DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

VOLUME I

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University of Maryland
Shady Grove Campus 9640 Gudelsky Drive
Rockville, Maryland

PARTICIPANTS

Kathleen R. Lamborn, Ph.D., Acting Chair,
Nancy Chamberlin, Pharm.D., Executive Secretary

MEMBERS:

Gloria L. Anderson, Ph.D., Consumer Representative
John Doull, M.D., Ph.D.
Judy Boehlert, Ph.D. Joseph
Bloom, Ph.D.
Nair Rodriguez-Hornedo, Ph.D.
Jurgen Venitz, M.D., Ph.D.
GUESTS:
(Robert) Gary Hollenbeck, Ph.D.
Leon Lachman, Ph.D.
FDA :
Wallace P. Adams, Ph.D. Yuan-
yuan Chiu, Ph.D.
James MacGregor, Ph.D. Guriag Poochikian, Ph.D. Nancy B. Sager
Paul Schwartz, Ph.D. Helen Winkle

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. LAMBORN: I would like to welcome everyone here. This is the Advisory Committee for Pharmaceutical Science. I am Kathleen Lamborn. I am serving as the Chair for today in the absence of our permanent Chair, who will be with us tomorrow. The initial item on the agenda is the conflict of interest.

Conflict of Interest

DR. CHAMBERLIN: Welcome. The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in the firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions. Since the issues to be discussed by the committee at this meeting will not have a unique impact on any particular firm or product but, rather, may have widespread implications with respect to an entire class of products, in accordance with 18 U.S.C. 208 (b), each participant has been granted a

waiver which permits them to participate in today's discussion.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited guests, there are reported affiliations which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Tobias Massa is Executive Director for Regulatory Affairs at Eli-Lilly; Debra Miran is a consultant for Teva, DPT Labs, Bioavail, University of Maryland Pharmacy School, Vintage, Scinopharm, Warner Chilcott, and is temporary Head of Scientific Affairs for Generic Pharmaceutical Association. We would also like to disclose that Dr. Leon Lachman is the President of Lachman Consultant Services, Inc., a firm which provides consulting services to the pharmaceutical and allied industries.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. LAMBORN: Thank you. Before we go to our welcome, I would just like to ask each of the members of the committee to introduce themselves and mention their

affiliation.

DR. DOULL: I am John Doull. I am from the University of Kansas Medical Center.

DR. ANDERSON: Gloria Anderson, Morris Brown College, Atlanta, Georgia.

DR. CHAMBERLIN: Nancy Chamberlin, Exec. Sec.

DR. LAMBORN: Kathleen Lamborn. I am from the University of California San Francisco.

DR. BOEHLERT: Judy Boehlert, and I have my own consulting business.

DR. VENITZ: Jurgen Venitz, Virginia Commonwealth University, in Richmond, Virginia.

DR. RODRIGUEZ-HORNEDO: Nair Rodriguez, University of Michigan College of Pharmacy.

DR. BLOOM: Joseph Bloom, University of Puerto Rico.

DR. LAMBORN: Thank you. I believe Helen Winkle was planning to provide a welcome.

Welcome

MS. WINKLE: Well, good morning, everybody. In case you don't know me or recognize me, I am Helen Winkle and I am currently the Acting Director of the Office of Pharmaceutical Science.

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It is my pleasure today to be able to welcome the

members of the Advisory Committee for Pharmaceutical Science, to welcome as well the guest speakers, the representatives from the subcommittees of the advisory committee, and all of you in the audience who have taken time to share with us today your ideas and thoughts on many of the things that we will talk about. I know that one thing today is that this is not the best facility and I do, up front, want to apologize for that. We were going to have a joint committee meeting on Friday with derm. So, our timing was set around that meeting and there were no hotels available. So, unfortunately, this is not the best facility for the advisory committee meeting, and lunch is not going to be the best you have ever had but, anyway, I did want to bring that up.

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The Center and OPS consider this advisory committee to play a really significant role in addressing the scientific issues that we have in the Office of Pharmaceutical Science. The committee's input on these issues and the recommendations are very important to us as we go forward in making regulatory decisions. As we make these decisions, we want to be certain that we have the best scientific basis, and through this committee as well as other mechanisms we feel that we are getting that scientific input that we need to be able to make the right decisions.

We realize the significance of outside expertise, and we really feel that it helps to not only enhance but to maintain the science base necessary in OPS.

The new year has brought a number of challenges to OPS, and the agenda today for the advisory committee will actually focus on several of these challenges and, hopefully, the recommendations that will come out of the meeting today will be extremely helpful as we move forward in addressing these challenges.

I thought before I talked about the agenda it would be helpful to go over the current OPS structure. I think there are several new committee members, and there have also been numerous changes in the management structure of OPS. So, I thought it would be helpful just to give a quick overview.

As you can see, the chart for OPS is on the overhead. If any of you have ever seen Roger Williams talk, he has shown this many times so I am certain it isn't new to most of you.

Starting at the top of the chart, right now, as I mentioned, I am the Acting Director of OPS. Eric Sheinin is the Deputy Science Director for OPS. Eric will be here later in the day; he couldn't make it this morning. Just so you will know, we are in the process of selecting a new director for OPS. In fact, announcement for the position

just closed, and we hope that by January or February to have a new director.

Next in the Office of Pharmaceutical Science the change that has been made is that now Mei-Ling Chen is our Associate Director for Quality Implementation for BA and BE. This is a significant position because she helps in the Office coordinate a number of the activities that are going on in BA and BE as far as policy and guidance, and she is also helping to coordinate and ensure consistency between both the Office of Clinical Pharmacology and Biopharm., and our Generics Office on BA and BE issues.

Next, I wanted to mention the Office of Testing and Research. You will later hear from Ajaz Hussain who is currently the Acting Director of this Office. He is in the process of looking at ways for re-engineering this Office and, although he will talk more tomorrow about the initiatives that are currently going on, I think in the future we will be talking more to the advisory committee about some of these re-engineering initiatives that we have.

Jim MacGregor, who is the Director of the Office is currently on detail with Janet Woodcock. He is working with her on leveraging activities for the Center.

Next is the Office of New Drug Chemistry. In fact, one of our first speakers is Yuan-yuan Chiu. She is going to talk about one of the main initiatives we have in

this Office. This Office continues to grow. I think it has a significant place in the Center now, and I think there are a lot of activities in the area of chemistry that we will continue to talk about with the community.

The Office of Generic Drugs -- we also have an acting director in this Office. It is Gary Buehler. We are also in the process of selecting a new office director. I think this process will be over by the beginning of December and we will be able to make the announcement of that office director. This Office too is making a lot of changes. Gary has already incorporated some streamlining changes. I think there are a lot of other things that will be going on in the next year under the new leadership of the Office, and I think we will have some interesting activities. We do have one initiative today that we are going to talk about to the committee and get some input from the committee. Last is the Office of Clinical Pharmacology and Biopharm.

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Unless there are any questions, I am going to move on to the agenda. This morning we are going to focus on chemistry, manufacturing and controls. We are going to present an update on 314.70. Since we have been working on this area for a while, I think it will be beneficial for the committee to hear what is happening in this area and where we are going. We are also going to talk a little bit about

risk management activities, basically in line with what we consider to be one of our most important risk management initiatives in OPS, and that is reducing the regulatory burden for CMC.

After lunch, we will continue with an open public hearing to discuss the reduction of CMC regulatory burden, and present reports from two advisory committee subcommittees. This will be the orally inhaled and nasal drug products subcommittee and the non-clinical studies subcommittee.

Tomorrow, Thursday, OPS will provide an update on three of our more recent guidances. The first one is BCS. the second one is a general BA and BE guidance, both of which have been published, and we are basically wanting to bring the advisory committee up to date on what has happened with these guidances. The committee had a lot of input into the information that went into these guidances and we want to share where we are with them, and possibly look at next steps.

We also will talk about the statistical guidance for BA/BE which is a companion to the general guidance. It is not issued yet but we are ready to issue and we wanted to update the committee on this as well.

The rest of the morning on Thursday we will be focused on clinical pharmacology, modeling and simulation.

We are starting to use modeling and simulation in our reviews and we want to discuss with the committee what our next steps should be. It is important to us, in OPS, as we move more in this direction that we are ensuring consistency in how we do our reviews and that we apply the current technology in our regulatory decisions. So we will be hoping to get input. We will give you a little information on what we are doing and, hopefully, get input from the committee on the best way to continue in that direction.

In the afternoon, after the public hearing, we will hear an update from the Office of Testing and Research. I have already mentioned that. Besides that, Dr. Hussain will talk about the Product Quality Research Institute and bring the committee up to date on what that Institute is doing and some of the current projects and what we, at FDA and OPS, are doing in that direction.

We will end Thursday with a discussion of a proposed regulation change regarding failed bio studies for engineered drugs. This is an area that we have been working on and we have an interest in getting input from the committee on failed studies and how best to apply those to our regulatory decision-making.

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Friday is a joint meeting with the Advisory Committee for Pharmaceutical Science and the Dermatological

and Ophthalmic Drugs Advisory Committee. This joint committee will be to discuss dermatopharmacokinetics. I think many of you in the audience have probably heard some things about DPK. It is not a new topic for the committee or for OPS, but I think over the last year we have had more issues that are associated with DPK that we would really like to discuss with the joint committee, and we have opportunities for other uses. We also want to run information by the two advisory committees to obtain some useful direction for our current focus.

I hope the next two and a half days will bring an awareness of many of our initiatives in OPS, as well as provide some scientific information and justification to us from the committee which will help us in answering questions relating to many of our ongoing projects.

As Dr. Lamborn said, she will chair the committee today since Dr. Byrn could not be here. He will be with us tomorrow. So, unless there are any questions from the committee I will turn the meeting over to Dr. Lamborn.

DR. LAMBORN: Thank you. Any questions from the committee?

[No response]

I think then that we are ready to move on to the first agenda item.

314.70 Update

MS. SAGER: Good morning.

[Slide]

I am Nancy Sager, and I have been tasked with giving you an update of fifteen years of history in ten minutes. So, I will have to talk fast.

[Slide]

CDER's approach to regulating post-approval CMC changes has been evolving over the past fifteen years. Initially, a 21 CFR 314.70 regulation was written, in 1985, that provided the basics for what to do when post-approval chemistry changes were being made by a company.

Then there were the SU/PAC documents, and I am going to talk about all of these in a little more detail after the initial slide. The SU/PAC documents were from the early '90s to present. In 1997 the FDA Modernization Act was passed by Congress, and we are in the process of implementing FDAMA Section 116, which deals with post-approval changes. Then, there is the question of "next" which Dr. Chiu will discuss after my speech.

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21 CFR 314.70, when it was written in 1985 -- what it states is that the applicant shall notify the FDA about each change in each condition established in an approved application beyond any variations allowed in the original

application. What the regulations do is they provide a general listing of changes with a reporting mechanism. These changes are very, very general. Basically, it is a general approach. There is no distinction between different types of changes within a class. For example, manufacturing site changes for drug product, all of them were prior approval changes. It didn't matter if you were making a sterile injectable or the only thing you were doing was packaging solid oral dosage forms, or even putting a label on the bottle. They were all site changes, and they were all prior approval. So, there was no distinction.

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Then, in the early '90s FDA, with industry feedback of course, was recognizing that this was not the most appropriate approach because not all changes were created equal; there are differences. Some are of more concern than others. So, what FDA did in the early '90s was start on a project which many people on the advisory committee are probably familiar with, and in the audience. What we did, we wrote various guidances. There were three dosage form specific guidances that basically down-regulated the regulations. We wrote an immediate release guidance, a non-sterile, semi-solid and a modified release solid oral dosage form product guidance. The guidance basically spelled out various types of changes, for example,

formulation changes or site changes and allowed for lower reporting mechanisms than what was specified in the regulations. It also provided information on what tests to do to support the change.

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Then, in 1997 Congress pass the FDA Modernization Act. Part of that was Section 116 that dealt with post-approval changes. It basically recognized the importance of the SU/PAC approach. It also amended the Food, Drug and Cosmetic Act to additional a new section dealing with post-approval changes. It also required for FDA to revise the current 314.70 that was current at that time to make it conform to the new Act. FDA decided we also had to prepare a guidance to go along with the new 314.70.

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The main thrust of FDAMA Section 116 was that the reporting categories are based o the potential for the change to adversely affect the identity, strength, quality, purity or potency of a product as these factors may relate to the safety and efficacy of the drug product. So, it basically took the SU/PAC approach and put it into a regulation which said don't treat all changes equally. Try to base it on potential, the scientific potential for change to have an adverse event.

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FDAMA also specified four reporting categories. Before FDAMA we only had three. What got added was supplement changes being effected 30 days, which requires a company to delay distribution of the drug for 30 days once they submit that kind of supplement. During those 30 days FDA can get back to the company and say this shouldn't have been a changes being effected supplement; it should have been a prior approval supplement or that information is needed. It is more of a screening period; we don't do a significant review during that time. That was added because of we were going towards down-regulating quite a bit and we felt that there needed to be some kind of check to make sure that something really didn't have a significant potential; didn't get out to the public.

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The implementation status of FDAMA 116 was that we wrote a guidance and a regulation and published them both on June 18, 1999 in draft proposed form. Why we needed a guidance is the statute is very, very general dealing with post-approval changes. The regulation is a little bit more specific but still very, very general. It is hard to deal with specific case-by-case type of specifying what the filing mechanisms are in a regulation. So, we wrote a guidance to give examples of where certain changes fall in the reporting scheme.

So, we published the draft of the proposed regulation on June 18, 1999. The guidance had a closing period of August 27 and the regulation had a closing period of September 13. We got quite a few comments. We had over 30 comment letters, with the draft guidance having about 1200 individual comments. Some of them were repeats or talked about the same issue. On the regulation we had 30 comment letters and about 300 individual comments.

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Just to go further, the changes to an approved NDA if ANDA guidance that we published was modeled on the SU/PAC guidances, recommended reporting categories only. We could not cover what type of information to be submitted. It also covered all dosage forms.

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So, the FDAMA 116 implementation status was that we had two years to get the regulation published, which was November, 1999. And, if we did not have a new regulation published by November, 1999, then 314.70 basically disappeared and we were regulating only under the statute because we were given two years to make the regulation conform. We were unable to complete the regulation in that time period. Two years is quite a short deadline for any type of regulation with all the clearance process that has to be done with it.

So, what we have been doing since November, 1999 since we have not had a regulation is that we finalized our guidance, changes to an approved NDA or ANDA, and that represents FDA's current thinking on how it will apply to the requirements of Section 506(a) of the Act. So, basically, we have the Act, the statute and the guidance right now, without 314.70 in between.

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This just continues on. That is what we have been doing until the 314.70 publishes.

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So, what is the status of both documents? First of all, we did publish a final the guidance in November, 1999 and we are still working on the regulation, finalizing the regulation. It is in the clearance process but it takes quite a bit of time and has to go through OMB review and legal review at the agency. We expect it possibly winter or spring. I guess I should qualify that, we are expecting it in 2001, not 2002 or whatever, but this date has been moved several times already because we have expected it sooner than that. So, we are hoping that it will be no later than spring of next year. When we do publish the final rule we will also be publishing a final changes to an approved NDA or ANDA guidance at the same time, an updated version that will conform to whatever we have done with the 314.70

regulation so that there will be no conflicts between the two. Thank you. That is my talk.

DR. LAMBORN: Thank you. I think we are ready to move on to risk management initiative.

Risk Management Initiative

MS. WINKLE: The next topic on the agenda is risk management. I wanted to talk a little bit today about the Center's risk management initiatives and OPS' current focus on risk management. I think this is an important area in the entire Center and I wanted to be able to update the advisory committee on what we are doing in OPS.

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Risk management is now a Center priority. Dr. Woodcock is focusing a lot of attention on risk management. She is actually setting up a risk management office and has, as well, set up a working group on risk management. She is putting a lot of emphasis on this.

I think as all of you know, the Center's mission is to ensure that safe and effective drugs are made available to the public, and the Center feels that in meeting this mission, the whole mission can be improved through better risk identification and risk management. So, it has become a really important priority in the Center. If the Center knows what the risk of the drugs are, then it is much easier for the Center to work toward preventing adverse

events, etc.

So, we are all, in the Center, focused on ways we can do this, and the reason I wanted to talk about this is that, again, we are going to talk a little bit about what we are doing as CMC reduction and we consider this to be an important risk management activity.

