like drugs, which brings me to drugs.

The first definition most of you I'm sure

already know this. So I won't go into detail with regard to that. Essentially defined by the Food, Drug, and Cosmetic Act, and the primary definition, I guess, would be the last three bullets really: those things that are intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or animals. Today we're really focusing on those that are for man.

And then things that are intended to affect the structure or function of the body and/or things that are intended for use as components of any of the above fall into the legal category of drugs.

And then biological products are defined by a different act, the Public Health Service Act. And I won't go through the definition of this, but the main idea here is that they are considered to be drugs as well, in general. From a regulatory perspective, many of the regulations that apply to drugs also apply to biologics.

And then within a subset of the biological products are the specified biologic products, these are defined by regulation as being therapeutic DNA plasmid products, which is not the topic today, and then synthetic peptides of less than 40 amino acids,

monoclonal antibodies, and the therapeutic recombinant DNA drug proteins.

These last three categories are really what we're primarily dealing with in this meeting.

Drug product is a definition that's important to consider because it is the finished dosage form of a drug that contains the active ingredient as opposed to drug substance which is the active ingredient that's intended to furnish the pharmacological activity.

Drug substances generally include intermediates though. So really it's talking about the final purified active pharmaceutical ingredient.

For biological products and specified biological products, potency is a critical quality attribute, let's say, and potency is defined in the 600 regs. as the specific ability or capacity of the product to effect a given result when it's administered in the manner intended.

Surrogate endpoints are something that are important for situations where you can't really look at the clinical efficacy that you want, and they're defined as a laboratory or physical sign that's a substitute for some clinically meaningful endpoint,

and usually it should be a direct measure of how the patient feels or functions where they survive. And it's expected to predict the effect of the therapy you're using to treat.

Now, we get into some of the more relevant terms for the topic today. Bioavailability is defined in the regulations as the rate and extent to which the active ingredient or the active moiety is absorbed from a drug product and becomes available at the site of action.

Okay. That brings us to bioequivalence, which is another relevant term for today, and that's essentially the absence of any significant difference in the rate and extent to which the active ingredient or the active moiety in pharmaceutical equivalents or pharmaceutical alternatives, which I'll define later, become available at the site of drug action when they're administered the same dose, under similar conditions in an appropriately designed study.

Okay. So what are pharmaceutical equivalents? Those are drug products that have essentially identical everything, identical dosage forms, identical amounts of identical active drug ingredients, and they should deliver identical amounts

of the active drug over the identical dosing period. So we're talking about serious sameness here.

Pharmaceutical alternatives, on the other hand, are products that contain the same therapeutic moiety or its precursor, but not necessarily the same amount or the same dosage form.

Okay. Now, the central question with regard to exchangeability is the idea of therapeutic equivalence, and therapeutic equivalence is an important term. Drug products are considered to be therapeutic equivalents only if they're pharmaceutical equivalents. So they have to be the same, and if they can be expected to have the same clinical effect and safety profile when they're administered to patients under conditions specified in the labeling, and that's the definition from the orange book.

Now, for what we are calling at this point follow-on products, the Europeans have defined a term which is biosimilar products, and I bring this definition up just really as a point of comparison to what's being done in Europe, and biosimilar products have been defined, and I have to say at the first point I was having a difficult time finding a regulatory definition for this. The best I could come

up with was the "EuropaBio" newsletter, which I think is probably good, but may not be perhaps as accurate as we would like, but anyway, they're defined as being subsequent versions of a biological product that's independently developed and approved, and they depend upon the same mechanism of action, and they're intended to be used for the same therapeutic indication.

Now for the definitions that we would like to address in this meeting. First is the follow-on protein or follow-on protein product, and our proposed definition that we've put forward is that this is a protein product which is intended to be a similar version or a duplicate of an already approved or licensed protein product.

Throughout the day we certainly welcome your comments.

Then the other definition, the second generation protein product, and our proposed definition for this type of product is that it's a product that's similar to an already approved or licensed product, but which has been deliberately modified to change its product's characteristics, and generally that's for favorable purposes of better

pharmacokinetics or a decrease in immunogenicity.

And again, I mention that, you know, comments on the terminology are certainly welcome here, but the second generation protein products from manufacturing and clinical potencies' perspective really are not the topic for today that we would like to focus on. We really want to focus on the follow-on products.

And our goals for today, just to refocus here, are to determine the scientifically relevant factors that should be considered to assure the safety, efficacy, and utility of follow-on products, and we would like to work on establishing terminology to foster clear communications as we develop policy for the follow-on products.

And one last thing I might do is just for the other speakers. The way these work is you just click on your topic once your name will come up, and at the end it will come to a blank screen, come back to the previous slide and moving on to the next talk.

Thank you very much.

(Applause.)

DR. HUSSAIN: We have two presentations on terminology. We are ahead of time, but I'd like to

simply continue the discussion and make up our time through questions or break at a suitable time.

So the next presentation on terminology is by Gordon Johnston.

MR. JOHNSTON: Thank you, Ajaz.

My name is Gordon Johnston. I'm with the Generic Pharmaceutical Association.

It was interesting to hear this morning in Dr. Woodcock's opening remarks and a reflection of this meeting that they've included terminology as one of the issues for discussion, and actually we're very pleased about that. Now, they may not be pleased that we don't really agree with the term "follow-on," but it's a great place to start the debate.

We do believe appropriate nomenclature is critical, and it's critical to convey a common understanding in the health care community and with the patients, and this is one of the areas that we really want to focus on as we move forward towards the pathway, an abbreviated pathway, rather, for biologic products.

I think there are some lessons to be learned from the term "generic." If we turn the clock back to 1984, there wasn't much thought given to the

term "generic," and everybody believed that people would understand what it is, and in fact, during the 1980, clearly the health care community, nor patients really understood that generic drugs were equivalent to brand drugs. They underwent a very vigorous review process by FDA and had the same therapeutic effect, and it was really only after a lot of work by both the industry and the FDA in increasing awareness to consumers and practitioners that we kind of overcome that definitional issue.

And today I think most people in health care or in the public truly understand what a generic drug is as approved by FDA.

The term "follow on" in our view does lead to misunderstanding and probably does not have the clarity that we believe is necessary for products approved through an abbreviated process. We certainly recognize not only in the title of today's meeting sponsored by FDA the term "follow on" was used. It's used in Europe and a number of other regions around the world.

But in our investigations, we could not determine that there has been much of a vigorous debate on this terminology, and so I think the

opportunity to take a careful look at this is going to be important in the coming months.

It kind of presents a negative connotation as it's kind of a second rate or just what is it, and I think, again, it could be confusing in the public, both the public and the health care sector.

I want to take a moment just to review kind of the terminology, the general classic terminology used in drugs or in some cases there aren't specific terms used in various drugs. Probably the closest thing we have when we think of follow-on proteins is the 505(b)(2) process. These are approved typically with some type of abbreviated data package, and there has been historically no unique terminology utilized for these products. They're approved, determined to be safe and effective by FDA, and enter the marketplace.

There's the term "multi-source," which often refers to whether they're (b)(1) or (b)(2), but essentially pharmaceutically equivalent products that are approved by FDA, but not necessarily interchangeable, and then, of course, the term "generic" with the viewpoint of those being interchangeable drugs.

And I'm going to come back to this in my next slide, but I think we can see there has certainly been a paradigm on the drug side, and I wouldn't say that when we look at that that there's confusion based on either lack of terms or, for instance, the term "generic" in today's society.

There's an interesting proposal that we've heard coming from a few different venues, and the manufacturer does not dictate the terminology, and I have to say I haven't heard this from FDA, but I wanted to get this out as part of the debate.

And let me explain what we mean by that. There have been some suggestions from various factions saying that if your typical business model is that of a generic company and you seek approval of a protein by an abbreviated process, there should be a term given to that, again, based on your business model.

If you are a brand company by your business model and you seek approval of the same product via an abbreviated process, it would have another term.

And, again, as I said, I haven't heard this emanate at all from FDA, but when we hear things like that, you can see the type of confusion clearly

that would result from that sort of proposal, and certainly from the Generic Association's standpoint, we would be opposed to moving down that pathway.

And human growth hormone being probably the most prevalent follow-on protein approved, there have been no terms in terms of specific terms applied to those, but basically are marketed by brand product.

Now, reflecting back to the 505(b)(2) process, I think one of the questions that we can include in our discussions over the next several months is if a protein is approved via an abbreviated process and is not interchangeable, is there a need for new terminology?

Clearly in the 505(b)(2) process there has not been, and when we're looking for clarity and trying to prevent confusion in the marketplace, I think that's something that we should consider as part of the debate.

Certainly if it's interchangeable, we can look at using generic terminology, which is now well understood in the U.S.

So nomenclature considerations for interchangeable products, biotherapeutic equivalents, generic biopharmaceuticals; certainly there are others

that can be considered as well.

In the process, we certainly believe that we need to work towards descriptions that will be acceptable to the stakeholders, and the stakeholders being not only people in this room, patients and the health care community as well. Certainly terms that would be scientifically justified and resonates with the public and would be understandable are very important as well, terms that would convey certain equality and trust in the product approved by an abbreviated process, and if they're interchangeable, clearly indicating that it is equivalent, that product is equivalent to another approved product.

We may also want to consider the use of focus groups before we come to a final decision that includes an amalgam of practitioners and patients as well to just clear first hand what the understandability of some of these terms might be.

So I think there's a lot of good options, and working together will certainly bring us probably to the best possible solution that we can have.

So in summary, on terminology, it clearly is important to the public. We have learned that through our generic drug experience. GPhA does not

believe that follow on is the term that should be settled upon, but in saying that, we don't have a universally accepted term from the industry at this standpoint, but we do look forward to working with FDA and the other stakeholders in the coming months to work on the issue of terminology.

With that, if there are any questions; otherwise, thank you very much.

(Applause.)

DR. HUSSAIN: I think we'll move on to the next speaker. I'll request each presenter who comes up here to state their name and their affiliation. It will be helpful.

MR. CARRADO: Good morning. My name is Joe Carrado. I am Senior Director of Regulatory Affairs for Duramed Pharmaceutics, Duramed Research.

I would first like to thank FDA for having this forum and, second, for the opportunity to speak on terminology. It seems that we have been debating names for a while, and in fact, I look back probably to the year 1591, when I think Juliet said, "What is a name? And I believe we are still here today trying to debate that.

FDA has put two questions forward

regarding terminology, and what I'd like to do is directly address them.

In the Federal Register, they ask about the appropriateness of the working definition of a follow-on protein as a protein that is intended to be similar or a copy of or a duplicate of an approved product.

And I think inherent in that question is the idea of sameness. And if that is the case, I think we need to realize that follow-on protein probably is not appropriate, given that definition. It is confusing.

I think Gordon has articulated this better than I. It is confusing insofar as, I think, health care providers, I think, patients, and I think those concerned don't understand the meaning of it.

Second and probably more important is that it connotes different things to different people. It connotes to some people the idea of a second generation product. It also connotes to most people that it is not the same, that is, the approved product, and therefore, is not appropriate.

I think, in fact, when we hear later today from the preclinical and clinical section that the

signs behind these products will show that they can be developed as equivalent products and, therefore, in the totality of it, that "follow on" is not an appropriate term.

The second question that the agency put forth, and I know it's not for debate here at the meeting, but we'll address it anyway briefly, is the use of the term "second generation protein product" to describe a product that's been changed in some way, shape or form. And I think the question has to be asked: is really this term necessary?

I know from the drug side changed products happen all the time, and we deal with them, and I know from the biologics side, there are examples such as pegylated alpha interferon, which does not have a second name.

However, if we need to categorize them and if these products aren't shown to be therapeutically equivalent, then perhaps this term is appropriate. However, I think I need to say that regardless of what we call them, they should be regulated by what they are, not what they are termed.

This slide can probably go on forever, and what I decided to do is just redact it just to two

possibilities. I think in looking at terminology we need to consider three factors, and I think they were already articulated by Dr. Webber and also by Gordon, and that is they need to be clear; they need to be accurate; and they need to be understandable.

These are just a few possibilities that meet those tenets.

So let me conclude as follows: I think it is reasonable to say that the terminology of follow-on protein is probably not accurate when describing these products.

That second generation protein products does not appear to be necessary terminology within this realm.

That terminology, such as therapeutic equivalent biological product, is more appropriate in this case.

And last, I think more importantly, more dialogue and continued dialogue with FDA to reach a consensus on terms that are clear which are understandable and which are accurate is necessary.

Thank you.

(Applause.)

DR. HUSSAIN: Looking at the time, we are

almost 35 minutes ahead of time. That's good, but I have a couple of jokes now.

What I would like to do is request the general panel maybe to come on the stage so that this way we can actually get the panel members to be up here, and they can introduce themselves, and we can start the set of five presentations, which would be on broad topics as well as different topics.

And Keith Webber is the panel lead, and I'll request him to not only introduce the panel members, but to set the stage for how the panel might work.

DR. WEBBER: Okay. As Ajaz mentioned, we have a general panel really to allow those who had general comments to address those as a consolidated presentation, and to start off, I'll introduce the panel, although they have been introduced before.

For any late comers, Keith Webber. I'm currently Acting Director of the Office of Biotechnology Products, and I'll let each of the panelists introduce themselves because I'm one of those people who as soon as I try to recover someone's name, it's gone. I won't embarrass myself.

DR. KOZLOWSKI: Steven Kozlowski. I'm

Acting Director, Division of Monoclonal Antibodies.

MS. BROWN: Janice Brown. I'm a chemistry reviewer in the Office of New Drug Chemistry.

DR. CHERNEY: Barry Cherney. I'm Deputy Director of Division of Therapeutic Proteins in the Office of Biotechnology Products.

DR. ROSENBERG: Amy Rosenberg, Director of the Division of Therapeutic Proteins in OBP.

DR. JONECKIS: Chris Joneckis, Senior Advisory for CMC Issues, CBER, Office of the Director.

DR. WEBBER: Okay. So let's move on to our first speaker who is Yafit Stark.

DR. STARK: Good morning. It's a pleasure to come all the way from Tel Aviv to Washington, D.C. It's also a pleasure to work both on the innovative products, as well as on biogenerics. So thanks, again, for inviting me to give this speech.

And I would like to introduce you into the clinical development plan on pharmaceutical biogenerics. After we have solved all of the technology problems, let's talk about the clinical development plan.

We feel that it's our responsibility to

justify the clinical comparability of the pharmaceutical generic to the innovator, but the question that we should have asked ourselves this morning is: when and how would it be appropriate to streamline or to eliminate certain human studies during the development of biopharmaceutical generics?

And the clinical development plan can be built out. We can to a full fledged clinical development plan. That's what we want today? The answer is probably no. But we can go to a very limited clinical development plan, and the scale is very, very large.

Let's discuss every case. Now, how shall we justify the clinical similarities? We know that it's a very complicated issue, and we know that the clinical similarity depends on a lot of variables, including, but not limited to, the clinical experience of both the therapeutic area, as well as the product.

It's also very important to know the hour and the funding of all the limitation of clinical trials as evolved recently. We know that clinical trials are less likely to detect subtle differences than analytical comparison. In order to see this type of differences, we have to follow the clinical

studies. We will have to pay insight and, of course, the power for expected differences will be very, very high.

It may cause that we will use an unreasonable patient number to detect these subtle differences.

I would like to divide my talk into two different parts. The first one will deal with analytical identical products. I was happy that the terminology was not been agreed and solved, but at least was prevented.

What I mean, the current discussion I'll talk about products that once analytical sameness is established, the question that we should ask ourself is what clinical data we contribute to justify the clinical comparability.

Another question that we should ask ourselves today and discuss: can a clinical study answer a sound scientific question? And what do I mean by that? The question is for analytically identical products, what do we offer to do, assuming, of course, that the sameness was approved analytically.

We propose to do a comparative Phase I

type study to establish pharmacokinetics, as well as pharmacodynamics, where it is applicable. Of course, this study can be crossover, it can be -- we must use the same dose, route of administration, and basically what we propose is to run a clinical development plan that will be similar to ANDA.

I'd like to describe several examples why do we feel that this is the right way to develop analytically identical product. Let's take, for example, insulin.

Pharmacokinetics is possible. Pharmacodynamics is available. We can easily measure glucose level or hemoglobin H1c. Human growth hormone, PK, is there. Pharmacodynamic is available. We can measure IGF-1. G-CSF, we know that there is a pharmacokinetic. Of course, the PD is available, absolute neutrophil count. This is not only the ANC. Absolute neutrophil count is not only pharmacodynamics molecule. It also can serve as a surrogate marker for febrile neutropenia, as well as severity of neutropenia.

Safety. Safety is a very important issue, and safety must be monitored closely on an ongoing basis. But we recommend to put more effort during the

post marketing. And why is that? It's also for the post marketing, we can expose large scale patient population. We can detect rare events. We also would like to suggest to one a risk/benefit assessment, and prevent an active pharmacovigilant plan prior to marketing.