The Center is also focusing on those drugs with the higher risk so that it can devote more time and resources to those drugs where the opportunity for risk is high rather than spend a lot of time and resources where, obviously, the risk is low. And, we have done that. I mean, we will spend just as much time on the low risk drug now and doing the reviews, spending effort and looking at all the documentation. So, this is an area that the Center is beginning to look at so that we can cut down on some of the time, the time involved by the Center as well as the firms that are submitting the applications.

Part of the Center's risk management initiative is to ensure that the information too is made available to both prescribes and patients. This is an important aspect of risk management, sort of like getting the risk information out there. I think all of us know there is a lot emphasis now on advertising various drugs. I think the American public is taking more interest themselves in making diagnoses or working with their doctors in figuring out how

to handle disease, and stuff, and we feel that more information has to be out there to the public so that they can make really good decisions on how to handle their own medical care.

Basically, we all share in ensuring the effectiveness -- the public, the industry and FDA -- and safe use of drugs, and without the appropriate information this isn't possible.

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As already mentioned, the Center has developed a risk management working group. This group is focused on a number of different area. Communication of information to those outside the Center I have already mentioned. This is the number one priority of the working group, to figure out better ways to communicate with those outside the Center, both public and industry.

Perform research to learn more about users and providers so that we are able to better communicated. There is a lot of information that we need in order to better understand how to communicate.

Identify and prioritize risk areas. This will be looking at off-label use, pregnancy information, etc., and being able to get that information out as well.

Share and learning within the Center. One of the things that we want to be able to do is talk within the

Center about how decisions are made. I mean, there are a lot of common drug product areas where they are going in separate directions, so we want to be able to share information within the Center. We feel like we will be better able to focus on some of the high risk versus the low risk products.

Last, and one of the reasons I wanted to talk to the advisory committee is that the group is also focused on expanding advisory committees to add risk management experts to the committees for pre-approval and post-approval discussions. This has already happened on at least one advisory committee, and one of the things we will be considering along the line is whether we want to additional someone to the OPS committee. One of the things that has actually been discussed at the working group level is whether to use the OPS committee -- additional some people on there who have risk management experience and let the OPS committee held all of the decisions as far as risk management that may come up in the Center that need outside input. So, we are still in the process of discussing these things but I wanted to bring it up to the committee, that some of these things are on the table.

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Obviously, risk management plays an important role in CDER and in OPS. As you can see from this slide, in many

cases the benefits of the drugs really outweigh the risk, and we want to talk a little about the OPS initiative that we have with this committee on reducing the CMC requirements.

To quote Janet Woodcock, risk-based chemistry product quality is the foundation for everything CDER does and underlies the safety and efficacy of all the products CDER regulates. It is our hope, through this initiative, to reduce the CMC requirements and be able to eliminate some of the NDA and ANDA manufacturing supplements and reduce the amount of information that needs to be submitted to the annual reports. Determinations for these reductions will be made through sound scientific criteria, thus ensuring that the benefits of the expedited reviews for some products would outweigh the risk associated with the products.

There are other areas in OPS that we are beginning to incorporate more of the risk management thinking, and we will bring a lot of these initiatives to the committee in the future. I just felt that today we wanted to at least form the basis for where we are going with risk management. Unless the committee has any questions, I will hand the podium back over to Dr. Lamborn so we can hear about the CMC reduction.

DR. LAMBORN: Questions from the committee?
[No response]

Reducing the Regulatory Burden

Concept, What and How

[Slide]

DR. CHIU: I am going to present for you a new initiative which is risk-based CMC reviews. This is a project we are taking beyond the SU/PAC concept.

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Before I start to explain the program, I would like to give you background information. The FDA's oversight of product quality really is established by law, and is also governed by the concern of safety. So, if you look at the same product, such as ephedrine, it would have multiple status under the law and under the regulations. It can be a prescription drug or an over-the-counter drug but require a submission of applications, either NDA or ANDA. Once it is determined that it should be an application drug, then it is required to submit full CMC information by the manufacturer, and it is also required to be in compliance with the drug GMPs fully.

However, it can also be an OTC monograph drug. The determination of a monograph drug is purely based on safety, whether the drug can be administered by the patients through self-medication. Once it is determined to be an OTC monograph drug, then there is no requirement for applications to the Center. Then the Center does not know

how the drug is made and does not know where it is made, not to mention any changes occurring during the years.

Although OTC drugs should be in compliance with drug GMPs, the agency has less authority in many risk respects. For example, they do not need to tell the agency that they are going to go through a recall like the application drugs, and when an investigator goes to the facility to conduct inspections, he will not necessarily see all the documents. So, therefore, there is really much reduced oversight by the agency.

However, as you all know, there can also be a dietary supplement which is governed under the law. Then, the product is considered to be safe and efficacy is not even part of the consideration, and it is actually traded more like a food. So, not only does the agency not have oversight of the manufacturing information, it does not require prior approval by the agency, and although DSH required the agency to publish a GMP modeled on food for types of supplements, so far the agency has not issued a proposal of the GMP for dietary supplements. So, in the meantime the dietary supplements are regulated on the food GMPs, which is really sanitary type of GMPs. So, it is much, much less regulated.

So, as you can see, none of these decisions were really based on product risk. Because of this type of

implication, we hope that the Center will take a look at whether, you know, all the products that require applications can be regulated in a different way based on product quality risk, rather than just looking at the safety or the law.

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So, this initiative is to make an assessment of the risk to product quality of all the approved drugs, and then to see whether we can carve out a portion of those products that we consider of little or no risk.

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So, the objective is to establish a set of quality attributes and acceptance criteria for little or no risk drugs. Then, to compile a list of little or no risk drugs based on the established attributes and acceptance criteria.

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Once a drug is on the list, what we can do is -- because we think those are of very low risk and whatever you do to the product, nothing much will happen to it, then the Center can have much less oversight in terms of filing requirements. So, for those products we would eliminate most of the manufacturing supplements except for certain changes listed in FDAMA Section 116. An example would be changes of drug substance, drug product specifications, changes of drug product components or composition, changes

requiring in vivo studies, and also we are thinking about including simple sterile products on the list so we will propose to have supplements when the changes occur to the sterilization process.

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If we just reduced the supplements and then everything else would be moving to the annual report. So, that does not really reduce the resource of the Center in terms of CMC review because everything now is in annual reports and someone still has to look at them. If we think the products are such low risk, then it would not be necessary even to look at the annual reports. So, we will propose to reduce the information required in our annual report. Once the drug is on the list, this program is implemented and a one-time submission to the annual report would much reduce the information, modeled on the technology documents for the ICH similar to the quality summary of the CTD-Q to establish a baseline. If the drug, indeed, is such a low risk, then we think, you know, it is not necessary even for a generic company to submit the full information in the original NDA. So, we would call it a truncated NDA. This would further reduce the resource of the Office of Generic Drugs. You know, so many applications are received, why should each drug be reviewed with the same intensity if the drug is considered to be of no risk in terms of product

quality?

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There are several important points to be made even though we are talking about reduced CMC requirements. There will be no reduction in scientific and validation data needed to be generated by the firms, by the manufacturers, to ensure that the identity, purity, quality, strength/potency of the drug, the documentation will be kept on site. So, therefore, the only reduction is the filing requirement. It is not to reduce for the manufacturer to do the things they ordinarily need to do. There will be no change in the pre-approval inspection program. So, a truncated NDA will still be inspected before its approval and all the documentation can be looked at if necessary. We propose there will be a joint inspection by the chemistry reviewer and the investigator of the field office to randomly audit the scientific and validation data that are not submitted to the applications.

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Another important point to make is that a reduction in CMC submissions should not be associated with other clones of product because even though we have full information in our application, it doesn't prevent counterfeits. It doesn't prevent adulteration of products, and doesn't prevent a company from making GMP violations.

And, there are some rare events, you know, like tryptophan, all of sudden they become toxic and the submission of the CMC information would not even help those cases. So, therefore, when one must dissociate the filing requirement with other problems which occur to products because that is in a different arena.

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So, together, you know, in our Center and with other organizations of the agency have discussed this and we came to a very preliminary list of attributes and acceptance criteria. We believe the attributes should include chemical structures, should be well characterized. If the drug substance is not characterized, then it probably should not be on the list. We think, you know, the manufacturing process should be a simple synthetic process. The quality should be fully assured by adequate specifications, and does not contain known toxic impurities. The physical properties, such as polymorphism and particle sizes, should be well characterized and can be controlled. The product should be stable and the product should be on the market for significant length of time. And, there are other attributes.

Those are just very preliminary thoughts of ours, and many of the substance criteria, you know, are not really quite defined. So, what is a simple synthetic process? Or,

how do you define that? That is the reason we are here. We are seeking input, technology and scientific input from the committee.

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We also made a similar table for the drug product. We believe all the oral, liquid and solid immediate release dosage forms and simple sterile solutions can be considered, and the manufacturing process should be easy. There should be adequate specifications for the drug product, and should be stable, and should be on the market for quite a while. We are also seeking input and advice from the committee on the criteria and the attributes for the drug product.

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Once that is established, the attributes and the acceptance criteria are established, then we can compile a list. That is the first phase of the program. Once the list is drafted, then we think they should move to the second phase. The second phase is safety considerations, to see whether there are any clinical concerns; whether any drug on the list medically should not be included.

Tomorrow you will hear more about BCS and, in our view, we do not think BCS is the limit, however, this will be discussed internally and externally. Once those considerations are made, then the final list will be there. Because products are made by multiple companies, we believe,

you know, if a manufacturer has the privilege to use this process, it must have good GMP standards and record. So, the eligibility of a manufacturer is based on GMP consideration.

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In order to make this program proceed and be successful we have already started our internal discussion, and we have started brown-bag meetings with our reviewers. We have also met with our Office of Regulatory Affairs at the agency level -- the field office.

Today, we are here discussing this with this committee and we believe we will come back to you next year once the program is further developed. We would also like to seek public comments. So, we plan to have a scientific workshop in June or July next year. Then, after the workshop, we will issue a draft guidance on the attributes and acceptance criteria. We will seek formal comments.

Then, we believe that sometime in the late 2002 we will be able to issue a final guidance on acceptance criteria and the attributes. At the same time, we will be able to issue a draft list of the candidates of the drugs.

In addition, at the same time we will be discussing internally and, again, externally what the reduced annual reporting information should be. Then, at the same time we will issue a draft guidance on the CMC

filing requirements for the annual reports. We believe an original truncated NDA could also model on annual reports. It is our legal advice in order to get the truncated ANDA going, we will require a proposed rule, we will require a change of the regulation.

Then, once all the comments come in to the draft guidances, then we will be able to formalize the entire program in the year 2003, we hope. Then we will start to implement this program in the meantime and we will work out all the administrative details. So, here today we are seeking advice from the committee on technical and scientific input for the attributes and acceptance criteria.

[Slide]

We also believe, once the program is implemented, we will be able to learn from it and also to learn from further product quality research. We may be able then to expand this.

[Slide]

Finally, I would like to show you the names of our people who are working on this project. They represent the Office of Generic Drugs, Office of New Drug Chemistry, Office of Compliance of CDER, and also the field office, Office of Regulatory Affairs. Thank you.

DR. LAMBORN: Yes, you have a question?

DR. ANDERSON: Yes. I think it is the pie chart

on your third slide, how does that relate to the last one?

DR. CHIU: You mean objectives?

DR. ANDERSON: Does this represent the current state of affairs?

DR. CHIU: No, this is just the beginning. The objective of the program is to establish a set of product attributes and acceptance criteria.

DR. ANDERSON: So, the one on the third slide and the last slide --

DR. CHIU: Oh, you mean the pie chart. What we want to do is to carve out a group of drugs which are determined little or no risk based on the attributes and substance criteria to be established through the internal and external discussion. The last slide, that slide just shows that in the future we would like to expand the pie so more drugs can be included to be considered little or no risk because, once we learn more, we will be able to add other attributes or acceptance criteria so more products can be included.

DR. LAMBORN: Could I try and restate it to make sure I understand? So, what you are saying is that at the moment there is no group that is defined as little or no risk. You hope to carve out a piece, and then over time to increase that piece. Is that what you are saying?

DR. CHIU: Exactly.

DR. LAMBORN: I think what we should do right now is if we have specific questions for clarification, we should cover those, and then I know we are going to come back later to do the discussion but it would be pertinent now if there are other clarification questions.

DR. BLOOM: Excuse me, is there a definition between little or no risk in terms of the drugs?

DR. CHIU: No, we will have to define what is little or no risk by establishing the attributes and the acceptance criteria.

DR. BLOOM: So, that has not been established yet?

DR. CHIU: That has not been determined.

DR. DOULL: Madam Chairman, that is a problem. There are no drugs with no risk. I think that should be little or minimal risk, or something, but that term "no risk" is offensive to toxicology because every drug has some risk.

DR. CHIU: We are not talking about risk based on quality. We are not talking about safety risk because, absolutely, you are right, all the drugs have side effects. But we are talking about maybe certain drugs, you know, are just rock stable and so easy to make, therefore, whatever you do to it -- you know, it doesn't matter how you store it, how you ship it; it doesn't matter if you change the manufacturing process, it stays the same drug. That is what

I mean.

DR. LAMBORN: Yes, I tend to agree that just about everything you could to, enough to it, to create a problem but I think we understand the concept, which is a minimal risk group.

DR. BLOOM: Are you planning on defining little risk in terms of time to?

DR. CHIU: I am sorry, in terms of what?

DR. BLOOM: In terms of time.

DR. CHIU: Yes, I think once we approve a new drug, you know, we will need to know a little bit more about the drug's marketing history. So, one of the criteria we put down is that maybe it should be on the market for ten years, but that is just a number to throw out for discussion.

DR. LAMBORN: Seeing no additional clarification questions, I think our next topic is an innovator industry perspective, Tobias Massa.

Innovative Industry Perspective

DR. MASSA: Good morning.

[Slide]

I am here representing the Pharmaceutical Research and Manufacturers of America to provide an innovator industry perspective on the risk-based CMC review proposed by FDA.

[Slide]

Having seen this presentation a few times in several trade meetings, and representing PhARMA at those meetings, I can say that PhARMA does welcome this approach. We think it is a bold and innovative proposal by FDA. Over the years that I have been involved in CMC at PhARMA, I know that we have had lots of discussions about taking an approach something like this although we have made proposals that were slightly different than this, but we do agree that once this proposal is implemented, if and when it does happen, this will truly represent the spirit of FDAMA Section 116.

[Slide]

I want to reemphasize the point that Dr. Chiu made, that it should be understood that this proposal in no way reduces the data required to support a manufacturing change. What we are talking about here is a reduction in burden that results from not having to file for prior approval or CBEs for these manufacturing changes. The amount of work that would have to be done would be identical both before and after this change gets implemented.

[Slide]

One of the things that we have had a lot of discussion about in canvassing some of my colleagues in the innovator industry is that we all have older products that

might want to be considered for this, and in considering those products these products need to be brought up to current standards. The products that were approved in the ICH era probably would not fall into that older product category, but when you are talking about some of the older products, they may not have impurity profiles comparable to today's impurity profiles. They may not have all of the specifications that have been outlines in Q6A or Q6B. The validations may have been appropriate when those products were approved but they don't meet the standards of today and i think if we are going to establish a program like this, where we are concerned about risk, all products should be operating in a level playing field. Again, we want to emphasize the importance, as Dr. Chiu has, of cGMPs.

[Slide]

We think that trying to carve out a group of ten percent of the products is an appropriate first step, and we think that is a wise to move to try and ensure that there is minimal risk. In deference to Dr. Doull, as a former toxicologist, I agree with his position very strongly. We want to minimize the risk to consumers and customers.

Ultimately, we also agree with Dr. Chiu that ten percent would not be the end goal of this thing. Looking at the burdens that are on FDA reviewers, we realize that they get approximately 1500 manufacturing supplements a year that

have to be reviewed. If we can reduce some of that burden while not reducing product quality, that will allow these reviewers to be doing other things that they need to do.

I think it is also important to remember that -- the numbers that I have heard -- approximately 77 percent of the products that are on the marketplace right now are immediate release oral products. So, there is a lot of opportunity here to get products into this minimal risk category depending on what some of the other criteria are.