Now I would like to talk about another class of product that was previously described as similarly analytically product. Now, this is another issue. Here we feel that clinical data probably will be needed when the analytical comparison is not 100 percent identified.

Now, depending what type of clinical data do we need, what amount of clinical development plan should we do for this particular project or product? Of course there are many questions that should be asked, and this can be judged case by case. We have to go back and to see how much data exist both for the innovators as well as for the indication, and then we suggest to do an abbreviated clinical development plan.

So the scope can be very limited, but it can be very, very large. We can do for an identical product pharmacokinetics/pharmacodynamic, and suffice

with that, and for similar, we can do an abbreviated clinical development plan, but of course for new molecular entity, new chemical entity, needless to say, that we will need the full fledged clinical development plan.

So the scope can be very varied. So what do we suggest under the abbreviated clinical development for analytically similar products?

First of all, our belief is that only one confirmatory trial will be performed for one relevant indication. We should demonstrate therapeutic equivalence. Of course, we will try to use clinical outcomes for the most part, but in case a surrogate marker is accepted and validated for the innovator product either for the indication or for the product, we should consider the use of a surrogate marker.

Of course, needless to say, we must show comparable safety profile, and importantly to mention is that once we get therapeutic equivalence demonstrated in the selected indication, it should be extended to other indications.

So in summary, for both pharmaceutical generics analytically identical to the innovator, we would like to suggest relatively limited clinical

studies, as I said before, pharmacokinetic, pharmacodynamic.

For biopharmaceutical generics that are analytically similar to the innovator, we would like to suggest abbreviated clinical development plan.

Thank you.

(Applause.)

DR. WEBBER: I just want to check if there are any questions from the panel, if we have time for a question or two.

DR. ROSENBERG: Yes. I noticed one thing that you left off of your schema was immunogenicity testing. Where do you see immunogenicity testing as being important?

DR. STARK: This is a very good question. Of course, I left it aside because I know that tomorrow there is a whole session for immunogenicity. But, again, I think that the same here should apply for immunogenicity since in clinical studies it will be very difficult to detect subtle differences in immunogenicity.

So we would like to recommend to do more during the post marketing in which we can expose more patients and detect antibodies to the product.

Yes, please.

DR. CHERNEY: I have a question actually with your talk and the talk on terminology. Given that you're asking for looking at the safety post approval, a lot of the safety data because there could be subtle differences in the safety data, but some of these subtle differences can have dramatic impact on the patient obviously.

Should we be using the term "therapeutically equivalent" when we haven't absolutely established that at the time of approval for relying on post marketing studies?

DR. STARK: Well, I think that during my talk I tried to refer to two different types of products. For those who are identical, completely identical, we would like to focus on the safety follow-up during the marketing phase, and the reasons were there.

But for those biosimilar, we should do something pre-approval, during the clinical development, during the abbreviated clinical development, and the reason for that is that we feel, strongly feel, that the clinical studies are less sensitive to detect subtle differences even in the

clinical. That's why exposing large patient populations and large scale will contribute more to the understanding of the safety profile of the biopharmaceutical generic product.

DR. CHERNEY: I understand that. I just wondered if the term "therapeutic equivalent" would be the appropriate term in that situation where you haven't absolutely defined the therapeutic equivalence because you're relying on additional data to come in, and how do we frame the terminology so the public understands what is there and what's not there at the time of approval?

DR. STARK: Are you referring to the efficacy or to the safety?

DR. CHERNEY: Well, primarily the safety data is what I'm asking about. This is the terminology. Is the terminology that's proposed something that you think is the appropriate terminology, given what you'd like to do?

DR. STARK: Bioequivalence in terms of safety could be a problematic issue. What I'd like to refer maybe to a comparable safety profile between the two products.

DR. ROSENBERG: But what he's saying is

that if most of your data is coming following marketing, what can you say prior, before you market? I mean, if what you're saying is, yes, we're going to study lots and lots of patients post marketing to make sure everything is the same, what can we tell people before?

That's what the question is.

DR. STARK: Yeah. The basis for this recommendation comes from the fact that we strongly believe the analytical should do the job. It means that nowadays, although I'm not an expert in analytical methodology, but my understanding is that today we can rely more than ever on the analytical studies.

Once they show that the two products are identical, we don't foresee any differences in terms of safety. That's why we may rely more on the comparison to the innovator and then show it during the post marketing phase.

DR. KOZLOWSKI: Related to that, another terminology question. You're using the terms "identical" versus "similar," and "identical" is a word that we've tended to avoid. Certainly in comparability we don't use the word "identical."

So I think defining what exactly you mean by those two classes of similarity, and although, again, characterization has advanced greatly, there are views about whether we are still capturing, you know, every possible variance, certainly with things that had a lot of heterogeneity.

DR. STARK: Again, talking about identical, what I mentioned, and of course, I'm sure that it will be elaborated during the manufacturing session, is that I'm referring to products that are identical in terms of structure and show the same bioactivity, biological activity.

When it comes to biosimilar products, they may have some slight differences in their structure, but still share the same bioactivity.

MS. BROWN: I've got a question for your biosimilar products. You're proposing to have one clinical study and then get all of the indications like for growth hormone. There's many types of indications for that. You would just do like a pediatric population, then extend it to the adult?

DR. STARK: Yeah, I would suggest one study because if we really believe that we can show a clinical comparability, why do we need to duplicate

the efforts into one, each indication that is listed in the labeling?

For example, if you're talking about interferon-1, we show that interferon beta is effective in multiple sclerosis. Why should we have to repeat and do the antiviral activity or the oncological type therapeutics?

We successfully have shown that the product is efficacious in one indication. So we can extrapolate to other indications. That's my recommendation.

DR. KOZLOWSKI: In that particular case, I think it varies by proteins, but certainly in interferon there are mutations that affect one activity and not another.

Now, it may very well be that in most cases when you get a structural change it will affect both, and these are defined mutations, but still there's a theoretical possibility you can affect one aspect of a molecule's function and not another.

DR. STARK: Yes, absolutely. That's why we tried to classify the two products, at least trying to get all of us to agree on the terminology, identical versus similar, biosimilar.

DR. WEBBER: I would propose just one last question in the microphone so that it gets recorded. If you could comment on how extensive the analytical comparison in terms of, not in vivo comparison, but just analytical comparison of products and should those be done at only the drug product stage or attempt to do that at the active pharmaceutical ingredient as well?

DR. STARK: I'm not sure if I'm the right person to answer about analytical, and I'd like to leave it to the manufacturing experts because I'm coming from clinical, and so that's not my expertise.

DR. WEBBER: Thank you very much.

DR. STARK: Thank you.

DR. WEBBER: Okay. We're doing well on time, and we'll move on now to Doron Shinar, who will give our next presentation.

DR. SHINAR: Good morning and thank you for inviting me. I am Doron Shinar, and I'm head of nonclinical safety and biological development at Teva Pharmaceuticals.

DR. WEBBER: I think that's a mic that has been turned off now. This mic is not working now.

DR. SHINAR: Okay. And I'll be speaking

today on the preclinical program for biogenerics, and I'm coming from the perspective of working for many years on innovative preclinical plans, but the task today is completely different.

And I will start with a few words about toxicity. Toxicity is, I believe, or as I understand it, is an intrinsic property of the chemical structure, and it reflects the interactions with the target organs in the body.

The role of the toxicology program is actually to define and understand these interactions, to define what are the target organs, their severity, their visibility, and to communicate with the physicians those risks and the therapeutic index and communicate all of this before clinical trials start or when we start to exposure various populations, special populations, to the drug.

Toxicity studies are usually done on the drug substance. It is done on a small group of animals, especially when we do it with non-rodents, and it does not by way, mean, or is capable to detect substantive difference in quality of the product.

So the burden is mainly detecting comparability of sameness, is on analytical persons

and analytical methodology, and the premise which I'm working on is that if sameness of comparability of structure is demonstrated by analytical means, then the activity of the safety of the product are assumed to be equivalent to the prototype.

So the basic issue is actually, as I mentioned, the burden on the analytical chemist and can comparability be demonstrated based on chemical analysis. So I'm not the expert in the field, but there are a few basic issues which I want to point out.

And first of all, which I believe are trivial and be accepted, is that the power of demonstrating comparability depends on the structural complexity of the molecule and on the accumulated experience that the industry have to this molecule. We believe that nowadays there are many biopharmaceutical generics or there are biopharmaceuticals that are well characterized and for which the structure is well established, and analytical methods are adequately available, and these can describe adequately the identity of the product and its purity.

The state of the art methods are

sufficiently sophisticated and powerful for this protein. Of course, not all proteins have the same complexity, and some proteins will have more complex and analytical methods are evolving, and proteins which now are considered to be difficult to describe with this evolving technology will be easier to understand and identify.

Examples for well defined and well characterized pharmaceuticals are insulin, human growth hormone, G-CSF or interferon, and you'll hear more about it from our analytical persons who will describe in detail the capabilities and methodologies in which these are characterized.

The issue of comparability. I want also to mention the testing of biopharmaceutical generics should be conducted according to the principle outlined in the guideline for the industry about CMC comparability protocols for biotechnology derived protocols, and also there the burden is mainly on the analytical, and critical studies are not mentioned unless there is some real scientific issue to be considered.

So demonstrating of comparability. Usually when you go for changes, for major changes in

the manufacturing process or by analogy trying to register new biogenerics, there will be more analytical testing required, more than the routine lot release.

And as part of this increased analytical testing, we should consider additional bioassays, and for example, the interferon in addition to the cytopathic assay, we should consider the antiproliferation assay, immunomodulation of major histocompatibility complex, NK activities.

We can differentiate, of course, the results after doing all of this complex analytical and bioassays. If no changes are detected or if the changes are within the specifications set by the originator, then we can consider this to be equivalent, and for this reason no preclinical safety testing is required.

If, of course, there are changes and especially changes in bioactivity, in the bioassay are detected, then we should consider more testing, more preclinical testing and more safety testing, and think this is quite understandable, and this really should be decided on a case by case, depending on the extent of difference and on safety considerations.

I'll skip on this one because I have already discussed this one.

And another point I want to make is about animal welfare consideration, and performing toxicology studies for biopharmaceutical generics for which analytical comparability was demonstrated violate the principal of animal welfare to prohibit studies which duplicate previous work.

This is an especially sensitive issue in Europe where there is much public sensitivity about the issue, and of course, if there is a scientific issue or a real safety concern, then all preclinical testing in animals is justified, where if we just duplicate for no scientific reason work done by the originator in animals, then it has a very sensitive and problematic issues.

I wish to conclude my talk about the conclusion that assuming comparability is demonstrated by analytical means and bioassays, then there is no need for toxicology, toxicokinetic safety pharmacology, mutagenicity, reproduction, metabolism of carcinogenicity testing.

If, however, comparability is questionable either because we cannot prove it because of an

extreme complexity of the product, then preclinical/clinical testing should be considered on a case-by-case basis.

Thank you very much.

(Applause.)

DR. WEBBER: Are there any questions from the panel?

DR. KOZLOWSKI: In your talk you mentioned comparability guidelines as a basis for doing these studies. So do you think because there's lack of some of the process information for this type of comparison as opposed to the comparability exercise within an innovator that there should be additional characterization or analysis that goes beyond?

DR. SHINAR: No, I am trying to make the analogy with the comparability of the manufacturers that actually if a change in process has been exercised by the manufacturer, it's quite equivalent to changes made by the biogeneric in the process, and you will hear more about it. It's not necessarily the process which defined the product, but it's actually the product.

And if you have an adequate means to analyze the product, then it should solve the issue.

DR. KOZLOWSKI: No, I was asking but would there be any additional analysis. You would say that the characterization would be --

DR. SHINAR: For instance, as representing also an innovative company which is also doing innovative, when we introduce changes in product usually we introduce more analytical methods than for routine lot release. So there are also when changes are taking place, major changes, I mean, major changes in production, and definitely in biogenerics with change like the cell, the host cell for the production, you will need to do more analytical methods or methodologies than for routine lot release.

DR. JONECKIS: If you followed the comparability protocol or -- excuse me -- the comparability guidance that's outline in the FDA guidance, I'm wondering while that guidance does talk about hierarchical approach, it also talks about the need for complementary approaches as well.

So, for example, some of your underlying premises based on having comparative analysis within specifications, within certain acceptance criteria, other things of that nature do not necessarily preclude the need to do other types of preclinical

toxicological, immunological studies, and that is all predicated on having very sensitive methods and such.

What are the kind of factors that would cause you to reconsider this hierarchical approach that you have taken here?

DR. SHINAR: Right.

DR. JONECKIS: For example, how would the sensitivity of the test influence your hierarchical approach? How would the complexity of a molecule influence this?

DR. SHINAR: I believe that if the analytical methods, as elaborate as they are -- and I don't want to define what this should be, and for each protein it would be a different analytical methodology, and I believe that they will be discussed and evaluated -- we have to look at the results of this analysis and to determine how much, let's say, biogeneric compound -- how it relates to the originator.

Is it within the specification or is it, as you'll see tomorrow, one of the presentations, almost identical if identical can be defined?

In that case we can determine that no additional studies, preclinical studies, should

determine. If, however, there are differences, subtle as they are, but within the specification or if the specifications are not well defined; there is some possibility that we don't have or the industry will not have the specification in front of it; then we should consider and reduce the changes, but the changes do not affect in any meaningful way the activity.

We should determine on a case by case what should be the next steps to be taken in the preclinical and, of course, in the clinical setting.

MS. BROWN: You discussed the characterization of the active, but when second manufacturers come and manufacture one of these drugs, the impurity profile is different, and some of the tests are very, very specific for some of the impurities, like for example host cell proteins.

And could you tell me how you would qualify, even though the active has been demonstrated to be comparable, different impurities?

DR. SHINAR: Different impurities, there are some industry standards, I believe. I have seen the rates. I believe that our analytical chemists are in a better position to answer it, but I believe there

are standards in the industry about impurity by host, and it should be followed.

And of course, if we are seeing something unusual impurities, there are always some means of qualification impurities. I mean, as I mentioned in the beginning with my talk, I don't think that preclinical safety testing -- and this is the major topic of my talk -- so I don't believe that preclinical safety testing are there. I mean to qualify impurities. Unless we have a certain impurity, there is this ICH guideline Q3, which we should follow if some unusual impurities are there, but the general program or the comprehensive program of doing chronic toxicology and reproduction toxicology and carcinogenicity is not there to quantify impurities.

DR. CHERNEY: You suggested that we should be using the established specifications for the innovator.

DR. SHINAR: If they're available.

DR. CHERNEY: Well, in most cases that would not be available. So how would or at least a given situation that's not necessarily available. How would you establish that in the absence of that

information?

DR. SHINAR: Okay. First of all common sense should be exercised in the name that there are some standards of the industry about what could be from CDER in assay to be a normal variation. You can show also some variation in the host cell. I believe that the innovator will have some access to in some cases there are international standards, and we can look, and in some cases there are pharmacopeia, but again, I think that it's a very good point that should be discussed. But I'm coming from the assumption that this was sorted already by the analytical chemist, and I'm working on the premise that this sameness or comparability was established.

DR. ROSENBERG: Many products relating to the impurities, many of them have potential immunologic activity that could cause a difference in immunogenicity of the product.

DR. SHINAR: Right.

DR. ROSENBERG: So the question is: how are you going to be able to just by those characterizations alone figure out if the immunogenicity is the same?

DR. SHINAR: You're pushing me to this.

So one of the issues is that we believe, and you'll hear again from the chemist or there will be a lecture about immunogenicity, that many of the comments, analytical assays can address risks for change in immunogenicity, especially looking at aggregates.

And the other issue is, of course, there will be a whole safety program in the clinic to detect immunogenicity if this will be the issue. But I was representing or trying to represent the preclinical issues. In looking at the immunogenicity in animals is not a good model for looking for or analyzing immunogenicity in humans. This would be the task of the clinical trials, wherever this would be, before submission or post marketing.

DR. ROSENBERG: So you don't think that animals would be good even to look at differences between two products. So what if one product is minimally immunogenic in animals, in animal testing, and you're --

DR. SHINAR: I mean, I will consider everything --

DR. ROSENBERG: Wait a minute. Let me finish.

And so then the follow-on has a much

higher rate of antibody formation. Does that tell you anything or no, if it's in animal?

DR. SHINAR: We can consider and there is a big debate, I think, among the industry. If we have predicted models in animals, also in culture, and this should be considered, but on the other hand, especially if we know that some compounds are extremely immunogenic in animals where they are not immunogenic in humans --

DR. ROSENBERG: Right, but this question only gets at the difference in products between products. So that if you have an animal, you don't need a fancy model. If you have an animal that gives you a given rate of antibody responses to a protein, to one protein A, and then you come in with protein B and you get a much higher rate, does that tell you anything intrinsically about --

DR. SHINAR: It might.

DR. ROSENBERG: -- the difference between those molecules?

DR. SHINAR: It might. I don't exclude this possibility.