[Slide]

I think it is important that we recognize that there are a number of efforts ongoing right now dealing with manufacturing changes, and those efforts should not be slowed down while we are trying to deal with the minimal risk proposal. Nancy Sager, this morning, talked about trying to get the reg. and guidance out for 314.70, and we think that needs to come forward.

There are also updates to SU/PACs that are in process. We are waiting, BACPAC too, which is the post-approval change to bulk drugs. There have been ongoing efforts on and off to try to do something about sterile products. Just recently industry made a proposal on packaging changes. We think those things need to keep going forward while we are trying to deal with this as well.

[Slide]

I think this kind of makes the point that while we have a goal of trying to get ten percent of the products out there, the vast majority of products still are going to be governed by these other guidances. That is why it is important to keep the progress going on these other guidances as well.

[Slide]

As far as some specific comments, we think quite clearly, and there has been a lot of discussion about biotech products of late. Clearly, biotech products would not fall into this category. They are just too complex to have changes considered in this proposal and, therefore, we would not consider them part of this.

[Slide]

The most important thing in assessing this proposal is establishing what are the inclusion criteria. I am going to talk about this in a slightly different order than Dr. Chiu did because I think I am trying to lump some of my comments together here.

We would propose that when we talk about drug substance or drug product characterization that there are already guidances out there that address how a product should be characterized. We have spent many years of ICH trying to establish guidances on specifications, impurities and stability, and those criteria should play a very big

role in establishing what the criteria are in this particular program.

Of course, one would have to address, as I said before, what you do about products that were approved prior to ICH guidance coming into play. I think that is where you would have to exercise some judgment. For example, although we have not seen the final stability guidance, one of the things that has been discussed in that guidance, or at least in drafts of that guidance is that a manufacturer would have the option of keeping their existing stability program if it was still felt to be adequate to support the product or converting over to an ICH-like program. I think you have to consider what your existing data are and how robust the product is. You would have to look at whether or not the assays that it lacks would jeopardize it being part of this minimal risk program. Again, what we want to try and do is establish an even playing field here so that we are minimizing risk to patients.

[Slide]

It has been proposed that this proposal be effective on BCS classification 1 products -- high solubility, high permeability. When we discussed this internally in some of our PhARMA committees, there was a lot of discussion that maybe this may apply to categories 2 and 3 as well, depending on whether or not you have in vivo, in

vitro correlations.

[Slide]

Issues about product validation, again this gets back to the issue of cGMP. Product validation is a GMP requirement and those of us who have some older products and have been deemed certainly 483s, those validations don't necessarily come up to today's standards. So, clearly, it is the responsibility of all of us to make sure that we are current -- that is what that little "c" means in front of GMP. So, we are expected to keep these validations current. We are expected to keep product specifications, i.e., what specific assays do we run on these products current with today's standards.

[Slide]

Clearly, the issue of the facility being BMP is paramount. We have talked about what establishes a facility in being GMP. You know, some facilities have kind of gone through coming to Jesus, as you may want to term it. We have had some difficulties and we have seen the light, and we now have good GMP status. So, I think you need to look at what has been a recent history and what that time frame is I think really needs to be determined. A facility has to have adequate quality systems. I am going to come to this again later on because you want to have systems in place that will be able to detect when problems arise. Without

those systems you can't claim, regardless of how simple a product is, that you are minimal risk. I think some of the GMPs that have been outlined in Q7A which has been proposed for drug substances outline a lot of the things we need to have in place to be considered in this program.

[Slide]

With regard to process and physical properties, I don't think the issue should be revolving around is it a simple procedure, whether or not chirality exists, whether or not polymorphs exist. I think the key is whether the process is validated and whether or not it consistently and reproducibly results in a product that meets whatever its specifications are. If you have polymorphs -- it shouldn't matter whether or not polymorphs are present but is your manufacturing process such that you always get the same ratio of polymorphs and that that does not change on stability. I think that is a key that we need to look at, the same thing as it relates to stereoisomerism. The difficulty of a process is not necessarily that determines risk. The key is how well do you control that process.

[Slide]

Do you have the appropriate manufacturing experience and controls in place to detect potential changes? I think that relates to product characterization more than anything else. Do you have the ability to detect

when something could "go wrong?" Do you have adequate assays for impurities, for example, that would detect new impurities occurring in the face of a manufacturing change? As Dr. Doull pointed out, there are always safety implications here.

As far as manufacturing history, we have had a lot of discussion about the proposal of ten years and we, quite frankly, think that is too long. We don't see that as being of any benefit certainly to the innovator industry and in most cases those products, once we get them approved, are really off patent then and there is really no benefit to us there.

If you look at the definition of what adequate experience is in SU/PAC, for the immediate release products it was termed to be three years of experience, and for the MR products it was said to be five years experience. I think the history maybe is not necessarily something we ought to talk about in terms of temporal time but how many batches of the product have we made, or perhaps we ought to be talking about one real time shelf life to look at stability out of the commercial plant. We need to have some sort of discussion around what really constitutes adequate time on the market. Clearly, we agree with Dr. Chiu that there shouldn't have been any recalls in whatever that period of time is. Certainly for a newer product you don't

want any recalls. For an older product you would have to establish a time in which there had been a recall.

[Slide]

One of the things we also think ought to be considered here is uncoupling drug substance from drug product. It may be that certain manufacture of a drug substance is such that it is well controlled but the drug product it goes into may be a little more complicated and may not qualify as being a minimal risk product.

Now, we recognize certainly that drug substance characteristics have impact on drug product and that needs to be considered as well. If you are talking about innovation products or some of the extended or modified release products, clearly, substance issues come into play and we need to look at that. But you may be able to distinguish low risk bulk or bulk changes from higher risk product changes, and vice versa.

I think we have already established the precedence for that in delineating certain changes that can be made early in the synthesis of a bulk and BACPAC1 where you have liberalized quite a bit what we can do in the manufacturing change arena. Although we have not seen BACPAC2, we know that that is going to be a lot more conservative because that deals with changes that are occurring in the last steps of synthesis. I think if you have a long synthesis it may

actually be to the benefit of the drug substance because there are more steps where, for example, impurities may be eliminated as a result of recrystallizations that may occur in the process.

So, I don't think there is any magic formula here that says what should and shouldn't be up for consideration. We have wrestled an awful lot with this because when we came up with what our criteria were, quite frankly, we thought they could apply really to any drug substance or any product type, but we agreed with FDA that at least initially we ought to be talking about immediate release oral products, oral solutions and simple sterile solutions, and we are encouraged by the fact that when we talked about sterile solutions included in there were solutions made by aseptic process. We are not just limiting this to terminal sterilization. I think, again, what needs to be considered here is how well controlled these processes are.

[Slide]

We, on the innovator side, are prepared to actively support process and we would like to participate in open discussions about this. I think the guidances that have come out recently where there has been a lot of industry participation, before we have got guidance to paper, have been the ones that we though have worked out the best, and if we think this one is going to work there needs

to be an awful lot of discussion because establishing these inclusion criteria is going to be very important.

[Slide]

To summarize, we obviously support this approach. We look forward to discussions on establishing what these criteria are, and we think that is going to be the key, and in keeping certainly with some of the comments that Dr. Woodcock has made and my colleagues in OPS have made, this needs to be based on sound science, not on "what if." We can't rely on anecdotes here. This has to be based on sound science. Thank you.

DR. LAMBORN: Thank you. Are there any clarification questions? Please?

DR. VENITZ: Yes, in one of your earlier slides you mentioned ten percent inclusion of products. What products are you talking about? Products on the market, NDAs, ANDAs?

DR. MASSA: My understanding is that the initial proposal was trying to carve out approximately ten percent of the approved products that are on the market right now. I think, you know, one of the things we need to be careful with here is that, at least as it was initially described to us, the criteria were and criteria, not or criteria. As one of my colleagues in FDA pointed out to me, if we only look at BCS1 category products, I think only seven percent of

products on the market right now are BCS1. So, if we make that and criteria we very quickly get down to low single digits in terms of what products would be eligible to be in this program. So, again, I think the criteria that we use are going to be really important here.

DR. DOULL: I would like to ask about the criteria. Did you talk about type of effect as a criterion. I am thinking, you know, surely you would be more concerned about something that causes cancer than something that causes nausea. Therefore, one would have a type of effect criterion but it is not in here.

DR. MASSA: Actually, you are right. We did not look at that although we agreed with Dr. Chiu that we need to look at product type and what diseases we are trying to treat; whether or not we have a high or low therapeutic index; are they using critical care settings. We agree with those and we think those need to be carefully considered for products that are considered here.

DR. DOULL: And, you are thinking of that as part of the safety effect?

DR. MASSA: Yes, we are.

DR. DOULL: So, incidence and type of effect.

DR. MASSA: We think that as we get into this in the next six or twelve months we are going to have to have lots of discussions around what are the inclusion criteria

and all these things, I am sure, are going to come up for discussion. I know we are trying to work with Dr. Chiu on the workshop that we have talked about for the summer of this year, establishing what things need to be discussed there and, clearly, those will be discussed.

DR. DOULL: Good. Thank you.

DR. LAMBORN: Our next speaker will provide a generic industry perspective. Debra Miran.

Generic Industry Perspective

MS. MIRAN: Good morning everyone, and good morning to the committee.

[Slide]

Generic Pharmaceutical Association would like to thank everyone, and especially FDA for inviting us to share our thoughts on this exciting new venture that the FDA is embarking on.

[Slide]

In listening to Toby and his comments from PhARMA, I think you will find that we overlap in the generic perspective a lot with the general thinking and philosophy, and we too in the past, from the generic perspective, have support ed the SU/PAC initiatives, have supported FDAMA 97, Section 116, and will continue with this in the support of the FDA initiatives to further down-regulate and establish CMC requirements based on sound science.

[Slide]

We too, as PhARMA has suggested, strongly agree with the FDA that there should be no reduction in study, data or documentation requirements for ANDA applicants and ANDA sponsors. All these established CMC requirements should be maintained, and the difference in the proposal versus the current standard would be a filing reduction, not a testing or documentation reduction.

[Slide]

GPhA also supports the phased-in approach, as we have defined it, which begins with the simplest minimal risk products and evolves over time so that the slice of the pie can be expanded. I think that it is important to look at these on a product and manufacturer quality attribute, which is a concept I will discuss in a few minutes.

[Slide]

Here I may depart slightly from some of the previous comments, but we believe that the focus of the initiative should be on product quality and chemistry and manufacturing controls. I am not suggesting that the safety category, as FDA has proposed, be overlooked or eliminated but I think that we need to remember that this is the product quality initiative that the FDA has taken on, and that the focus really should be the CMC attributes.

[Slide]

We agree that the important attributes and acceptance criteria are the key to establishing this qualification, as FDA calls it. As previously shown by Dr. Chiu, the four categories that FDA proposes are drug substance, drug product, safety and GMP compliance. As I previously mentioned, we strongly support three of those four, meaning drug substance, drug product and GMP compliance.

[Slide]

The focus of my next few slides is really to pose some questions and some issues that our group internally, within GPhA, have discussed. I am not suggesting we have answers to these, and I realize that the committee has plenty of questions to deal with already today, but take these as some food for thought and, hopefully, these will be addressed in the months to come and in the upcoming spring workshop, next spring.

To begin with, as we thought this through, it is hard to imagine one list in the current FDA thinking if you think of the drug product, drug substance and then the combination of drug product and drug substance. Could this suggest three lists instead of one? Could the drug substance qualify but maybe the drug product does not? So, I think that when we think about this practically, it is a little difficult to think about how this would be

implemented with one list.

[Slide]

Secondly, if you consider the FDA proposal in the four categories, there are numerous attributes under each. In this concept, do all criteria for all the categories need to be met? Or, is it sufficient that some of those attributes be met? I think here, again, that would be a process to consider in the ongoing discussions in the next workshop.

[Slide]

The list, as it has been coined, will that be developed by FDA only or with some industry input? Thinking beyond the initial creation, how will new products or substances be added to the list and what process will be used to keep it dynamic and growing?

When looking at the attributes that are being suggested, we are a little bit concerned that many of these attributes aren't necessarily inherent properties of the drug substance or the drug product but are more specific to the product, manufacturing process or the company manufacturing the product and, therefore, a generalized list with a generalized set of attributes may be difficult to fit into some of these less inherent properties.

[Slide]

As I previously suggested, we are also curious

about how the safety category which FDA proposes will correlate with the product quality attributes. I am not trying to be rebellious and suggest that we are against this concept of looking at higher risk from a safety perspective, but if the focus is meant to be on drug product quality and drug substance quality how is that going to tie into the safety category?

Like PhARMA, we question the definition of history, and is this the sponsor's history with the product or simply the years that the product has been on the market? Once again, your company history with the product may be irrelevant to the general history of the product being manufactured by all companies over a period, and the ten-year concept we too think is excessive, knowing that in existing guidances SU/PAC has already defined a three-year period, which is defined as a significant body of information for immediate release products.

[Slide]

With respect to the manufacturing procedure, the proposal suggests two categories, easy and, as we call it, everything else. Neither is very well defined at this point but here, again, it is not so much that it is a concern but, rather, as we all know in the manufacturing world even with simple immediate release products there are multiple processes available to the manufacturer and what may be easy

for one sponsor may not be for another.

[Slide]

Turning back to the subject of drug substance versus drug product, another concern that we perceive is that if the acceptance criteria for the drug substance are established, it may not be relevant once it is formulated into a drug product. The example that I show on the slide is that if a drug substance is known to be sensitive and stable from light or moisture or any other environmental factor, it is possible to formulate into the drug product a more stable drug product, thus, minimizing or eliminating those sensitivities. So, the drug substance may not fit an attribute on one hand but the drug product may, and does this product need to be on the list or not on the list?

[Slide]

We, at GPhA, have also thought a lot about this concept and would like to take a few minutes to propose a slightly less radical approach maybe, and a version of what the FDA proposal suggests that will take into consideration all the objectives that the FDA wants to meet but, at the same time, I think addressing our concern that these really should be more product and manufacturer driven attributes.

We think we can create a concept which, as I said, meets FDA's objective of down-regulating and providing relief from filing requirements. This can be based more on

the qualification of the sponsor, the drug manufacturer and the product that they are making.

[Slide]

Replace may be a strong word and if I had had a chance to edit these slides I would have said reconsider the concept of the truncated ANDA, and that may come as an interesting message from the generic industry which always is trying to suggest that we have too much filing requirements already. But I think in this case the concept that we are trying to put forward here is that for an ANDA the traditional approach meeting requirements per 314.94 may be the way to continue, and then, after a period of time, after the product has been approved and on the market, and for the sake of argument I am suggesting three years when the sponsor has had a chance to manufacture a product and develop a history and understand that the controls that they have in place are adequate to detect potential problems, to control the product and the process and the quality, then the sponsor would be eligible to submit this annual report or whatever filing mechanism the FDA arrives at to down-regulate.

[Slide]

But we think that this could help to expand the pieces of pie with, of course, the FDAMA exceptions which we know are governed by law. We also think that this approach

rewards quality and compliance. The whole concept of what FDA is proposing does put more and more responsibility on the manufacturer which they already bear per GMP, but for the responsible manufacturer, as always, it is important that this concept of reward be in place and that the diligence pays of in the reducing filing requirements.

This approach may not depend on a list concept. There may be a way of not having to create, and add, and maintain the list that has been suggested this morning. Importantly, this would probably not -- I am not a lawyer but it would probably not require regulation to implement as the TANDA concept would likely.

[Slide]

In summary, I would like to say that GPhA does support the FDA's efforts to establish this risk-based CMC approach. We too are eager to be involved and to participate in the discussions going forward with the agency.

All the questions the committee has today before them to review and discuss we feel are relevant and challenging, and they do apply generally to all drug substances, drug products and manufacturers, generic and innovative alike.

Finally, we feel at GPhA that our proposal might attempt to implement the FDA concept in a customized

approach for the drug substance, drug product, and manufacturing and, thus, the attributes are created and complied with, with both the FDA and the sponsor working together in the process. Thank you.

DR. LAMBORN: Thank you. Are there questions?

DR. VENITZ: Can you define your concerns about the safety considerations that you object to?

MS. MIRAN: I figured I was going to face that question. I think that it is inappropriate to say that we object. What I was trying to say, and maybe I wasn't completely clear, is that we feel that the focus should be on product quality attributes because this is a CMC of chemistry, manufacturing and controls initiative. So, the focus, the primary consideration for a list or the concept that we propose, or whatever ultimately comes out of this should be driven by the CMC attributes.