DR. KOZLOWSKI: Regarding preclinical models, if the product you're dealing with has a

preclinical model with a defined toxicity, because one of your comments was that toxicity wouldn't be that sensitive of a measure compared to charactization, but if this molecule is known to have a toxicity in a particular model, that you could easily power to show whether or not that toxicity is the same.

In that case would it make sense to use the preclinical model as part of the development of the product?

DR. SHINAR: We are working under the assumption that if analytical shows sameness and comparability, then also the safety is comparable, and certainly I can attest that clinical or preclinical trials are never as accurate in variability in preclinical trials. It's always larger than analytical. Analytical is always more sensitive to small differences than preclinical.

So actually we're trying to reverse the order because what will be the most sensitive to changes definitely would be analytical.

DR. KOZLOWSKI: Although in a case where, for instance, you couldn't define the mechanism for the toxicity, it was a toxicity that occurred in a model, and that occurred at a rate of and at a dose

that was fairly predictable.

So then, you know, from being sort of an insensitive assay, because you know what to expect of it and it will appear, it may make it an assay where there is more meaningfulness to looking for that.

DR. WEBBER: We're doing well on time. I have one final question just for you in terms of what role do you see stability testing playing in analytical characterization.

DR. SHINAR: Okay. I mean, do you mean stability testing in animals?

DR. WEBBER: No, stability testing as a measure of the ability of the product, or the stability of the product from a shelf life perspective, as a method for comparison of the two products and for establishing the new product's shelf life.

DR. SHINAR: It definitely will be part of the analytical program to develop the stability and show that I believe it's part of the routine CMC program. I believe that it will be part of the comparability or should be considered at least.

DR. WEBBER: Thank you very much.

I certainly want to thank all of the

speakers for maintaining their time very well and, since we are ahead of time, providing us with the opportunity to ask good questions or many questions to the speakers.

Let's see. I'm afraid I skipped Caroline Lowe just because of the color there, but I do want to bring her up for speaking, and I certainly apologize to you for jumping over you to the next speaker.

DR. LOEW: Good morning, and thank you to FDA for organizing this meeting today.

My name is Dr. Caroline Loew, and I'm the Vice President of Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America, also known as PhRMA.

PhRMA represents the country's leading research based pharmaceutical and biotechnology companies which are devoted to inventing medicines that allow patients to lead longer, healthier, and more productive lives. Member companies invested more than $33 billion last year in discovering and developing newer medicines for American patients.

PhRMA welcomes the opportunity to be a constructive participant in the discussion of scientific issues on follow-on biologics and commends

the FDA for holding this public stakeholder workshop on the scientific issues.

PhRMA believes that the paramount goal of discussions must be to preserve the health and safety of patients and to preserve patient confidence in their medicines. PhRMA thus continues to support sound, science based regulatory decisions for all drugs and biologics. All pharmaceutical products, whether small molecule or biologic, innovative or follow-on, must be subject to the same high standards of safety and efficacy.

Unlike typical small molecule drugs, biologics raise special concerns due to their complexity and the close relationship between a biologics manufacturing process and its clinical attributes. Any regulatory approach to follow-on biologics must address these concerns from a sound scientific perspective to insure that the high standards of safety and efficacy now applied are not compromised.

Based on the current state of scientific knowledge, all follow-on biologic applications should be supported by appropriate studies using the investigational follow-on product.

The study requirements applicable to different products can be expected to vary based on relevant therapeutic, manufacturing, and other concerns as evaluated based on evolving science. While these considerations may commit the approval of follow-on biologics based on scientifically justified different data sets from the original innovative approvals, each follow-on product should be supported by full chemistry manufacturing and control section and by data generated from appropriate preclinical work and clinical safety and effectiveness studies, and be followed up by robust post marketing surveillance.

In addition to the scientific issues that we will be discussing today, there are substantial legal and policy concerns that need to be considered, particularly with respect to the protection of trade secrets and other intellectual property rights that support innovation. These issues will be addressed in our written comments to the docket.

In the meeting announcement, the FDA used the term, and I quote, "follow-on protein pharmaceutical products." We've heard some discussion of this statement this morning.

Throughout my statement I will use the term "follow-on biologics" to mean, and I quote, "biologics including therapeutic proteins developed and manufactured by someone other than the innovator, produced either through recombinant technologies or from natural sources," end quote.

Our comments today will address the following three issues:

Firstly, analytical characterization and manufacturing;

Secondly, safety, especially immunogenicity; and

Thirdly, therapeutic equivalence.

Throughout I will emphasize the special considerations for biologics, contrasting these with small molecule drugs to highlight the unique challenges associated with producing safe and effective follow-on biologics.

Firstly, I'll address analytical and manufacturing considerations. The term follow-on biologic implies abbreviated approval requirements for the follow-on products predicated on the sameness of the product. However, there are significant analytical challenges to achieving adequate

characterization of biologic products to establish the identity of the manufactured products.

These challenges reflect to a large extent the significant physicochemical differences between biological drug products and small molecule drug products. The analytical capability to demonstrate true identity or pharmaceutical equivalence between innovator and follow-on biologics is currently, at best, limited. The chemical composition and structure of a small molecule drug active ingredient can be determined precisely by widely accepted physical and chemical assays.

On the other hand, characterization of a biologic with the same degree of precision is typically impossible because of the structural complexity and because the final product is usually a heterogeneous mixture of molecular species.

Many analytical tools for characterizing biologics currently have a low resolving power to detect subtle but potentially important changes. When changes occur, it is often difficult to assess how they may impact clinical performance or immunogenicity. Even when the analytical resolving power improves, the new information may make the

existing heterogeneity of a biologic even more apparent.

To achieve identical composition between biologics produced by different manufacturers is virtually impossible because of the nature of biological manufacturing where the manufacturing process determines the product characteristics.

The manufacturing process is for biologics based on the synthetic capabilities of living cells that have inherent medical variability. To handle the complexity of the biological manufacturing process, extensive analytical testing is done at key process steps using validated assays that are often proprietary with appropriate sample qualification to insure that the process intermediates are suitable for progressing to the next step.

Each biologic manufacturing process will result in a unique product, including the mixture of active and inactive molecules and the levels of process and product related impurities.

Small differences between manufacturing processes may cause significant differences in the clinical properties of products. Chemically and pharmaceutically identical biologics will not result

from different manufacturers.

The commercial biologic product must be tested to meet predefined criteria to demonstrate that the product batch is representative of the material tested in the plant and demonstrated to be generally safe and effective. These specifications are realized through knowledge of the clinical performance, process development experience, analytical methods' design and validation, and in process testing to define the product.

Biologics are approved by the regulatory authorities in the context of this entire body of knowledge. One cannot standardize the analytical testing and specification ranges of the biologic through monographs because each manufacturer has a different proprietary process, different reference standards linked to that clinical experience.

The manufacturing and analytical challenges in dealing with the complexity and heterogeneity of biologics are the same for a follow-on as for an innovator manufacturer. The question is how to determine the significance of this heterogeneity for product quality for the follow-on biologic.

Innovator preclinical safety, clinical trial, process validation, and development data support only the degree and forms of heterogeneity of the innovator product. Process validation for biologics is more complex than for chemical drug products due to the number of process steps and the sensitivity of the biological process to external perturbations, e.g., batches of raw materials, working cell banks, and harvest times.

Validation of an adequate control strategy, including in-process controls can only be determined once the manufacturer has gained thorough knowledge of the product and understands how the manufacturing process impacts the resulting product.

Therefore, while thorough characterization of the physicochemical and bioanalytical properties of the drug substance and product are essential, these tests alone can never assure a quality product.

The FDA has faced a question of controlling changes in manufacturing processes by innovators. When considering a process change for an innovator biologic, the manufacturer views an extensive body of knowledge generated over the life of the product which allows for an understanding of the

significance of differences that may be detected and provides a baseline for comparison of changes.

The knowledge gained about the manufacture of an innovative biologic includes an extensive database of every step in the manufacturing process, established in-process controls, and defined reference standards to allow for a detailed comparison between product made before and after a manufacturing change.

Developers and manufacturers of follow-on biologics do not have access to the same extensive data or proprietary analytical methodologies to allow for the same scientific comparison. Conclusions regarding similarity or differences cannot be drawn across manufacturers. Therefore, it would not be appropriate to apply comparability principles designed as a means to assess changes made by the innovator of the biologic as the basis to approve a follow-on biologic developed by another manufacturer.

The second area I'd like to address is safety and immunogenicity. The manufacture and clinical testing of biologic drugs must include additional safety control measures beyond those used for small molecule drugs.

For example, adventitious agent control is

a critical element to the manufacture of biologics and is done on both input raw materials and output fluids from the cell culture. If adventitious agents were to enter the manufacturing process, they could be amplified through the production.

This type of safety assurance is not often required in the manufacture of chemical drug products because the process environment is inhospitable, and to the propagation of most adventitious agents, and the characteristics of most chemical drugs facilitate terminal sterilization.

Safety concerns related to a biologic can involve a wide variety of effects on multiple target organs, in addition to the more general concerns related to immunogenicity. Product specific concerns are heightened for molecules with pleiotropic biology and a complicated or unknown mechanism of action.

Preclinical safety assessments of biologics are often more difficult and complicated than for small molecules because of unique issues. However, based on the current state of scientific knowledge, all follow-on biologic applications should be supported by appropriate preclinical safety studies using the investigational follow-on product as

described in the ICH S6 guidance.

Because fewer preclinical studies are routinely available to assess safety of biologics than for small molecules, safety assessments for biologics must depend more heavily on clinical studies.

Assessment of immunogenicity is a key component for determining safety of biologics. It is well established that the immune system is exquisitely sensitive to and capable of responding to subtle characteristics of biologic that may not be detectable by analytical methods.

Such an immune response can stimulate the production of antibodies that combine to the therapeutic protein and inactivate it or otherwise alter its activity. In these cases, the product no longer provides effective therapy to the patient and the disease progresses. If the therapeutic product is similar to a naturally occurring protein, the antibody may bind to and inactivate the native protein making the underlying disease even worse or causing other serious side effects.

In other cases, the induced antibodies have no observable effect.

There are many examples of biologics that

have resulted in problematic immune responses in patients. In some cases these problems were detected in clinical trials during the development process leading to termination of the product development. In other cases, the problem was recognized only after the product was commercially launched.

In yet other cases problems arose after manufacturing changes were made. Sometimes the potential cause of immunogenicity was determined. In other cases, it remains unknown.

As I noted earlier, unlike small molecule drugs, the complex manufacturing process for a biologic is a significant determinant of that product. Even a small change to a well established manufacturing process for a biologic can result in unpredictable and undetectable changes to the product which can have marked clinical consequences.

Because a follow-on biologic by definition will be produced with materials and a manufacturing process different from the innovators, unpredictable and undetectable differences are likely between the innovative and follow-on products.

There is broad scientific consensus that problems with immunogenicity cannot be dependably

predicted from physicochemical characterization, epitope analysis, or animal studies. While some product characteristics such as aggregation and impurities may play a role in increasing the likelihood of an undesirable immunogenic response, the multitude of factors triggering antibody production remains poorly understood and largely unpredictable.

Of particular concern is the potential for contaminants and impurities to act as adjuvants to increase the immunogenicity of a biologic.

The lack of reliable, nonclinical models to predict the immunogenicity of a biologic in patients underscores the absolute necessity for immunogenicity testing in clinical trials for all biologics, follow-on and innovative. Antibody evaluation must be conducted over the course of treatment in the intended patient population because it is well established that the incidence of an immune response and the consequences vary from one population to another.

Consequently, immunogenicity testing of a follow-on biologic must be as rigorous as that required by today's standards for an innovative biologic.

The number of patients in clinical studies that should be tested for immune responses, as well as the frequency of testing, must be adequate to insure a low risk of patients taking either an innovative product or a follow-on biologic. There can be no shortcut. It does not follow that if an immunogenic event associated with an innovative product is too rare to be detected in even a full clinical program, the clinical testing for its follow-on should be minimal.

A rare or unusual immunogenic event triggered by one factor related to one biologic does not guarantee that such an event will be just as rare when triggered by another factor related to the follow-on product.

There should be no differential application of these principles and testing requirements regarding immunogenicity to innovative and follow-on products. That might otherwise result in an increased risk being assumed by patients taking the follow-on product.

Furthermore, any rationale for minimal or reduced clinical testing of immunogenicity would leave the true testing to after marketing. Post marketing

surveillance cannot replace the scrutiny that is applied to testing done in clinical trials.

Patients taking marketed products rightly assume that the risk associated with their medicine has been comprehensively evaluated by the testing conducted before approval.

The final area I'd like to address today is therapeutic equivalence. Therapeutic equivalence is the basis for substitution of one product for another by a pharmacist. The underlying assumption is that therapeutic equivalent products are interchangeable. In other words, therapeutically equivalent products are assumed to have the same safety and efficacy profiles.

The starting point for therapeutic equivalence is a showing of pharmaceutical equivalence and bioequivalence. Pharmaceutical equivalence is very difficult and in many cases impossible to demonstrate the biologics, and therefore, therapeutic equivalence will not be demonstrable either.

Even if pharmaceutical equivalence and bioequivalence could be shown, however, these criteria alone are not adequate to assess and assure true therapeutic equivalence for biologics. Pharmaceutical

equivalence when achievable, plus bioequivalence testing, do not support the assumption of comparable safety, including immunogenicity and efficacy profiles, and hence do not support an assumption of therapeutic equivalence of biologics.

For biologics, in addition to pharmaceutical equivalence and bioequivalence, comparable safety and efficacy profiles must be shown with well designed, adequately powered clinical trials in order for two products to be deemed therapeutically equivalent and, hence, substitutable, one for the other.

In summary, PhRMA welcomes the opportunity to become an active participant in the discussion of an approval pathway for follow-on biologics. We have highlighted some of the many scientific and safety challenges in the manufacturing characterization of all biologics and how these pose additional challenges in contemplating an abbreviated approval pathway for a follow-on product.

The gray nature of biologics themselves and the current limitations of science are at the heart of these. The tight dependence of product quality and clinical performance on the manufacturing

process, the complexity and heterogeneity of biological systems and their products, and the unpredictable response of the immune system, because of these properties the safety and efficacy profiles for an innovative product should not be assumed to apply to a follow-on biologic produced by a different manufacturer, and attempts to do so raise important patient safety concerns.

Based on the current state of scientific knowledge, all follow-on biology applications should be supported by appropriate studies using the investigational follow-on product. Each follow-on product should be supported by a full chemistry manufacturing or control section and by data generated from appropriate preclinical work and clinical safety and effectiveness trials and followed up by robust post market surveillance.

Finally, I would like to thank the FDA for holding this public workshop and for giving PhRMA this opportunity to address the scientific issues of follow-on biologics. We welcome the opportunity to submit to the docket more detailed comments on all of the issues concerning follow-on biologics.

We recognize that this workshop is a first

step and look forward to more in depth discussion of the relevant issues, including discussion of a scientific and regulatory challenges in the proposed 2005 workshop.

PhRMA believes that the paramount goal of these discussions must be to preserve the health and safety of patients and patient confidence in their medicines.

Thank you.

(Applause.)

DR. KOZLOWSKI: Regarding your presentation, you made a broad distinction between small molecules and therapeutic proteins, and so what I was wondering, is there any more of a range to that. In other words, obviously the complexity of protein varies, and their heterogeneity varies with the level of post translational modifications. Where would that range fit into your discussion of what's necessary?

DR. LOEW: We certainly agree with you that there is a range of biological products. However, we believe that the issues defining complexity, although there is a range, apply across the board, and that in consideration of approval of any of these products, we need to look at all of the

aspects that I mentioned associated with having a full understanding of the manufacturing process, assessing product safety, particularly of immunogenicity, using clinical studies.

So, yes, we agree that there's a range, and there is certainly going to be an assessment within that range of the requirements, but we believe that there is a clear distinction between small molecules and those products in terms of the requirements.

DR. KOZLOWSKI: Do you think that primary distinction is immunogenicity or that distinction extends throughout doing full safety and efficacy studies other than that?

DR. LOEW: We believe that it extends throughout, largely driven by the complexity of the manufacturing processes compared to small molecule drugs, and also the complexity of the products, the fact of their heterogeneity, and today we believe the limits of analytical characterization suggests that there are other studies required beyond the standard that one might apply to small molecule drugs.

DR. KOZLOWSKI: Right, although would you say that the limits for, say, a small E. coli derived

protein that has no glycosylation and no known post translational modifications are the same as for a complicated, larger, heavily glycosylated molecule?

DR. LOEW: Yes, and we would agree, as I said earlier, that there is a range here. However, I think that there is all of the question in the analytical area as to what, you know, observed granularity in analytical data actually means in terms of the biology and the mechanism of action and the activity of products in vivo.

DR. ROSENBERG: Given the extensive amount of information out there on innovator products, you know, some that have been on the market for ten years, both therapeutic effects and adverse effects, is there anything in all of that data published and potentially available through study of the innovator's product that would in your mind allow for any lesser degree of study in order to gain approval?