DR. LAMBORN: I guess I have one question. I just want to make sure I understand. Your proposal with regard to the timing is that you would like the timing to be linked with a particular manufacturer having produced that product for a period of time. Is that right?

MS. MIRAN: Yes, and the suggestion of three years I guess is arbitrary but it comes from the SU/PAC documents that have been published that we are working with and already using that time frame for other change types.

DR. LAMBORN: Thank you. We have the unusual benefit of being a little bit ahead of time, but I think what we should do is take our 20-minute break now. We then have a list of questions that have been posed for discussion by the committee, and I think that is what we will turn to following the break. So, a 20-minute break and then we will reconvene.

[Brief recess]

Committee Discussion

DR. LAMBORN: Everyone should have a copy of the questions to the committee, as well as two tables that the questions refer to in the back of what you received. So, although we have put this table up here, we are counting on people being able to reference what is in front of you. It is both in our background and it is also in the agenda that we received today.

Also, we are fortunate to have two guests with us for the purpose of this discussion and I might ask them to introduce themselves.

DR. HOLLENBECK: Sure. My name is Gary Hollenbeck. I am associate professor at the University of Maryland School of Pharmacy.

DR. LACHMAN: My name is Leon Lachman. I am an industry consultant on regulatory matters.

DR. LAMBORN: And we have two additional folks

from the FDA who are here to participate in this discussion. If you could introduce yourselves too?

DR. BORING: I am Dan Boring, from the Antivirals Group.

DR. SCHWARTZ: I am Paul Schwartz, from the Office of Generic Drugs.

DR. LAMBORN: Thank you. I appreciate you all participating in this sort of strange structure rather than our usual circular table.

So the first set of questions that we have are questions to Table 1. I think Table 1 is on the screen above but, for the committee, have you all found the questions?

So, regarding the drug substances, is each of the identified attributes important in determining potential risk to product quality? Or, are they potential sources of product defects? I guess the attributes that we are talking about are chemical, synthetic process quality, physical property, stability, manufacturing history and then we have the lovely generic "others."

So, if we start with the ones that are better defined, perhaps our guests would like to start.

DR. HOLLENBECK: I would like to ask a general question first, if I could, maybe a point of clarification from this morning's speakers.

DR. LAMBORN: Please.

DR. HOLLENBECK: I noticed in all the presentations this morning there was a discussion that the basic scientific structure behind product quality is not going to change as a result of this proposal; that only the filing requirements would be changing. Yet, there is, in your presentation, Dr. Chiu, the comment about reduced information in the filing itself. Could you comment a little bit more about what you mean by reduced information?

DR. CHIU: You know, in the original filing of an NDA, we would have the full CMC information required by our regulations and also recommended by our guidances. However, if a drug is on the list, then we are thinking the company could submit one annual report. The annual report would not contain all the information which is required originally. It would have reduced information. Just to give you an example, in the original submission we will have a full description of the synthesis in terms of all the steps, the conditions, everything -- the quantity, everything is in there, a full description. Sometimes that description is actually substituted by an SOP. In this reduced annual report they will mainly just consider a detailed flowchart.

The reason to have a reduced annual report concept is if we do not have that, then any changes to the annual report information still are required to be submitted in the

next annual report, even though we don't require supplements. But if the annual report itself is reduced, like the flowchart of the synthesis, then in the next annual report only changes to that flowchart would be reported. So, that is why I call it the reduced annual report information. And we were thinking that the concept applied to the truncated NDA, even in the original NDA submission, will be reduced information. However, the manufacturing site companies still have SOPs. They can't get away without an SOP for synthesis.

DR. HOLLENBECK: Thank you. Looking at the question under number one, it would seem that for chemical entities we are not talking about the entities resulting from recombinant DNA or biologic fermentations, whatever the chemical structure, once it is on the market -- the product has been on the market a while and it has been shown to be reproducible, the same thing for the synthetic process -- we are talking about a number of years. So, I think we are going to have a process here, a synthetic process that we have been able to optimize resulting in reproducible characteristics of quality. This includes, you know, the polymorphism, as was discussed this morning. Do we have a constant ratio of the various forms, or do we have the more stable polymorphic form? All this I think is based on the process. We have identified, characterized and finalized

the synthetic process once you get into the NDA approval phase. In order to change it later you have to go through some kind of an amendment before approval or supplement.

So, assuming that this has all been done, I think you then have a repeatable active pharmaceutical ingredient as shown after three or five years of production. So, that would be the repeatability of that process and of that ingredient. I think I may even look at some other things here from a processing point of view. I would be interested in some of the physical property of solubilities being critical as to decision points on whether a dosage form is going to have any problem with the actual ingredient or not. So, I think that is what I would look at.

DR. LAMBORN: So, specifically solubility?

DR. HOLLENBECK: Solubility would be one thing I would add to this physical property. That is an important part in dosage form. Whether a dosage form has a role or not will be dependent on the solubility of the active ingredient.

DR. DOULL: Where does purity go in this table? Does purity go in? Where does that go in?

DR. HOLLENBECK: Purity would be part of the quality specification where we are talking about the impurities of the degradents and related substances. That should be picked up in there.

DR. LAMBORN: Are there some folks on the committee who would like to comment?

DR. BOEHLERT: Under quality, I would agree that the purity and impurities come in there. The other thing that we might consider for some products is microbiological quality. That can be key for some products. It is not included here specifically. It could be added.

With regard to manufacturing history, while I think that is important, I think two of the speakers this morning said it is not the length of time necessarily that you manufacture, it is how many batches you have made. There are certainly products on the market where you make one batch every two years. So, ten years gives you five batches. There are other products where you make a batch every day. So, in a year you would have a lot more history than in ten years. What is important is how often you produce that material, not the number of years. Certainly, we should be looking at some of the years that are mentioned in SU/PAC, three and five rather than ten.

DR. LAMBORN: Other comments? What other attributes need to be considered is I think where we are right at the moment.

DR. HOLLENBECK: I have to do things in a very logical manner for my slow brain sometimes. First of all, I think you have high risk here when you venture into the

untried and the unknown. Clearly, Debra Miran's comments this morning really focused on when you can counter that risk. I would like to think that all of the products that we make have a CMC portfolio sufficient to characterize their quality, and that they are understood well enough by the companies that manufacture them, and that the specifications are meaningful.

So, I think if you have had experience manufacturing a product and you have followed perhaps the other guidelines that Debra Miran presented this morning -- compliance with cGMPs, no recalls, those kinds of things, that is an important proof that this product can be manufactured and maybe that should qualify a company for the opportunity of reduced filing requirements. I could see that almost as an initial screen for this kind of reduced filing requirement.

It seems to me when we get to the questions on this list, and that is the thing we are really asking, how can we ensure that we could have a list where we just have general decreased filing requirements and still be confident that there isn't high risk associated with that. As we move in that direction, it is very hard to exclude anything as a possibility for influencing quality of the product. But my sense is if you have meaningful specifications in place it is pretty straightforward. If you comply with those

specifications, why aren't you maintaining that product's quality?

DR. CHIU: That had to be debated while we were discussing FDAMA. Specifications tell the whole story -- the agency, you know, both CBER and CDER do not support that specifications tell the whole story for every drug because, for example, if you have a complex mixture or you have a very complicated molecule, even though you do certain release tests, physical, chemical, biological, you are still not sure you have the product consistent unless, you know, you have the process control well in place. So, therefore, that is why it is not just focused with adequate specifications. We were thinking about whether the drug substances are well characterized. If you cannot characterize the product, then you cannot really say that the specification is adequate.

DR. LACHMAN: Someone mentioned earlier that the inspections that would take place in the future would be a combined inspection between the reviewing representative as well as a compliance representative. I think also important would be to look at the number of all the specification results, looking at the deviation reports, and is there reprocessing taking place in order to get the final pure material, and what is the yield. Is the yield repeatable or is it variable? So, these are some of the other attributes

that could be determined during the pre-approval inspection. That adds on to the assurance that the product or the bulk drug is of the appropriate quality and repeatable quality.

DR. BOEHLERT: I would just mention that in addition to that, product complaints is another good thing to look at because if, indeed, there are complaints coming in from the field, physical defects of lack of efficacy, that could point you in the direction of a product you might not want to consider.

DR. LAMBORN: Just to see if I am understanding, what we are talking about is, first, that the company needs to qualify and that is where you are suggesting the whole process should start.

DR. HOLLENBECK: I am suggesting that that could be an initial opportunity into a process like this, a company-based kind of process. I think we referred to some of this before as creating your own SU/PAC, if I remember, in the initial follow-up discussions. That was basically a reward for experience with the product and performance. That is a possible way into this kind of regulatory field. The other approach is an alternative as well.

DR. CHIU: And, we felt, you know, the agency needs to be very active. So, the first step to be more objective is to have universal criteria, attributes to identify a list of drugs with those characteristics. Then,

based on GMPs, we will say which companies then have the privilege to use that list. But if we have the other approach, then we will have a company-dependent list, and the list can be perceived to be subjective because each company has a different list.

DR. LAMBORN: Except, if I am understanding correctly, I guess I would look at it more as a listing but there are two sets of criteria that have to be met. One is related to the product and one is related to the company. So, whichever one we start with, ultimately to have a product manufactured by that company have the minimum filing requirements you continue to have both a company and a product requirement that has to be met. Am I correct in my understanding?

DR. CHIU: Yes, and I think in which sequence you do the list really doesn't matter. However, if the proposal is just to look at the company and see how many products they make and they decide which drugs will go with which company, it kind of becomes, you know, subjective.

DR. LAMBORN: Thank you.

DR. HOLLENBECK: Well, my suggestion would be objective criteria that you use to determine a company's ability to participate in this program. So, that would be one point.

I guess my point is that I don't necessarily feel

like we should reject any drug substances from possibly being eligible for a program like this. If they are well understood -- if the product is well understood then, it seems to me, the filing relief makes sense. In many respects the decision based on a drug substance can be quite arbitrary. You know, some products are easily made by some folks and not so easily made by others. But if you have a well characterized substance -- all the criteria that you have listed here I believe are important parts of that process, but if you have demonstrated that you can do that, then you should be eligible for relief on a program like this.

DR. LACHMAN: I don't think I would support that if the criteria is objective, it is independent of companies. That is the basis for it, the objective criteria that you have to develop.

DR. LAMBORN: One of the things that I note on this first table is that there are well characterized, and then we have others to be defined -- simple process to be defined.

DR. ANDERSON: Those are the two areas that I would like to comment on. First of all, if you know the chemical structure it probably has already been well characterized. So, I think we are talking about maybe compound here instead of the structure.

Secondly, there are some things that chemists, organic chemists usually use to characterize compounds so that they can identify the structure, and I assume that is the goal here. I can talk to you about that later because I do that every day.

Secondly, I think we might want to distinguish between simple synthetic process and a simple synthetic process which may have a sequence of steps in it because, as I have looked through the literature, most drugs are made through a series of synthetic processes and they may not necessarily be simple, and that may be where the problem comes in. So, we might want to amend this so that it doesn't rule out multi-step synthesis but, in fact, look at whether or not within each of those steps we are talking about a simple synthetic process. Let me just add quickly that I am a great believe in simple synthetic processes.

There is a question down here, it says, should a drug substance we multiple chiral centers be excluded? Can you elaborate on that for me, why that question is raised?

DR. SCHWARTZ: Well, we think that if they are many chiral centers you get a series of diasteriomers and perhaps I think may not be as controlled necessarily if there are not multiple chiral centers. By making changes in the synthetic process, could that possibly affect the eventual purity of the material if there are many chiral

centers?

DR. ANDERSON: As I am sure you know, there is just beginning to, I think, become understood a little bit better about what is actually the active compound or the active isomer in the drugs. So, it is not quite clear to me, if there are multiple chiral centers in a compound, how that might affect the activity. If the drug is active and is working, the multiple chiral centers may really not have any problem. Maybe one is acting or both, whatever.

You are right about the diasteriomers and probably you should have taken my test last week and would have done better than my students. You are right about the diasteriomers but if that is, in fact, the case, then what you do is, theoretically you can separate those if that is what you are talking about. If you are talking about the other part of it, then that may not be a problem in terms of activity of the drug.

DR. BLOOM: I think the diasteriomer isomers can affect also the efficacy of drug in terms of drug receptor interaction. So, that should be taken into account. There is efficacy of the drug and it might be affected by the syntheses also. So, if you are looking in terms of a structure already in terms of the diasteriomer isomers, they should be looked into in terms of the efficacy of the drug.

DR. BOEHLERT: I think there is no question that

diasteriomers are important and if you have a drug with five chiral centers and have numerous diasteriomers, I think what it depends on in the last analysis is whether you have acceptance specifications, and that is to test the methods and the limits, and if, indeed, you do, then the issue is not whether there are chiral centers or not but how well it is controlled and whether you can get chiral changes when changes are made. You know, I think the focus should be on whether, indeed, you can follow those changes and not where the drug started to begin with.

If we are talking now about a place to start, you probably won't start with a drug with five chiral centers; you would start off with drugs that are a lot easier to control. But I would not exclude such drugs if, indeed, you have good acceptance specifications.

DR. LAMBORN: I think one of the things that I am hearing is a repeated theme that fits in with where I think you all want to go anyhow, which is that part of the distinction is where do we start versus where do we ultimately want to be, and how far can we expand that section of the pie? So, I don't think there is disagreement to start with the simplest end of the spectrum but how quickly you move away from that may be dependent on the comment that I heard a minute ago, which is that if we start with the absolute simplest we will practically not involve

any of the products that we are trying to deal with and, therefore, we will want to expand that perhaps at least to assure that the first pass includes enough to make something that is meaningful, keeping in mind the other discussions that will go forward.

Let's look at these other questions that we have been asked to address. One of the things that I am wondering about is what should be the standards for adequate specifications? How should product specific, i.e., specific to a manufacturing's product, impurities be handled? Since I have not heard anybody comment on that, I will pass that for comment. That is question 3c, on that first page.

DR. RODRIGUEZ-HORNEDO: I would like to make a comment also related to question 3b.

DR. LAMBORN: Please.

DR. RODRIGUEZ-HORNEDO: I think in my view of the synthetic processes and adequate specifications, I raise the question what are the endpoints of the synthetic process? What is the endpoint? Is it the active ingredient with the well-defined particle size and polymorphs? Is that the endpoint? I am a little bit confused with the synthetic process and its ties to the adequate specifications. Maybe adequate specification is just a final active product ingredient, and where does the synthetic process end?

DR. LAMBORN: I think this is up to you all.

DR. SCHWARTZ: The synthetic process ends with the active drug substance and its impurities, and what is the level of impurities that might be found acceptable and also the physical properties, like you mentioned the particle size and polymorphs if that is an issue. In certain drugs it is an issue in some drugs it is not an issue. For example, for highly soluble drugs we are not particularly concerned about particle size or polymorphs. Even if there are different polymorphs, if it is a highly soluble drug it is really insignificant. The same thing about particle size. Certainly for a solution particle size is not going to be an issue and even for a lot of soluble drug substances, for example salts, probably particle size won't be an issue. But what we are talking about is characterized chemically and physically, final product plus whatever side products from impurities associated with that synthesis, and when physical properties are important that is included too.

DR. RODRIGUEZ-HORNEDO: So, the in-process controls would be applicable to the adequate specifications.

DR. SCHWARTZ: It comes after the adequate specifications.

DR. HOLLENBECK: Yes, I think this is a key point to focus on for a minute, and that is the definition of risk in this context. I have heard the panel refer to toxicology and safety of drugs. That isn't really the risk that we are

looking at here. That is an important risk and maybe, indeed, we should start with drugs that are really safe from the safety perspective, but the risk that we are looking at here is what is the risk of changing the filing requirement. We have in place a set of specifications for drug substances and drug products that in most cases is adequate to characterize materials and ensure product quality.

So, the question that we are really asking is what is the risk of changing from a supplement to an annual report. And, it seems to me, the risks are will the immediate nature of both the active substance and the product be the same now, and will there be any untoward time-dependent effects introduced because of this relief in regulatory filing requirements?

We keep getting back to the same message here, if the set of specifications upon which a product is approved is adequate and in general it covers all of the issues we have been discussing here, then the question is by moving it into an annual report what would we really risk?

DR. LAMBORN: Cold I just ask for a clarification? I had thought that in your presentation you had said that you were not going to move it simply from immediate to an annual report, that you were also proposing to reduce the burden in the annual report. Did I misunderstand that?

DR. CHIU: Yes, you did. The annual report will

be reviewed. The reason we put the simple and synthetic processing here is -- you know, my personal experience is I have reviewed drugs in the past and they had hundreds of steps. To synthesize, it took six months. So, even though you say you have specifications there, sure that drug might not be included because we would not have any information on the changes of the synthesis process because the annual report was just a flowchart, and we would not even know of all kinds of changes and will that create a risk by reducing the requirements. So, many of drug substances have very few steps, a dozen steps or half a dozen steps, but there are products, you know, that really take a long time and hundreds of steps to synthesize.

DR. LAMBORN: So, again, just to make sure I understand, the concept here is could there be something that is missed that will have a bigger impact if we have a lot of steps or the process is complex and, therefore, you want to be assured that there is a backup process in terms of filing for those, with the thought that accumulation of items might be more likely to cause a difficulty that was unexpected.

DR. CHIU: That is right.

DR. HOLLENBECK: I guess that gets back to the inextricable linkage between experience and the products. I don't think for the compound that you were just talking

about it makes sense to allow a manufacturer to do the first batch that they have every made under these reduced requirements. But, having successfully manufactured a product meeting the specifications, then you can look at using the reduced filing requirements.

DR. CHIU: Let us consider the process doesn't change. Under this program, a process change will not require any filing, you know, beyond a flowchart change.

DR. DOULL: I just want to respond to that comment. It is hard for me to conceive of a risk-based list that excludes biology. These are all chemistry things, and maybe it is a two-step process as you say. You first need to do the biology but you have to ask about therapeutic purpose -- you know, what are we going to use this drug for? If it is going to cure cancer it has different kind of requirements than if it is going to be used for a headache. And, what is the therapeutic index? You know, what are the adverse effects that this thing produces? That is all part of risk. You can't just shove it over there and say, you know, we are just going to deal with the product specifications unless, as you say, you have already taken care of that other step. But I think we are excluding biology here and I don't think we can, if we are talking about risk, because biology is right in the middle of risk.

DR. LACHMAN: This is not for new drugs; this is

for existing drugs.

DR. DOULL: Well, that is true.

DR. LACHMAN: So, you will have the biology done, and the only time you will change biology is if you change the characteristics of the drug itself -- if it is not going to be available, if you have new impurities or something like that, otherwise it shouldn't change the biology.

DR. LAMBORN: Let's get clarification, Dr. Chiu.

DR. CHIU: Yes, I think our proposal includes three phases. The first phase is to look at your process characteristics. That is what we are discussing now. That is what we are seeking advice about. The second phase is, once we have the list of drugs based on the product characteristics, we will look at the safety. Whether there is a narrow therapeutic index, whether it is for critical care, to determine whether any of the drugs which we are considered not safe, then we will remove those drugs from the list. That is the second phase.

DR. DOULL: That might be my first question, whatever order.

DR. LAMBORN: Perhaps we could say that, once again, there are two different pieces to this. Just as there is the manufacturer and the substance, there is also going to be the issue of the third piece which is the purpose of the product, and whichever order as long as all

of them are covered, it is a matter of efficiency. But the point is, as I understand it, you are trying to put that one piece in place so that we have that together -- you are trying to put two of the pieces together --

DR. CHIU: Right, because this initiative is based on risk of product quality. So, first we lay down, you know, the risk in terms of drug substance, drug product characteristics. Without the objective criteria we will not be able to even compile to a list because we need our objective criteria first.

DR. VENITZ: I am still confused about what you mean by risk. We heard a definition that risk means that if you change your filing requirements, does that make any difference with respect to product quality. I guess I am with Dr. Doull, to define risk as if you change your processes right now to assess product quality, is the consumer going to take any additional risks?

DR. CHIU: We are talking about the risk if we are reducing our oversight in terms of product manufactured at our Center -- will that create a risk of producing product quality not meeting the standards.

DR. VENITZ: Does it also mean that it would potentially expose the public to a greater hazard?

DR. CHIU: Yes, the consequences will produce the hazards because the quality is the basis for safety and

efficacy.

DR. VENITZ: But then you do have to incorporate the biology or whatever it is you are talking about.

DR. CHIU: Yes, we are. We are incorporating the biology. We have three pieces. And, if we permit a company to have reduced filing all three characteristics, three elements have to be met.

DR. VENITZ: Thank you.

DR. HOLLENBECK: If I may respond to that, let's remember we are talking about an approved drug that has gone through the entire approval process, a product that is manufactured according to Good Manufacturing Practices, and a product that meets its specifications. So, it is in that context that I framed the question. The risk that we are really exploring with these changes is changing the filing requirement. You still have the whole gestalt of all of that safety-efficacy data that is part of the original development and manufacturing record.

DR. CHIU: Yes, in addition, firms still have to do the right testing, studies, assessment and validation for any changes. It is just the filing requirements that are reduced.

DR. VENITZ: But then the question that you are really asking, at least in my mind, is by changing the way you assess product quality, is it going to have a clinical

impact or not? In other words, are there ways in which you can loosen up your specifications in your CMC and still maintain the same clinical safety and efficacy for a product?

DR. CHIU: If you are talking about using the specifications, our proposal is if you change product specifications you will require a supplement, as required by law, by FDAMA.

DR. ANDERSON: I was going to ask for a bit more clarification on 3c. Adequate specifications and specific manufacturer's impurities -- can you give me a little bit of information on what you do now?

DR. SCHWARTZ: Well, I think what we mean in this case is that there could be several ways to synthesize a particular drug substance, and each way may generate its own impurity profile, and each manufacturer might have a different set of impurities associated with their particular synthetic method. So, if the specification is for a certain amount of impurities, specific impurities, and they change the process and now generate a new set of impurities, how do we handle that type of situation?

DR. ANDERSON: Well, a couple of things, one is the impurities affect the structural determination and if you are going from one process to another, then it seems to me like you have to have another whole set of whatever you

do to approve that or to at least clear it. I don't see how you can take one set of impurities and one set of reactions and apply the regulations to another process because, as you said, if you are generating a different set of impurities then you may have problems in terms of how they affect the patients or the consumers.

DR. SCHWARTZ: So, that comes back down to adequate set of specifications. If the impurities are not well characterized, then a product may look like it passes when, in fact, it wouldn't because it would have other impurities that may not even be accounted for. I think that is part of this issue.

DR. RODRIGUEZ-HORNEDO: I guess the impurities would change the chemical stability --

DR. SCHWARTZ: That is true too.

DR. RODRIGUEZ-HORNEDO: -- potentially the dissolution rates, although not necessarily, and maybe the appearance of other polymorphs.

DR. BOEHLERT: We are talking about products that have been on the market for some time and, with regard to impurities, I think Dr. Massa talked about the standards that we use for these older products may not meet today's requirements, and you see many old products that have limits for impurities of no more than a total of one without any reference specifically to what those impurities are. So, I

think this is an area we need to take a look at because, indeed, you can change the profile and have a whole different set of impurities and they still meet the same requirements because it is one percent of anything and 0.2 percent of this or that. So, I think that needs to be a factor in what we consider when we talk about meeting specifications. It could, indeed, meet the same specification and be different. The burden of proof is on the manufacturer because when the process changes the impurity profile well may change.

DR. SCHWARTZ: It is not unusual to see specifications with a certain percent of unidentified or unknown -- the unknown comes up a lot, and I think that is probably not very adequate.

DR. LAMBORN: It sounds to me like one of the things that we keep circling around on is recognition that initially this would be applied to products that have been on the market from a long time ago versus newer products that then will reach time frame that will have been characterized in more complete fashion. So, dividing that in two pieces clearly makes a difference in terms of how we might respond to your questions.

There are two sets of questions here, and I realize to some extent they may be overlapping but I want to make sure we cover both of them. There are a couple of

pieces here that we have not really addressed. For instance 3e, stable substance, does anyone have a comment or any thoughts that you would like to make sure we cover on that topic?

DR. ANDERSON: I do.

DR. LAMBORN: Go ahead.

DR. ANDERSON: Just quickly, I think the way you define a stable substance depends on how you are going to use it. Sometimes it is defined by shelf life. If you are talking about a drug, it seems to me like you might be concerned about the chemical reactivity when you dissolve it in something, or you may be talking about decomposition or degradation when it is taken as a drug. I guess you already know all of that but, in my mind, shelf life would be different than how you are using the drug or how you are trying to dissolve it. To me, shelf life is a good way to define what I use but it is probably not a good way to define what a consumer is going to take.

DR. LACHMAN: You have two pieces here. You have the active pharmaceutical ingredient and then you have the active pharmaceutical ingredient put into a dosage form. So, I would look at a stable substance as the active pharmaceutical ingredient, and you can determine that by stability studies. Then you are going to use that active pharmaceutical ingredient with other materials to make a

dosage form. Then you have to relook at that stability of that ingredient with the other materials, and there could be two different stabilities. So, I think there are two pieces to this pie.

DR. BOEHLERT: Stability is a factor of how it is stored and how it is packaged as well. You can have a material that is stable for twenty years when it is stored and packaged appropriate, and unstable in a day when it is stored inappropriately or not packaged well. So, you need to take into consideration appropriate packaging and storage conditions when you talk about stability. Very often there are drugs that are unstable in a pure state but once they are formulated they are stable. So, you need to consider that as well.

DR. SCHWARTZ: I think we are also considering the opposite where drugs that are stable in a pure state might be reactive with excipients, for example. That is what we meant by chemical reactivity. So, should drugs that have those type of reacting groups be excluded from the list because they might interact with potential excipients in a formulation?

DR. HOLLENBECK: I think this is a screening question again. Let's start with those things that are rock solid stable, and I think there is a group of those that we can begin with. That is an excellent screening criterion to

begin with, and then progressively move towards the ones where packaging may be critical or excipient selection may be critical.

DR. BLOOM: I just want to make myself clear. These are little or no risk product quality assessment after a product is already known. Basically that is what we are saying. We know all these characteristics and chemical structure and everything. So, my question is do we have to go through this to have less of a burden in terms of paperwork for a product for an annual report? My guess is the annual report should encompass all these characteristics or properties, or whatever and then send the information and with that information you can tell if it is going to be stable or not stable, or whether the formulation is going to change. My guess is we are going through a process where these characteristics are already known. My thought is, well, are the properties or the principal properties going to change in a product when the annual report comes in that might change the formulation, and it will provide a risk to the people that might be taking this drug or formulation. Is that what we are trying to get to?

DR. CHIU: In our files we know the product characteristics. Whether they are reactive or, you know, whether they can be stable for twenty years when they are properly packaged, we do have an idea but what we are trying

to find out is among this vast number of products which ones we can really consider stable and not have a risk when we are require certain filing information. So, one suggestion is rock stable. Then, how to define rock stable? It doesn't react to anything and has a shelf life of twenty years or five years? Eventually, to be objective we have to very concrete, definitive criteria.

DR. LAMBORN: I think one of the things that I have seen, having served on this committee for a period of time, is that there is always a conflict between wanting to come up with something that is objective and, yet, realizing that every time we try to come up with something that is objective we keep coming up with the exceptions and we either end up with something that is so narrow it doesn't serve a purpose, or it gets to the point where it is a judgment call each time and by the time you have finished making the judgment as to whether it qualifies you might as well have done the filing. So, I understand the tradeoff that you are trying to come up with and, hopefully, some of the comments that we are making are helpful in that regard.

Now, one thing before we switch to the second list of questions, how many years of marketing history? We have heard a couple of comments, I think to the sense that it is the number of batches -- something to do with the frequency with which you are going through the manufacturing process

that would have an impact perhaps, and the general sense that ten years, while it might be applicable for a first pass on the older ones, should not be the criteria that would be used, but that that should be reduced over time assuming a reasonable number of batches are being produced. Are there some other thoughts or comments that the committee would like to share on that topic?

DR. BORING: I would like to ask one question.

DR. LAMBORN: Sure, please.

DR. BORING: You were talking about numbers of batches earlier, and that your familiarity with the process could be overriding in your assessment of this. How many batches would you think is a good number? This is also tied in with the stability. How much experience with the stability of a substance would you be comfortable with?

DR. ANDERSON: Reproducibility I think is extremely important.

DR. LAMBORN: So, what you are really saying is, yes, but what do you need to be sure of reproducibility?

DR. HOLLENBECK: You know, in the absence of any explicit data that I am aware of, I would feel most comfortable with recommendations like those in the SU/PAC guidances which define a significant body of information.

DR. LAMBORN: Perhaps we could turn to the second set of questions, which really are similar to the first

except that they are now focusing on the same kinds of general kinds of questions but now with regard to the drug product rather than on the drug substance. So, again, let's start perhaps with the questions of attributes with regard to dosage form since that is obviously something that is different from what we have been discussing. Anyone like to comment on which type of dosage forms they feel we should start with?

[No response]

I assume that means there is really no disagreement with the selection that is in place.

DR. LACHMAN: I think the solubility of the active pharmaceutical ingredient is one of the major controlling factors on the characteristic particularly of the solid dosage forms, and if you have a very soluble drug you are not going to do much with the excipients you put in there. It is going to come out, and it is going to come out normally pretty satisfactorily.

Also, when you have a drug that may be 75 percent and above the content of the dosage form, it is also going to be readily available by the correct formulation. So, I think those are probably two of the major elements. The solubility of the active ingredient and the concentration of the active ingredient in the dosage form may play a role in deciding.

DR. HOLLENBECK: Yes, I agree with the approach taken here to focus on oral drug delivery systems from the safety perspective. I think as we begin to look at a risk-based system that makes sense. I would also endorse using the biopharmaceutical classification system that we have already invested a lot of effort into. I guess I heard a number this morning for the first time, that seven percent of marketed products fall into class I highly soluble, highly permeable. If that is the case, that is not a bad place to start. That almost gets you to the ten percent goal that you have sort of established as a beginning point.

DR. CHIU: You know, highly soluble, highly permeable are definitely good criteria to decide whether you need to do in vivo bioequivalence studies or not. However, a low solubility drug doesn't mean it is not stable. It doesn't mean it is not characterized easily. It doesn't mean you cannot control the manufacturing process. So, if we limit ourselves to the class I BCS seven percent, within that seven percent there are products not characterized and not easy to make, and then we will probably end up with single digits, as Toby mentioned. Therefore, we really need to look outside the context of the clearance issue and look at the risk purely by product quality.

DR. LAMBORN: So, you are saying that that is a good group to include but should not be sufficient and we

want to go beyond that.

Could I ask for a clarification? Question 3b that you have here, should only products that can be manufactured by multiple processes be included? My question is why is it that you would think that only those that can be manufactured by multiple processes -- why would that be proposed?

DR. CHIU: What we are saying here is if a product can be made by a multiple process, it means that the product is really prone to changes. But if there is only one way to make it, with a change from wet to dry that you will change the product characteristic then is a higher risk.

DR. SCHWARTZ: I think maybe the question should be worded should only products that have been manufactured by multiple processes be included?

DR. BORING: In other words, products that have used many different processes and have all ended up with the same result is a very robust product despite that process.

DR. LAMBORN: So, clearly what you are saying is that if multiple processes produce the same thing, that would give you an extra degree of comfort. But, then that poses the question of if we had a product that has only been produced by one process, how uncomfortable would the members of this group be? I mean, how strong a criteria do people feel that should be?

DR. LACHMAN: I would look at the characteristics of the active pharmaceutical ingredient to give me a little bit more indication as to my concern. If the active pharmaceutical ingredient has a stable polymorph or it doesn't have any polymorphs and doesn't have any chiral characteristics and is soluble, I would have little problem with it. If I had other difficulties that I experience with the active ingredient, then I would be concerned with the dosage form.

DR. LAMBORN: I saw some nods, but could people sort of verbalize their comments so we can get them on the record?

DR. BOEHLERT: I think you have to look at the whole picture and not just one aspect here. If, indeed, all the other attributes are favorable, then you might want to consider a product that is made only by one process. You need to look at everything, not just one aspect.

DR. DOULL: And that would include, again, biology in that. The implication here is that now we are talking about formulation and you could make a minor change in formulation and that really wouldn't put that drug out of the low category back into the high category. Few of you, I am sure, will recall the Massengil situation. We had sulfonamide and we had propylene glycol and it worked like a charm. So, they simply changed the solvent over there

because it didn't dissolve very well in propylene glycol and they put it in ethylene glycol. Well, it made a huge difference. If you were just paying attention to the chemistry, solubility and what-have-you, you would never have really much worried about that change, and a lot of people didn't until we started poisoning people.