DR. LOEW: Again, I believe that that's something that you would have to assess on a case-by-case basis. Very specifically, you're potentially touching on issues of innovator intellectual property. That's not something that we came here to discuss today, but we will address in our written comments.

I think more generally there are in certain areas. There is published literature that addresses, you know, perhaps the resolution of particular analytical testing or perhaps the existence of certain preclinical assays that may be appropriate. Then, yes, that may determine a different requirement for studies from one product to another.

We are certainly not disagreeing with the concept that there's a range there and there may be, you know, different study requirements based on the body of knowledge that exists in the scientific literature.

DR. ROSENBERG: Also, one other question regarding immunogenicity. You're saying that there should be extensive premarket assessments. To what level of worry?

So, for instance, if some rare events occur in one in 10,000 patients and which occurred for an innovator product following a manufacturing change, what should be the requirement for testing for the future innovator changes, as well as for follow-on, in terms of patient extent of study pre-market?

DR. LOEW: I think as we try to make a distinction here, while a lot of the scientific

principles that apply to innovator and follow-ons are the same, the innovator does have a very extensive body of knowledge that may define a certain ability to reduce testing in that situation as compared with a follow-on manufacturer.

DR. ROSENBERG: But the innovator in the cases I'm referring to didn't pick up the subtle changes and didn't pick up on post marketing until years after.

So, you know, what in the innovators -- if the innovator can't pick it up, then why should requirements necessarily differ?

DR. LOEW: We certainly wouldn't advocate a reduction in testing to assure the quality of product that goes into the marketplace and to maximize the opportunity in development to assure that the most safe and efficacious product is made available.

I think what you point to is an extremely interesting point because it demonstrates that an innovator, even with a very extensive body of data, can still bring a product into the marketplace that has issues in this extremely difficult safety area, and that to me would suggest that, you know, we should be applying very substantial standards to the follow-

on product as to the innovator because we know it's such a complex area and it's extremely difficult; in fact, I would argue it's almost impossible to predict immunogenicity profiles of products.

DR. CHERNEY: You mentioned though during your talk that the innovators have access to key process intermediates and that that analytical analysis of those samples would be critical. Can you give an example where one couldn't evaluate that potential attribute at the final product, but it could only evaluate it as an in-process material?

DR. LOEW: I'm not an expert in that area, but we will certainly try to address that point in our written comments for you.

DR. WEBBER: Okay. Thank you.

DR. LOEW: Thank you.

DR. WEBBER: Okay. The next presenter will be carole Ben-Maimon, and I'm sorry if I slayed that name.

DR. BEN-MAIMON: Pretty close.

DR. WEBBER: Pretty close. Okay.

DR. BEN-MAIMON: Good afternoon, everybody. Good morning actually, I guess it still is.

I also would like to thank the FDA for holding this workshop. I actually look at it from a different perspective though. I think, you know, we all came into this room as members of industry, both brand and generic. We've come into the room as regulators, participants and employees of the FDA, charged with making sure that patients get safe and effective products.

But I think it would be worthwhile if we stepped back for a minute and recognize that we are all also users of the health care system. We all have children, husbands, wives, brothers, sisters who participate in the health care system and use these products as we go to market, and I think it's absolutely essential that we recognize what generics have done for the health care system and the compelling public policy issues that we're dealing with today.

Clearly generics not only control costs, but they also help to stimulate innovation, and that is really essential to what we're talking about today, and the issues that we're dealing with clearly, first and foremost, whether or not we are brand or generic or representatives of the agency itself, is to insure

that patients have access to safe and effective products, and none of us -- I'd like to really reiterate that -- none of us want to compromise on that.

But it's also important that we insure that patients have access to these products because if they can't afford them and they can't get them, it doesn't do them any good.

And so with that in mind, I'll launch into my talk and talk a little bit about our view of biogenerics and what we think can and should be done. And I've got to figure out how to do this. There we go. I think I've got it. I am truly technologically impaired.

I'm Dr. Carole Ben-Maimon from Duramed Research, which is the wholly owned subsidiary of Barr Laboratories, and I'm going to divide my talk actually into three different categories today. I'm going to talk a little bit about biogenerics and the definitions thereof, and then I'd also like to move in and sort of talk about the actual process of drug development and what we truly are charged with as we go ahead and develop new therapeutic modalities.

And then finally, I'd like to end with a

discussion of surrogate markers and some of the issues surrounding therapeutic equivalents.

First of all, when we talk about biogenerics, we are talking about new products that come to market that are pharmaceutically and therapeutically equivalent. We are not talking about products that rely on proprietary innovator data either for process, for specifications or for clinical safety and efficacy.

Clearly, generic drugs do the same thing. We develop new products. We are charged with insuring that they are therapeutically and pharmaceutically equivalent, and then they get reviewed and approved by the agency. We develop our own specifications. We do our own impurity testing. We do our own stability testing, all of which are issues, I think that have come up before, and I don't think we see it any different with biogenerics.

Clearly, we would be charged with characterizing our own products, making sure that the impurity profiles are well defined, and insuring that they are therapeutically equivalent, and that the process is well qualified, sound, validated, and reproducible.

And so, therefore, we really don't rely and don't need to rely on proprietary information generated by the innovator.

From the standpoint of therapeutic equivalence, there are actually a whole host of ways that this can be demonstrated, and depending upon how well characterized the product is, we may or may not need to implement some of these modalities, and as I think came out at the last presentation, this is really a continuum that we're talking about.

We're not really here talking about drugs or small molecules versus complex proteins. What we're talking about is simple versus complex, whether it's drug or whether it's protein product. And so what really is essential to recognize is that the simpler products will require less, and the more complex products will require more.

And the fact of the matter is that's no different than with small molecules. There are still products on the market today that have been off patent for many years, and we can all name them, and they have no generic equivalent because nobody has been able to convince the FDA that they can make a therapeutically and pharmaceutically equivalent

product.

And so the issue really here is not whether it's protein or small molecule. The issue is whether it can be characterized with a pharmaceutical equivalence and therapeutic equivalence can or cannot be demonstrated.

I'd like to step back a second and talk about the drug development, protein development process. The fact of the matter is this is all a matter of risk-benefits. When a physician, nurse practitioner, health care provider prescribes a product for a patient or, for that matter, when a patient goes to the pharmacy and picks up an over-the-counter product, they make a risk-benefit assessment. They decide whether or not the benefits that they are going to obtain from that product are worth the risks that are associated with taking the product.

The agency essentially does the same thing when it assesses and reviews either an NDA or a BLA. It sits down with a huge amount of data, probably more than I would like to acknowledge, and starts to sift through it and tries to balance the benefits and risks associated with that compound.

For products that are what we call life

style type products, you require a much lower risk with a much greater benefit in order to approve the product, with a much greater assurance that you understand the clinical and safety profile. And for products like chemotherapeutic agents, AIDS drugs, we require less. The burden is clearly less because the benefit in getting the product out more quickly that could be reaped is so much greater.

And so I don't think we're in any different set of circumstances. We all know that clinical trials are flawed. When you look at an NCE or a new therapeutic protein, there is a limited amount of data, whether it's tox, preclinical, clinical data, but there is a limited amount of data with which to make this assessment, and it's imperative that we recognize that when products first go to market, this clinical safety and efficacy profile is not totally well defined.

We all know of products that have gone through an evolutionary process that have either had to have been removed from the market, that have had black box warnings added, that the way they have been used totally changed.

So at the time of approval, these products

go out into the marketplace only having information from clinically well controlled trials that clearly do not reflect what occurs in the normal clinic and in the normal health care marketplace.

And what happens over time is there is more and more information obtained about these products as use is expanded, and we clearly get through pharmacovigilance information, risk management programs additional information that helps us to validate or modify the initially approved label.

It's only at about 14 years after the initial introduction of brand products that generics even come into the marketplace. On average, some come a little earlier; some come a little later, but on average, it takes 14 years for the regulatory requirements, the patents to expire, all of the legal issues to be sorted out for these products to come into market.

So there is actually a whole host of information out there in the public domain held by health care practitioners, innovators, chemists, a whole host of information that is actually publicly available and accessible by the time the generic product comes to market, and it is at that time when

we're looking at the introduction of generics and biogenerics today, which is what we're talking about, that we should be looking at what is the burden that needs to be placed on the biogeneric company, the company making the new product.

Because it's not the same as what was 14 years or 18 years or 16 years, nine years, whatever the time frame is before. It's different. At that point, what the company should be charged with is insuring pharmaceutical and therapeutic equivalence.