So, you know, even though you are manipulating the formulation and the chemistry you do need to keep track of the biology because if you don't we are going to have another Massengil.

DR. HOLLENBECK: Well, I think that is an extreme example.

DR. DOULL: True.

DR. HOLLENBECK: We are not talking about changing the components of a product here; we are talking about manufacturing changes. So, anything related to that would be a relatively small change in composition maybe, certainly nothing as dramatic as that.

DR. DOULL: True, but the implication of this is that we can focus on the chemistry and that the chemistry and biology pathways diverge, and what I am saying is they need to keep talking to each other and not diverge in order to protect the patient.

DR. HOLLENBECK: I wouldn't disagree with that, but I think the focus here is on things that have already

jumped through all those hurdles, and we are talking, from my perspective in many cases, about relatively minor changes in manufacturing that now consume a lot of the agency's time.

DR. DOULL: True.

DR. HOLLENBECK: If I could respond to your question in 3b and verbalize my head nodding, I think if you reverse those things -- what are the criteria for defining a robust process, one of them might be that you are able to make it by multiple processes and still have an effective formulation, and Judy identified some others, as did Leon. So, there are, indeed, multiple criteria that you could use to help give you confidence that you have a robust process.

DR. RODRIGUEZ-HORNEDO: First, regarding the formulation and the discussion between both of you, I think that sometimes it is my understanding that there could be a formulation change if there is a processing change. So, just an example presented here, manufacturing change between wet granulation and recompression so that sequence might be slightly different --

DR. HOLLENBECK: But those would be major changes that would not fall under this kind of a process.

DR. CHIU: No, change of composition components, under FDAMA by law, means prior approval supplement.

DR. RODRIGUEZ-HORNEDO: But then the specific

question 3b, I think that even taking wet regulation as an example, even with that process you can have so many variables within that process that could be vulnerable to the quality of the final product. So, it highly depends on the properties of the active product ingredient. I think robustness of a process -- it is not only the endpoint that we can reproduce; it is sometimes having control -- what are the variables that are the most important, whether we have an issue of polymorphism or solvent formation, for instance, or endpoint if we have spray drying, for instance. Monitoring the events in some specific processes, not for all but for some I think shows what the range is, for instance or rate of weight change in spray drying operations. So, some process may be more vulnerable and I think we need to be cognizant about that.

DR. LAMBORN: As I look at these questions, I think that probably we have addressed the others in part as we were discussing the drug substance. So, perhaps I would ask first if any members of the committee think we have something that we have missed in terms of giving comments. Dr. Chiu, do you have any particular pieces of this also, since you all put together these questions, that you think that we have not addressed?

DR. CHIU: Yes, I think maybe we need to come back to the drug substance and how to define well characterized.

We have had internal debates on whether we should just use molecule weight cut-off. You know, big molecules are difficult to characterize. Or, whether we should look at physical or chemical analysis, you know. That would be helpful.

DR. LAMBORN: Can I ask someone.

DR. ANDERSON: What did you say about big molecules?

DR. CHIU: You know, simple organic compounds usually are 400 and 500 molecular weight and usually they have simpler structures so, they are easy to characterize and you know definitively by just a simple IR test what you have. But when you get to a molecule like taxol, it is so big, so huge, and then how do you know? How can you say such a molecule could be considered well characterized? You know, if you make polypeptides which may have 15, 16 amino acids and tertiary structure, can we say those molecules are well characterized?

DR. ANDERSON: I don't think so. Are you really going to start with those complex molecules like that? It might be wise to look at something simpler where you have more information, where you can get a decent elemental analysis, a decent IR, a decent NMR and those kinds of things because, you know, I have some questions about a lot of those structures that they claim they have determined.

You know, you might not want to deal with those big molecules, at least not initially.

DR. BORING: We had also discussed about whether or not it should be only single molecules. Should all mixtures be excluded? Also, if you have an analytic method that is specific to the drug substance only, say a size exclusion chromatography or something that is specific, should those not be on this list?

DR. ANDERSON: Normally, when you characterize a compound the assumption is that the compound is pure. Now, if it is a mixture you really can't characterize it because you are characterizing one or more things and you really don't know what you have. So, it seems to me that you would want to exclude things which are mixtures if they haven't been purified because, otherwise, the structural data really don't mean anything.

DR. HOLLENBECK: I was just going to agree with that comment. Those would certainly be the more difficult ones. Unless I am mistaken, there is this concept of the well-characterized biological, and I know that you really aren't talking about biologicals here but certainly that portfolio of analytical tools used to characterize biologicals might give you the kind of confidence that you want here.

DR. CHIU: Well, several years ago we coined the

term well-characterized biotechnology products. However, down the line we actually stayed away from that word, well-characterized and we changed the word to specific biotechnological products. Since we restrict our products to synthetic products, most of them are not mixtures. Mixtures tend to be fermentation products or natural products. But even though we restricted to synthetic products, there a small molecules and medium sized and big molecules. Is the size a good criterion to use, or should we actually really base it on the capability of analytical methodology to characterize the molecule?

DR. BLOOM: The analytical methodology, would we use it according to the molecular weight? For example, if we have a 400 molecular weight compound that could be analyzed by GCMS which would give you structural information and you wanted to use proteins and you wanted to characterize it you could use NMR or you could use tandem mass spectrometry that could give you a sequence, and then you could use x-ray crystallography for tertiary structure maybe. So, it is depending on the molecular compound and the physical properties of it in terms of the analytical methodology that you could use. But, I think you should use more than one analytical method to characterize, as you say, a compound. It all depends on the characteristics of the compound per se.

DR. DOULL: Almost every script I write is for a mixture. Rarely do I administer pure drugs. Even, you know, in the pill that has the excipients and all the binders and what-have-you in there, it is in a mixture and you assume that there are no synergistic or antagonistic effects from all those ingredients in there, but you are also assuming that you can manipulate those to a certain extent without influencing significantly the effect of the active ingredient, and I guess that is where my concern would be. Mixtures are not unique. We deal with that. You know, it is in air, water, drugs, food -- everything is a mixture; virtually nothing is pure chemical in the way we use it.

DR. LACHMAN: I think an example of that is parenteral nutrition that is in large-volume parenterals that are mixtures of amino acids, vitamins, proteins.

DR. CHIU: Yes, we used to talk about multiple vitamins. Each one is made as a pure, single substance. Then they are combined together and become a mixture. Here, we are talking about each substance that is well characterized.

DR. LAMBORN: Other thoughts? Comments?

[No response]

We have just a few minutes and since we do, I would like to ask if there is anybody in the audience who

has a burning point that they want to make. If they wish to, we do have a couple of microphones. If you do, I would ask you to identify yourself and to speak briefly.

[No response]

Then, I think that we are ready to adjourn. We will reconvene promptly at one o'clock. We do have at least one presentation for the open public hearing. For the committee members, if you have not find it, since I didn't find it, we are meeting in room 2033 for lunch.

[Whereupon, at 11:45 a.m., the proceedings were adjourned for lunch, to reconvene at 1:00 p.m.]

A F T E R N O O N S E S S I O N

DR. LAMBORN: We will start the afternoon session. We are going to change topics to the topic of the orally inhaled nasal drug products, and we will start with an open public hearing.

Orally Inhaled and Nasal Drug Products

Open Public Hearing

Overview of ITFG/IPAC-RS Collaboration

DR. CUMMINGS: Good afternoon.

[Slide]

My name is Harris Cummings. I am with the Inhalation Division of Magellan Laboratories. I also site on the USP Aerosol Expert Committee.

I would like to start by thanking the advisory committee for giving us time to speak this afternoon. In my brief presentation, I am going to be introducing the collaborative work of two groups concerned about issues related to inhalation products.

[Slide]

These groups the Inhalation Technology Focus Group, which is a focus group of the American Association of pharmaceutical scientists and it is comprised of pharmaceutical scientists who seek to advance the science and technology and regulatory issues related to inhalation products. The second group involved is the International

Pharmaceutical Aerosol Consortium on Regulation and Science, which is an association of companies that develop and manufacture inhalation products for the treatment of both respiratory and non-respiratory diseases.

The work of the collaboration is to respond through a science-based and data-driven process to the three draft guidances which are shown here.

[Slide]

Both ITFG and IPAC-RS share the FDA's goal of assuring the highest levels of safety, efficacy and quality for orally inhaled products, and we also recognize the value of having the guidance documents to facilitate the development and approval of new medications. However, we believe that significant differences still remain concerning CMC and BA/BE issues in the draft guidances, and we believe certain sections of the guidances need modification. Finally, we are suggesting that additional meetings need to occur which can provide the opportunity to discuss these issues in depth in order to achieve the best possible guidelines.

[Slide]

I would like to give a brief overview of the completed work and also future commitments of the collaboration to addressing these issues.

Following the publication of the draft guidances,

ITFG and IPAC-RS independently and together submitted extensive written comments to the FDA. The collaboration then organized and implemented the current process of collecting and analyzing relevant data for both marketed products and products under development.

Members of the collaboration participated in the first OINDP subcommittee meeting in April of this year, and at that time committed to collecting data and preparing technical reports on the issues in the draft guidance.

It is the purpose of these technical reports to describe the conclusions reached based on the data that are collected, and to describe proposed modifications to the guidances which are based on these conclusions. Today, we have submitted four technical reports to the FDA, with several more to follow.

[Slide]

The organization of the collaboration is shown here. We have a steering committee with five technical teams, and the technical teams are organized around the CMC issues and the BA/BE issues.

[Slide]

The collaboration has certainly been a truly industry-wide effort, with over 100 individuals from more than 25 companies participating. The companies are listed here, and they include pharmaceutical companies, contract

organizations, academic institutions and component suppliers.

[Slide]

The technical teams are at different stages in their work. All have collected and analyzed data. As I mentioned earlier, four have submitted initial assessments to the agency. In the talks that follow mine, a member of each technical team will review the work of the team to date and give examples of issues related to the guidances which they believe warrant further discussion. They will also explain plans for future work.

[Slide]

We are asking the advisory committee today to support the continued scientific dialogue on these CMC and BA/BE issues before the draft guidances are finalized, and we ask you to support our request for meetings between the FDA and the ITFG/IPAC regarding the collaborations technical papers and data-based proposals to modify the draft guidances.

[Slide]

In summary, ITFG and IPAC-RS recognize and appreciate the agency's efforts in issuing the draft guidances and the agency's initial steps towards a scientific dialogue. We believe that a unique opportunity exists now to produce the best possible guidances for

inhaled products, and would welcome the chance to work with the FDA on achieving this goal.

I would like to again thank the advisory committee and the agency for considering our comments and proposals, and we are pleased to be able to participate in today's meeting and hope to be able to contribute in future meetings as well. Thank you very much.

DR. LAMBORN: It is my understanding we have a series of presentations. Will you just take yourselves through them?

BA/BE In Vitro and In Vivo Tests

DR. BORGSTROM: Good afternoon.

[Slide]

My name is Lars Borgstrom, and I am scientific adviser at AstraZeneca, and today I speak on behalf of the collaboration BA/BE group.

[Slide]

After the April 26 meeting of the OINDP system, the collaboration made two different commitments with regard to bioavailability and bioequivalence questions. We made a commitment to develop a position paper on the BA/BE question. We also made a commitment to respond to the questions raised by the FDA at the April 26 meeting. On August 30, the collaboration did submit these two technical papers to FDA.

The collaboration has developed two position statements, one on in vitro testing and one on in vivo testing. I would like to read them out as a philosophical background to our thinking.

[Slide]

In vitro testing is essential for pharmaceutical product equivalence and should be included as part of the BA/BE guidance for all nasal and oral inhalation products, but is not currently sufficient for determining BE without establishing in vivo BE.

On the in vivo side we have the following wording, for bioequivalence approval, BA/BE guidance documents for nasal and oral inhalation drug products for local action should require use of validated human models for in vivo testing for local and systemic exposure, efficacy and safety. This means that we have agreed that in vitro as well as in vivo testing is necessary.

[Slide]

Our assumptions that we have presented apply only to locally acting drugs. Our discussions include both nasally and orally inhaled drugs even though there is as yet no published guidance on orally inhaled drugs. An obvious comment is that this is an evolving scientific area and that the position statements reflect the current state of knowledge.

[Slide]

One of the findings on the in vitro side is that it cannot be generally stated that the in vitro tests are more relevant or discriminating than clinical studies for bioequivalence. It probably often is so, but the used in vitro method has to be validated with regard to the clinical outcome. If so done, in vitro analysis should be more discriminating as they tend to have a lower variability but also here exceptions do exist.

Similar reasoning can be applied to the assumption that for a nasal solution formulation in vitro studies should be sufficient to declare bioequivalence. It could be so, but the links between in vitro and clinical outcome are yet not strong enough to support such a general statement.

Finally, in certain cases a correlation has been shown between the in vitro outcome, lung deposition and clinical effect but these correlations are not strong enough to be predictive in a regulatory sense. Available information can be used in the pharmaceutical development work but not as a predictor for regulatory claims.

[Slide]

On the in vivo side, there is equivalence between the old and new drug formulation. A similar situation is at hand when a generic company makes a new formulation of an approved drug. None of the extent of the testing

requirements should be negotiated with the agency.

[Slide]

During the discussion within the collaboration, we have often been caught in a Catch-22 situation. There is, of course, a need to establish validated links to be allowed to predict the clinical outcome from in vitro data, but to establish these links the company has to do a rather extensive program and, thus, there is not anymore the need for the links.

[Slide]

We would like to get an opportunity to meet with the agency to discuss our findings and we are, of course, also willing to address further questions that can be raised. Thank you for your attention.

Responses to Agency's BA/BE Questions Raised at OINDP Subcommittee Meeting

DR. HARRISON: Hi. Good afternoon.

[Slide]

I am Les Harrison. I am section head of clinical pharmacokinetics at 3M Pharmaceuticals. I am also co-chair of the BA/BE team, and I was an invited guest at the subcommittee meeting in April, representing BA/BE for the collaboration.

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Today, what I would like to summarize are the

responses that the BA/BE team prepared in answer to the agency's questions that were proposed during the subcommittee meeting.

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To answer the questions, what we did, we formed small working groups for members of the BA/BE team and also from other experts within the collaboration. We used the scientific data that we could find. We used the literature and also company experiences to prepare our answers. The answers were reviewed by the entire BA/BE team, and we had to reach consensus for all answers. This process took several months and we submitted to the agency a report at the end of August.

[Slide]

In general, what we found as an overview is that the FDA, indeed, raised some difficult technical issues during the April 26 meeting, and it is our opinion that most of these issues are still open. What we were able to do is provide additional scientific substantiation for many of the subcommittee's answers. In add, we were able to provide responses where the subcommittee's answers were limited. So, going forward, what we really need is more opportunities to digest what we have found and to continue to address these difficult questions. We appreciate the pas opportunities we have had to really dialogue with the

agency, and we hope that this continues.

[Slide]

What I would like to do now is really walk through what our responses were to the questions that were raised by the agency, and they were divided really into two main areas, in vitro and in vivo.

Looking first at in vitro, one focus was profile analysis, and the question was should all stages of the cascade impactor be examined for BA/BE, and we agreed with the subcommittee and the answer there was yes for us.

[Slide]

The second question under profile analysis was should a statistical approach be used and, if so, how about chi-square? We agreed with the subcommittee that, yes, a statistical approach should be used and chi-square may be an appropriate metric but further assessment is needed. And, this is a position where we could help as a collaboration because we have many real data sets within our members that could be used here. In fact, we are attempting to get clarification from the agency that this effort would be useful before we actually undertake this new and probably large effort.

[Slide]

The next question in the in vitro area focused on DPIs. Here, we were very fortunate. Within the

collaboration we have really the key DPI manufacturers and we could bring a lot of technical expertise to answer this question as well.

The first part of the question was what design features would be needed for determining pharmaceutical equivalence. Our as was fairly general here, pretty much all the formulation and device elements would be needed.

[Slide]

The second part of this question though allowed us to get a lot more specific in terms of listing what type of tests would be needed. I draw your attention to the second bullet where we did actually customize some of these requirements to the uniqueness of DPI. Here, we are saying, in the second bullet, that particle size distribution certainly should be measured across a range of airflows and a realistic range of temperatures and humidities.