And we have to acknowledge and recognize that science advances. What can't be characterized today in two years may be very easily characterized, and all we're talking about today is being able to set up a system that looks at products on a scientific basis and requires only what is required to insure pharmaceutical and therapeutic equivalents, and at that point, that is when these products should be approved.

We believe that there are a whole host of these products today that that can be done for and still insure safety and efficacy for the patient population out there, and also control costs and stimulate innovators to now have a reason to innovate

and develop something new and improved.

Biologics are no different than the drugs. Clearly the emphasis on therapeutic equivalence can be done through surrogate endpoints. I think we forget sometimes that many, many of the outcome measures that we use in clinical trials are actually surrogate endpoints.

Hypertension, what is hypertension? Except for acute hypertension, hypertension is really a surrogate marker for stroke and heart disease. It's nothing more than that. Otherwise we wouldn't bother to take blood pressure from 180 or 210 to 120.

Weight loss is a surrogate marker for the morbidity and mortality associated with obesity.

Quite honestly, something we rely on every day to approve generic drug products and also to define innovative biologics and drug products are plasma levels, which are merely surrogate markers for rate and extent of absorption that will insure the same safety and efficacy profile.

So there's no reason to expect that glucose and hemoglobin and white blood cell count also can't be used in order to predict the long-term outcome for some of these products. So in our view

surrogate markers from the standpoint of therapeutic equivalence are clearly a mechanism by which we can do shorter, more limited trials in patients. I think Dr. Shinar raised the issue of exposing animals unnecessarily. It also is true we should not be exposing patients unnecessarily to clinical trial environment if it is not necessary because even that has its own risks associated with it.

With that I'd like to conclude. Biogenerics in our view when we talk about them are pharmaceutically and therapeutically equivalent products. We're talking about a continuum of products that are no different than drug products from simple to complex. The simpler the product, the easier it is to be characterized. The more available there are technologies to characterize these products, the less the clinical requirements should be.

And then finally, once therapeutic equivalents and pharmaceutical equivalents are demonstrated, these products should be interchangeable.

Thank you.

(Applause.)

DR. ROSENBERG: I don't mean to sound like

a broken record, but despite the simple to complex analogy which, you know, makes good sense on many levels, that doesn't really address immunogenicity because there are many factors that would cause even a simple protein to have immunogenic properties beyond.

DR. BEN-MAIMON: Yes, and I don't think that we want to be cavalier about immunogenicity, and I hope that none of our presentations have actually implied that we are because we are not. I think the issue here is twofold.

One, the one you raised during the last presentation, but even in addition to that, as data is collected and information is collected over time on the market, we become more and more comfortable, and actually as time advances and as science advances, we become more and more comfortable with some of the components and some of the things that actually do stimulate immunogenicity, such as aggregation, variations in tertiary structure, and things like that.

And there is no question that we should be charged with trying to insure and doing everything we can to insure that these products are comparable where we know that there are issues and where we know that

there are things that may stimulate immunogenicity. Clearly, the impurity issues, all of those kinds of things.

DR. ROSENBERG: If I can just interject something, I think that's true. There are many product qualities that could be predictive although, you know, it's really not understood how much, what kind of aggregates are really going to -- there's a lot that is not known, more that is not known than known.

But what about something like hypersensitivity responses, anaphylaxis to, say, foreign proteins? To my knowledge, there's no way of predicting based on physicochemical characterization, nor of animal models of predicting anaphylaxis.

How would you deal with that?

DR. BEN-MAIMON: I think, again, the issue really here is exposure, and again, I don't think that we should be held to any greater standard than the innovator is. Clearly, here we are being charged with comparative trials, whereas the innovator is being charged with overall exposure, which is slightly different.

But I think that if you look back

especially, for example, at the HGH compounds where you've got the same amino acid structure, the same molecular weights, essentially very well described, very well defined products, the innovators have really exposed very limited numbers of patients in order to come to the marketplace.

And I think if you look at some other products, and I don't want to go into the specifics, there are products where neutralizing antibodies' rates and neutralizing antibodies are actually described, and I think in our clinical trials where they are appropriate and when necessary, we should be charged with doing the same thing.

The question is whether or not we should be looking for, as you said, the one in 10,000 or one in a million, and I think in that case what we really are dealing with is a risk-benefit issue, where we have to openly discuss what the risks are and what the benefits are.

And in our view the benefits of cost competition and the stimulation of innovation in having competition in the marketplace actually serves the patient and serves the public very well. And so should we be looking why not to approve or should we

be looking for an adequate appropriate assessment that insures to the best of our ability the safety and efficacy while continuing, as Dr. Stark said, to continue to monitor in the marketplace is exactly why we've allowed for comparability protocols to be put in place, because it didn't make sense. We didn't want these products to be taken off the market. Patients needed them.

And so I think we need to just look at it scientifically and make sure we balance the benefits and the risks in such a way that we come to a consensus as to what is required.

DR. KOZLOWSKI: I have a question regarding your comment that you would develop your own specifications and your own testing of impurities. So I think as was mentioned in the previous talk, clearly during clinical development there's a lot of information that's gained about specifications that's in the hands of the innovators, and sometimes that may actually relate to efficacy, you know, or pharmacokinetics and so on.

So if you're truly independent in setting those specifications, you know, how do you capture this information?

DR. BEN-MAIMON: Well, I think, again, we sort of have to learn a lesson from the small molecule world. There are impurities and degradants and all of those other things in drug products as well, and what we do is we try and characterize them in the innovative product, not during the process, but in the innovative product; compare them to our own.

Those that are known and well described, so be it. Those that are new, we're charged with insuring that they aren't causing a problem or creating a situation that we have to deal with, and so I don't see that biologics should be any different.

Clearly, the CMC section, as all of you know, for the audience in case people don't, the CMC section of an AMDA is the most important, bulkiest, most labor intensive part of the application process, and I would envision that for biologics it would be the same, that the CMC section would actually take on a tremendous weight, and should, and clearly, the reproducibility and the validation of those processes and concurring with all of the GMPs and quality controls is essential.

I think in a biologics, a biogenerics application, clearly characterization would be also of

much more significance than it is in the small molecule world.

DR. KOZLOWSKI: But I think there can be a lot of variants that don't matter that the innovator may know about, and so that would put a large burden to characterize just about every possible variant.

DR. BEN-MAIMON: If they can do it, we can do it, and if they don't matter, I'm not sure they have to be characterized.

DR. KOZLOWSKI: Right, but the information about not mattering, I think --

DR. BEN-MAIMON: I'm not sure they have to characterize it either if they don't matter.

DR. KOZLOWSKI: Right, but I think that part of how they define that they don't matter is by characterizing them and accumulating clinical data with the --

DR. BEN-MAIMON: But, again, once they're characterized and it's determined that they don't matter, if it's in the public domain and they don't matter, then they don't matter. We should characterize them and say this is what they are. We should set limits on them and set specifications for them, but then they don't matter in our product

either.

DR. KOZLOWSKI: But the information that they don't matter, which matter and don't matter, may not always be available. I mean, that's the comment that --

DR. BEN-MAIMON: And if it proprietary, we respect that and we have to deal with that on our own. If it is not proprietary, then that's a different issue. And, again, I think that that is exactly the case even with drugs, you know, where excipients or impurities or degradants may be well described or have been tested and we don't have access to tox data when we have to generate our own or build an argument based on what's in the public domain.

DR. JONECKIS: So your pharmaceutical equivalence determination, again, would not at all rely upon any type of innovator's product. It would solely be based upon what you define and what, again, is available?

DR. BEN-MAIMON: I wouldn't say that. It might rely on information that's in the public domain. I mean, there's a lot in the public domain from patents, you know, published patents, from FOI, and I think obviously we would make use of some of that

information both in the way we develop our products, but clearly, you have to understand the generic industry is only as strong as the brand industry is.

And so we recognize and fully support the fact that brand companies have proprietary information that they need to protect. They need to make money off of their products and get their investments back, but we also recognize that a monopoly that will last forever, there's no reason for anybody to innovate. We've seen it over and over again. Products that don't get genericized ultimately most of the times don't have competition, for example, Coumadin, you know, and Premarin for that matter.

So it is really essential that competition exists in order to stimulate innovation as well as control cost, and so protecting intellectual property is essential. Clearly the courts will be, you know, very much utilized in this area, as they are in drugs, and it will probably be even more of a quagmire as we have seen even between biotech companies.

But I don't think we should shut the door and say we can't, given the compelling public policy issues.

DR. WEBBER: One final question, if I may.