[Slide]

In the in vivo area, the question we are focusing on is, first, local delivery of nasal aerosols -- local delivery really meaning local efficacy. The first question was what about the clinical designs that were presented? Are they reasonable for BA/BE and are there alternatives?

We agreed with the subcommittee here that really the proposed guidances for the clinical tests were reasonable and that the traditional treatment study probably

is still the most appropriate design. However, a real key here is that the statistical requirements need to be discussed in an open forum so that we can really better evaluate these type of tests.

[Slide]

The second question for nasal delivery was if you can establish bioequivalence for SAR, SAR standing for seasonal allergic rhinitis, can you get bioequivalence transferred for other indications?

Here, the subcommittee did not really answer that question, but what we came up with was an answer that, yes, we thought that you could be able to transfer indications once you establish BE for the SAR, at least in adults.

The second bullet certainly says that in children you need to be more cautious and you need to assess if the safety can be transferred as well.

[Slide]

Also in the in vivo area, the next series of questions focused similarly to the nasal but now for steroids, and they asked again what type of testing is there for steroids and are there alternatives.

[Slide]

Our answers there again were pretty much in agreement with the subcommittee. We thought that a comparative dose-response trial with pulmonary function

measurements is still the standard and still reasonable, but we do also recognize that the variability for this trial is large and the metrics really are not that sensitive. Just like for the nasal area, what is really needed here is some type of statistical input to help us really sort this out. Here, again, the collaboration could help. A number of our member companies have done comparative clinical studies on steroids which could be useful if there were an open forum where this could be discussed to get at the appropriate statistical requirements.

[Slide]

To answer the question about other biomarkers, it is our feeling that really there are none that have been established thus far that can be used. However, we were very intrigued by the crossover design that was suggested by Ahrens during the April 26 subcommittee meeting, and that actually has the potential of fulfilling what we are looking for in this area but it is premature to really accept it at this point in time.

[Slide]

The last question focused on PK issues and asked the question if you can show in vitro documentation as well as PK documentation establishing bioequivalence, is that sufficient?

Here, the subcommittee seemed to lean toward

answering no, and what we said was, yes, there could be situations where in vitro data plus PK may be relied on. The requirement there is that PK there would somehow have to be shown to be a surrogate marker for the clinical efficacy documentation, and we do admit that no drug at this point in time can do it.

We went further as well and said that if you can show in vitro and in vivo correlation for safety and efficacy, it may be even possible to waive all clinical studies.

[Slide]

In summary, the number of questions posed by the FDA on the guidance have underscored a number of open issues, and we feel that most of those issues are still open, and the BA/BE team collected a substantial body of information that, hopefully, bears on some of these issues, and what we would like to do is encourage that examination continues, utilizing existing avenues and we can have the OINDP subcommittee consider them, go through PQRI. We can have another broad workshop. Dialogue between the collaboration and the FDA is certainly welcome. And, there is also the possibility of federal research grants. We would love to see the studies that we talked about of Ahrens for steroids funded and actually taken to fruition. We hope that the agency and, indeed, this advisory committee is

receptive to our comments and continues to dialogue with the public before finalizing the current draft guidance or issuing further guidances. Thank you.

ITFG/IPAC-RS Technical Team CMC Specifications

DR. Olsson: Good afternoon.

[Slide]

My name is Bo Olsson. I am formerly scientific adviser at AstraZeneca. Now I am with Microdrug Development. I am a member of the aerosol expert committee of both the United States and the European Pharmacopeia. I speak here today on behalf of the CMC specifications team of the collaboration. In this team we have focused on dose content uniformity and particle size distribution specifications.

[Slide]

At the OINDP subcommittee meeting this spring, our team posed the hypothesis that the current state of OINDP technology may not allow general compliance with the dose content uniformity specifications in the draft FDA CMC guidances.

At the same meeting, the agency raised the question if there should be a single content uniformity standard for all orally inhaled and nasal drug products. They also posed the question if FDA should continue development of the proposed statistical approach to

evaluating content uniformity.

Our approach in addressing these questions is to collect the worldwide database to investigate the actual dose content uniformity capabilities and appropriate statistical approaches.

[Slide]

We have now collected data and this unique database comprises a total of 46,000 observations for 77 products originating from 10 companies. So, it is truly a multi-company effort. These products are on the market or in late development, meaning from Phase IIB, Phase III or NDA stage.

Our initial assessment of the data was submitted to the FDA this summer, and it is now available on the FDA web site.

We have further developed and submitted a plan for continued analysis of the database, which we will discuss with the agency on Monday next week.

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From the initial assessment, we found that for the key requirement in the draft guidances, namely that no observations may be outside 75-125 percent of the label claim, most products do not comply; 68 percent of the products in the main analysis show results outside these limits. Yet, the grand mean dose in the database is at 100

percent of labeled claim.

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From this, we conclude that our hypothesis that orally inhaled products are not generally in compliance with the draft guidances is supported by data. Additionally, the database shows a relatively large difference between products and also between product types, suggesting that a single one size fits all specifications is unsuitable.

[Slide]

To follow-up the initial assessment, we intend to continue with a more thorough investigation, specifically on the compliance with the more complex criteria in the guidance system we have done so far, and we will also investigate the interesting approach taken by ICH for dose content uniformity, and we will try to assist in the development of Dr. Hauck's approach of statistical hypothesis testing to dose content uniformity.

[Slide]

Turning now to particle size distribution, we have committed to examine the relevancy of the mass balance requirement as a product specification versus as a system suitability requirement, and also to investigate if fewer than 3-4 stage groupings can provide equivalent control.

Again, our approach has been to collect the worldwide database to investigate actual PSD capabilities.

[Slide]

This database comprises a total of over 3600 individual particle size distributions from 35 products. Our initial assessment of the data was submitted to the agency and is also available on their web site. We are now developing a plan for further analysis of the PSD database.

[Slide]

The draft guidance mass balance requirement is that the total mass of drug collected on all stages should be within 85-115 percent of the labeled claim. The key finding from the database is that only 4 of the 35 products showed no results outside 85-115 percent. The median product had 5 percent of the observations outside these limits.

[Slide]

From this, we conclude that products do not in general comply with the proposed mass balance requirement, and that, therefore, the proposed requirement is not suitable as a drug product specification but it could well be appropriate as a system suitability requirement with limits defined on a case by case basis.

[Slide]

To follow-up the initial assessment, we would continue the analysis of the PSD database to investigate further the relevance of the mass balance criterion, and to

compare different metrics and sets of criteria for characterizing protein size distribution of OINDPs. We are, of course, willing to meet and discuss with the agency.

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In conclusion, we feel that many unresolved issues surround CMC specifications for DCU and PSD. To address these issues, our team has collected and is analyzing DCU and PSD data. We strongly encourage continued discussions by all interested parties before CMC draft guidances are finalized. It is our firm view that developing statistically sound specifications based on real data is essential to creating a scientifically credible program of product quality control. Thank you for your attention.

CMC Tests and Methods

DR. EVANS: Good afternoon. My name is Carole Evans. I am here to present the work of the tests and methods team

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The team's objective in its work has been to assist the agency in developing CMC testing requirements that provide valuable information about product quality. We hope to do this by providing data-driven commentary on the testing requirements contained in the draft guidances.

[Slide]

I would like to start with some initial comments

on the draft guidances and general observations. Firstly, to clarify the requirements for each of the four dosage forms included in the draft guidances, the guidances should be further edited or separate guidances developed for each dosage form, thus making the testing requirements for each dosage form more readily understood.

Secondly, in some instances, the language in the guidances is ambiguous, and where we have addressed these they will be addressed by written comments not supported by data.

Finally, the need for certain tests should be driven by an evaluation of the data generated in dearly development.

[Slide]

We have reviewed the draft guidances and identified areas for comment. We started our work with the MDI test requirements. We have got work in progress on other dosage forms. But as the work for MDI is further along, I am going to focus on these today.

The team has developed position statements with respect to the tests listed here. These are the tests where we felt that the consensus industry viewpoint diverges from that of the agency. In particular, we focused on those areas where we are able to generate data to test our position statements. We believe that by conducting this

data-driven commentary we can make a commentary of a different flavor to those already submitted earlier this year.

[Slide]

This slide summarizes the processes that we have used for each of these tests. For some tests water, spray pattern, plume geometry, shot weight, and for the requirement to control temperature and humidity in particle size distribution we are in the process of collecting and analyzing data to test our position statements for these tests.

For further tests we have simply drafted comments on the requirements for MDIs, such as those for impurities and degradation products where we are simply requesting an alignment with ICH requirements, or for dose content uniformity where we have suggested alternate wording that we think is clearer. Finally, we have collected data from the scientific literature with respect to particle size distribution methodologies and pressure testing for single propellant and co-solvent mixture formulations.

[Slide]

We are currently in the midst of analyzing our data on MDIs but do have some preliminary findings to bring to you today. We have collected data for many products and have shown so far that tests for spray pattern, water

content and shot weight often don't provide meaningful information about product performance. For example, the guidance requires that spray pattern testing be performed to evaluate proper performance of valves and actuators, and the data to date does not indicate a correlation between the parameters of the devices and spray patterns gathered.

Further, there is a wide body of literature that lends support to the use of validated and alternate methods for particle size distribution and we will be submitting a paper outlining those.

Finally, the literature suggests that for single propellant and co-solvent mixtures the pressure testing is outcomes a sensitive approach for determining the appropriate ratios present. We feel that the integrity of the propellant alcohol mixture is better controlled by direct analysis of the alcohol content.

[Slide]

As I said, we are still in the process of analyzing our data. With respect to MDIs, we will be submitting technical papers containing our conclusions and recommendations to the agency, and the expected date is December of this year.

We are continuing with other dosage forms and will, early next year, collect data and analyze data with respect to those other dosage forms. Like the other teams

who are presenting here today, we would welcome the opportunity to meet with the agency to discuss our findings and data, and to try and work with the agency to address any other questions raised. Thank you.

CMC Leachables and Extractables and

CMC Supplier Quality Control

MR. HANSEN: Good afternoon.

[Slide]

I am Gordon Hansen. I am associate director of preclinical analysis at Boehringer Ingelheim Pharmaceuticals.

[Slide]

Today I will be reporting on the work of two technical teams, the leachables and extractables team and the supplier quality control team. Both of these teams are comprised of scientists from pharmaceutical companies and component suppliers with broad experience in the characterization of leachables and extractables. The team supports the agency's activities in developing the draft guidances and recognizes and supports the need for clearly stated and scientifically sound requirements with respect to leachables and extractables in inhalation products.

The team believes, however, that these guidances could benefit from additional study and dialogue. The team is committed to working with the agency and the subcommittee

to discuss these topics in detail.

[Slide]

After careful review, the team has identified key issues which we believe could be strengthened by the add of more detailed and clarifying language. For example, what are appropriate reporting and identification thresholds for leachables and extractables? How is a correlation between leachables and extractables established? What are appropriate practices for establishing safety of leachables? Is extractables profiling appropriate for control of component composition, and which critical components should be subject to routine extractables testing?

In looking at just one of these issues in more detail, currently the issue of reporting levels for extractables and leachables is not well defined and is currently substantially more stringent than is outlined in ICH Q3B. Is 1 mcg per canister sufficient, or are detection limits required that are lower than that? The situation at present appears to be driven by advances in scientific technology rather than pharmaceutical science.

The following steps have been taken by the team in order to investigate these issues in more detail: The team has collected drug product specific leachables and extractables data in order to investigate the concept of correlation. The team has also formed a toxicology working

group to address toxicology issues for leachables. The team has investigated current supplier practices for the control of component composition and extractables profiles.

[Slide]

Similarly, the tox team has reviewed the current industry practices for establishing the safety of leachables and is drafting a strategy for incorporation into the team's "points to consider" document which will be submitted later this year.

The tox team is investigating current practices for establishing the safety of leachables, and looking forward as to what industry requirements should be for the safety evaluation of leachables.

[Slide]

After the analysis of the available data, the leachables and extractables team has developed the following key points for the agency's consideration. These will be included in the "points to consider" document to be submitted to the agency by the end of the year.

These points are as follows: A leachables study should be a one-time development study and not a routine requirement. Secondly, a correlation is established between leachables and extractables when each leachable can be linked qualitatively to a corresponding extractable. Once a correlation is established, leachables are controlled

through the routine extractables testing of critical components which contact the formulation or the patient's mouth or nasal mucosa. Finally, the team strongly recommends that a process be developed for establishing reporting, identification and qualification thresholds for leachables.

[Slide]

The toxicology evaluation proposal consists of adding a separate section to each guidance to describe the toxicology evaluation process, including a flowchart.

Toxicological qualification should be performed only on leachables, and only on those leachables that occur above a data-supported threshold.

The guidelines should also distinguish between genotoxic and non-genotoxic leachables.

The issue of testing USP 87 and 88, these tests do have utility for extractables testing, particularly for component suppliers, however, for a pulmonary product, where there may be a substantial body of data, these tests may not have added value when the entire package is considered.

[Slide]

The team's next steps will be, first, to submit the "points to consider" by the end of this year. We will request the opportunity to meet with the agency to discuss team findings and consider appropriate strategy for how

toxicology thresholds can be established. In collaboration with the supplier quality control technical team, we will propose a control strategy which includes appropriate testing criteria for ensuring relevant performance and safety characteristics of critical components. As the other teams presenting today, this team is willing to address further issues and welcomes further dialogue with the agency.

[Slide]

At this time, I would just like to take a last minute or two to describe the work of the supplier QC team which reported its findings during the April 26 meeting of the OINDP subcommittee.

This team investigated the question what is the current status of compliance in the component supplier industry? This team conducted a survey of component suppliers in order to evaluate the quality and compliance practices at all stages of not only component but excipient, raw materials and active drug substance manufacture.

Findings of this team were that there, indeed, are no generally accepted guidelines for the components supply chains but, in fact, IPEC has developed GMP guidelines for the manufacture and compliance of excipient manufacture. Indeed, this team has endorsed the more widespread adoption of the IPEC guidelines. This team is eagerly awaiting

comment and guidance, and in consultation with FDA and the identification of the proper venue, would like to collaborate in the development of cGMPs for component suppliers. A formal report summarizing these findings will be submitted to the agency by the end of the year. Thank you.

Concluding Remarks

DR. FLYNN: Good afternoon.

[Slide]

My name is Cyndy Flynn, and I am the director of pharmaceutical sciences at Aventis.

[Slide]

I would like to take this opportunity to recap some of the highlights of the previous presentations that you have just heard. The collaboration is composed of more than 100 pharmaceutical scientists who represent more than 25 companies and institutions who have been working to address the key concerns in the draft CMC and BA/BE guidances.

This collaboration is committed to collecting and assessing all relevant data, and sharing these findings in a very timely fashion with the agency. The collaboration anticipates that these data-based conclusions and proposals will be useful to the agency in its preparation of the final CMC and BA/BE guidances, and that this will ultimately

benefit both patients and the pharmaceutical industry.

[Slide]

Based upon the data that has been collected and analyzed to date, the technical teams have concluded that certain aspects of these draft guidelines need to be revised. As described in the earlier presentations by my colleagues, the technical teams have prepared or are in the process of preparing specific data-based proposals for modifying the draft guidances.

[Slide]

This slide is a summary of the technical papers which have been prepared and submitted to date. Two papers have been submitted in the summertime by the specifications team; two papers by the BA/BE team, in the summertime also, have been submitted; and the tests and methods team is in the process of getting ready to submit a paper concerning MDIs, in the month of December; and the leachables and extractables team will also be submitting a technical paper in December.

[Slide]

This slide is a summary of the numerous CMC and BA/BE issues which have been presented to you today, which remain of great concern to the collaboration.

What needs to be highlighted here is that the collaboration sees that the majority of the issues revolve

around CMC issues, not necessarily only around BA/BE issues, although these are also very important to the collaboration.

[Slide]

We believe that it is of utmost importance that the collaboration's data-based conclusions and proposals for modifying the draft guidances be given full consideration before these guidances are finalized. As was mentioned in the morning session by Dr. Toby Massa on another topic, it has been found by industry that it is far more productive and efficient to have the comments of industry incorporated prior to finalization of these guidances rather than afterwards.

Hopefully, we have been able to demonstrate to you that these issues are of a very complex nature and that they have generated a huge industry response, and this has been demonstrated by the attendance levels at the June, '99 AAPS meeting as well as at the April 26 subcommittee meeting where we had a packed house.

In addition, at least 20 comment letters have been received concerning these guidance documents which comprise hundreds of pages of comments. In addition, there has also been this massive effort on the part of the collaboration to try and address these issues.

[Slide]

The collaboration, therefore, strongly recommends

that the agency continue to work towards resolving these very important CMC and BA/BE issues by utilizing all available existing avenues for in-depth interactive and scientific dialogues. Some of these are listed on this slide that could potentially be used, and I am sure there are many others. We feel that such dialogues will ensure that the guidances bring maximum value to regulators, industry and, most importantly, to the patients and physicians.

[Slide]

We would also respectfully request that the Advisory Committee for Pharmaceutical Science support the need for continuing scientific dialogue on these very important issues before these draft guidances are finalized. We would also request that the committee endorse our request that opportunities be found for continued dialogue between the FDA and the collaboration concerning the very unique and valuable inter-company databases we have been able to collect to date.

[Slide]

Finally on behalf of my colleagues, I would like to express our gratitude to the agency for holding this meeting. We very much appreciate the opportunity to present our work, and we thank the agency and the committee for considering our comments and proposals. Thank you.

DR. LAMBORN: Thank you. A couple of points of clarification -- this may seem a little bit of a reverse order of the way things should be done because of the need to have the open public hearing at the time it was scheduled. The material that has been presented to this point has been part of the open public hearing. We do have a subcommittee report, which Dr. Adams is going to present.

The other thing is that ultimately the subcommittee will continue to bring items back to this committee, and this is, in a sense, the advisory body that will ultimately recommend to the FDA, not the subcommittee but clearly a subcommittee was needed to move this forward.

Subcommittee Report

DR. POOCHIKIAN: Good afternoon.

[Slide]

My name is Guriag Poochikian. I am the chair of the OINDP CMC working group. I am also a member of the USP expert aerosol committee.

In April of this year, the OINDP subcommittee of this advisory committee met under the leadership of Dr. Vincent Lee, who is the chairman and professor at USC. Unfortunately, Dr. Lee is not able to make it today so I will try to summarize briefly and report the main discussion points. My intent today is to be a messenger only. I am not an advocate of any position today.

Dr. Eric Sheinin, Deputy Director of OPS, after introducing the topic on April 26 of this year, outlined the responsibilities for the subcommittee as follows: To address and discuss the two questions related to the content uniformity of OINDP, and present the findings to the Advisory Committee for Pharmaceutical Science, and that is what I am doing today.

[Slide]

As an outline, I will give a very brief background, raise the questions and also summarize the comments.

[Slide]

Almost two years ago the agency published these two guidances. The first one refers to MDIs and DPIs. As the name indicates, it refers to non-aqueous preparations from the CMC perspective. The second one addresses other nasal inhalation products which are necessarily aqueous based.

Now, the content of these guidances is based upon experiences and issues that have been dealt with during the development and review of numerous and different types of applications, particularly in the last decade.

In summary, these guidances organize the information acquired in a manner which is equally accessible to all interested parties. Thus, they do delineate the

current NDA practices.

[Slide]

A number of activities took place since the publication of these guidances. There were public comments periods for both guidances and we received numerous comments which are under evaluation. A workshop was sponsored by AAPS, FDA and USP a year ago. The three expert panels met in November of '99, followed by the subcommittee meeting in April of this year and now we are at the advisory committee of OPS.

[Slide]

To ensure the OINDP quality in terms of dose uniformity, the dose content uniformity issues need to be addressed, in our view, from at least two perspectives. First, dose uniformity among units from container to container within a batch and, second, dose to dose uniformity within a container. The second part, of course, relates to device metered situations.

[Slide]

The first question that was raised to the subcommittee is should there be a single content uniformity standard for all orally inhaled and nasal drug products, OINDPs?

[Slide]

Here, I would like to summarize the major points.

First, that there are needed, before this question can be answered, a single content uniformity standard would be desirable. Others -- in the last decade, drug products that were approved met FDA guidance criteria. Multiple standards may be the best approach. That is another comment. Existing drug products may be grandfathered until phase-out, especially when we are dealing with the CFC products which are going to be phased out. Other comments -- that content uniformity should be considered in the context of in vitro and in vivo assessments. And, the last comment came from clinicians that lack of standardization would be unfair to clinicians and to the public.

[Slide]

The next second question, should FDA continue development of the proposed statistical approach to evaluating content uniformity?

[Slide]

This particular statistical proposal was presented by Walter Hauck, who is a professor of medicine at Thomas Jefferson University in Philadelphia, Pennsylvania. He is also a member of the OINDP subcommittee. Unfortunately, he is not here and that is why I am doing this to the best of my abilities. I am not a statistician. Therefore, I do not feel that I am in a position to provide detailed information on his proposal.

However, in a nutshell, his proposed approach is tolerance interval approach in which the regulatory agency specifies three points. First, it specifies the maximum allowed false-positive rate. That is the consumer risk, like for example, five percent. Or, the degree of confidence needed. That would be 95 percent. Second, specifies the minimum coverage probability. That is, the minimum proportion of the batch that should be covered, for example, 90 percent of the units in a batch would meet that criteria. Third, specifies the target interval, or the target limit. For example, 85-115 percent.

If you put all this together, his statement says it needs to be demonstrated that with consumer risk of five percent in this example and that at least 90 percent of the batch, again as an example, will fall, for example, within 85-115 percent of the labeled claim.

On the other hand, the sponsor, under his proposal, will determine the sample size and also will determine the number of tiers to attain this desired level of the false-negative rate. That is, the probability that a good batch does not pass.

[Slide]

Having said that, the comments from the subcommittee were as follows: Yes, FDA should continue development of the proposed statistical approach by Dr.

Hauck. Data from existing products would enable the parametric statistical approach to move forward. Other statistical approaches may be considered. So in a nutshell, with Dr. Hauck's statistical approach, the agency sets the allowable consumer risk while the producer determines its own risk. Thank you.

DR. ADAMS: Dr. Lamborn, members of the advisory committee, FDA colleagues, ladies and gentlemen, good afternoon. I am pleased to be here.

[Slide]

My name is Wallace Adams. I am in the Office of Pharmaceutical Science, working on guidances for bioavailability and bioequivalence for nasal drug products and for orally inhaled drug products.

[Slide]

The slide indicates that in June of 1999 the agency issued a draft guidance for nasal aerosols and nasal sprays bioavailability and bioequivalence, and that under development is an additional guidance for orally inhaled drug product MDIs, DPIs and inhalation solutions.

[Slide]

We took issues with regard to both CMC and with regard to BA/BE to the OINDP system commenting in April of this year. The main BA/BE issues are summarized in these two bullets -- approach to developing a single test for

comparative particle size distribution, that is, a profile analysis based on the cascade impactor; approaches to bioequivalence in the presence of relative insensitivity of rhinitis and asthma studies to dose response; and consideration of in vitro and PK study of systemic exposure to assure equivalent local drug delivery.

You can see from these bullet points that the main issues that we took to the OINDP subcommittee were with regard to bioequivalence issues and comparability rather than with regard to bioavailability. [Slide]

First, I would like to go over the in vitro BA/BE questions. As Dr. Poochikian has indicated, my presentation is going to be a summary of the outcome of that subcommittee meeting. I am simply going to go through the questions. These are the same questions that Dr. Harrison had indicated earlier, and bullet points that appear in the official minutes to that meeting.

[Slide]

In the case of profile analysis the question was asked, should all stages, including the inlet, throat, of the cascade impactor be considered in the comparison of test and reference products?

[Slide]

Just to illustrate the point, I took a slide from the literature on beclomethasone, and what this slide shows

is that for two different products the impact cascade impactor profile with deposition on the various stages of the Anderson cascade impactor and in the throat, the actuator and the stem. You can see that it is plotting for each of the sites, each of the stages and auxiliary sites. It is plotting the amount of drug deposit on that stage.

The question for bioequivalence in in vitro studies is if there were a test on reference products, given two profiles, how do we determine whether these products are, in fact, the same in their cascade impactor profile or not? We have decided that profile is appropriate in that if we used a statistical comparison for each and every stage -- is the amount of the drug deposited on stage zero, for instance, the same between test and reference; the amount on stage one, and so on. There would be eight or ten individual statistical tests simply on cascade impactor data alone, and there are other tests that we are asking for.

So, we felt that a profile analysis is essential and the question then is how to assess that profile. Incidentally, this is not the type of profile that we would see for an ANDA. This is two very different products. This is an HFA-BDP versus a CFC-BDP product. They are two very different products and the profiles, accordingly, look very different.

One of the questions that we asked the

subcommittee was, should we be concentrating on a profile based upon the drug on all stages and auxiliary sites, or should it just be based upon a subset of those sites, thinking that for instance in terms of the respirable drugs, generally considered to be below five microns, perhaps that comparison should be based on the stages below five microns. But, there were concerns that the subcommittee raised.

So, going back to the question, should all the stages, including the inlet of the cascade impactor, be considered in a comparison of test and reference products?

[Slide]

The answer was yes by the subcommittee. The data are used comparatively to bioequivalence. The relationship of drug deposition on specific stages to safety and efficacy is not known, therefore, all stages and inlet should be considered. In other words, we know that the drug that gets into the lungs is going to be generally five microns and less, but the drug of coarser size is going to deposit it in the oropharynx and a lot of that will be swallowed and can be absorbed to the GI tract and contribute to safety issues. That is the gist of the response, that data on all the stages and sites should be compared.

[Slide]

The second part of that question, should a statistical approach rather than a qualitative comparison be

used for profile comparisons? If yes, does the chi-square comparative profile approach seem appropriate?

As Les Harrison had indicated earlier, yes, a statistical approach is preferred because it allows quantitation, and the subcommittee indicated that the chi-square approach is still in progress; it is premature to comment at this time.

[Slide]

Again, on in vitro another question, prior to doing in vivo studies to establish equivalence of a test dry powder inhaler product -- now turning specifically to DPIs -- a firm would need to design its product to have the best likelihood of being found equivalent in these in vivo studies.

This, incidentally, is an issue that at least in the Office of Generic Drugs we have not faced yet in terms of an ANDA for a dry powder inhaler. So, our guidance is intending to include dry powder inhalers, as it was originally indicated. So, this question gets to what sort of in vitro tests would be used to compare two different dry powder inhalers: a) what design features of the device and formulation and what parameters should be considered in determining pharmaceutical equivalence?

[Slide]

Operating characteristics of equivalent devices

should be as similar as possible. Match the airflow resistance and the flow-rate dependence of drug delivery. The devices must be functionally similar. It would be helpful to know what flow rates patients actually generate with the test and reference devices.

[Slide]

What comparative in vitro tests should be conducted to help support bioequivalence? It was suggested by the system that peak flow rate at particular pressure drops; rate of rise in flow in cascade impactor; variability of the devices at multiple flow rates, which I think is really related to the first bullet; and, the last bullet, goalposts for the in vitro tests should be clinically relevant.

[Slide]

Turning now to the in vivo BA/BE questions to the subcommittee --

[Slide]

Clinical studies for local delivery of nasal aerosols and sprays, and we divided these questions into nasal aerosols and into the orally inhaled products. So, specifically for the nasal aerosols and sprays, the first question was three study designs have been proposed in the draft guidance for drugs intended to have local action: the traditional treatment study, which is a two-week study

design; a days in the park study; or an environmental exposure unit study. These study designs are based on seasonal allergic rhinitis.

[Slide]

I wanted to indicate before going further on this that in order to get a sense of the issue involved here with regard to dose response and clinical studies for rhinitis, that we are dealing with a fairly insensitive measure for clinical studies. This is a paper on mometasone furoate nasal spray, published in the literature back in 1997. What it shows is a reduction from the baseline in total nasal system score, which is the clinical measure used to compare the products. It shows the data for placebo, and notice that there is a substantial reduction from baseline in the placebo. In other words, these products have a very pronounced placebo effect. Then, the reduction from baseline at four different doses, 50, 100, 200 and 800 mcg.

Our draft guidance recommends that for establishing sensitivity in a rhinitis study a dose difference of either two- or four-fold be used to look at the changes in total nasal symptom scores. But, we can see that with a dose range of 50-200 mcg it goes from 6.1 up to 7 units reduction from baseline, something like a 15 percent change only over a 4-fold range. Furthermore, in this study a range from 50-800 mcg, a 16-fold range in dose, gave even

less than 15 percent change in response. So, over a very wide range there is a low sensitivity to dose differences using this clinical endpoint. Is that acceptable for establishing efficacy of test and reference products?

[Slide]

That goes back to the question we were asking, and specifically, is it feasible to demonstrate a dose response for locally acting nasal drugs? If not, what other approaches can be relied upon to establish equivalent local delivery? I would say that the dose-response study that I just showed from the literature is fairly representative of the nasal corticosteroids in terms of the magnitude of responses that are seen. If not, what other approaches can be relied upon to establish equivalent local delivery?

[Slide]

The responses from the subcommittee were that, yes, it is possible to show a dose response but this requires hundreds of subjects and, in fact, in these studies it is typical that each treatment arm would employ something on the order of about 100 subjects in a parallel study design.

Crossover approach is a problem for seasonal allergy due to the shortness of the allergy season. If you try to do a crossover study the level of allergens in the air would have changed by the time you got around to a

washout and doing the second crossover arm. So, that would be a problem. If a clinical study is nondiscriminating to dose, rather than relying only on in vitro studies, it was suggested a scintigraphy study could be considered. however, it was pointed out that for a multi-phase product, i.e., a suspension, it is difficult to make a labeled product that duplicates the marketed product. I think here what is being expressed is the concern that if technetium is added to the product is it, in fact, associated with the drug and not to the micella in the vehicle? So, it makes a point that that is a problem in terms of labeling of the product.

[Slide]

Furthermore, for in vitro tests the concern was that in using other testing as a means of establishing equivalence for the rhinitis drugs in vitro tests might be used, but they may be so discriminating but irrelevant that they would keep an equivalent product from the market.

Now, we have heard that from individuals in the past that, in fact, these in vitro tests are less variable than in vivo testing and, in fact, statistically significant differences may be seen between products on a particular in vitro test and that, yet, has no clinical relevance, but Dr. Hauck pointed out that a key requirement of a bioequivalence test is the ability to show differences. Setting an

appropriate goalpost can deal with a very discriminating test. If we have differences, simply set that goalpost of ours wider in order to accommodate those differences if they have no clinical relevance.

[Slide]

Plasma drug pharmacokinetics could reflect equivalent deposition, dissolution from the nasal suspension formulation, and local concentration. The study may need to involve charcoal block. So, this was a suggestion, that PK data in fact could be used to establish local delivery.

I would like to point out that what we are talking about here is PK data to establish local delivery, our guidance indicates for suspension type products that PK studies are preferred to establish equivalent systemic exposure. But that is more of a statement issue. In this slide, we are talking about possibly blocking absorption from the gut and using PK data as a means of establishing local delivery to sites of action. No consensus was reached on this question, however.

[Slide]

Nest question, can bioequivalence established based on seasonal allergic rhinitis assure bioequivalence for other indications such as recurrence of nasal polyps or other non-SAR conditions?

I would like to skip over this question because,

in fact, since issuance, in June of '99, of our guidance the Division of Pulmonary and Allergy Drug Products has issued an allergic rhinitis guidance which addresses the issue of comparability testing for changes in formulation or device to a product and, in fact, their recommendations would fit very nicely, I think, for the issue that we are talking about here. So, in the interest of time, I would like to skip that question. Well, I will read what the responses were: More data are needed, and no known correlation exists between SAR and non-seasonal allergic rhinitis.

[Slide]

A number of approaches have been proposed to assess bioequivalence of inhaled corticosteroids -- now switching from nasal to the inhaled corticosteroids -- a number of approaches have been proposed to assess bioequivalence of ICS, such as clinical trials, bronchoprovocation tests, the steroid reduction model, trials with surrogate measures such as exhaled nitric oxide, and other measures. Are any of these study designs proven to offer better discrimination in terms of dose-response sensitivity?

Again, the issue implicit here is that just as for the nasal steroids there is a very shallow dose response for, the inhaled corticosteroids there is a similar observation.

[Slide]

So the recommendations or comments were to perform the bioequivalence study at lower doses to avoid plateau of response. It was said that of questionable value were exhaled nitric oxide, which is not yet acceptable as a surrogate marker; beta agonist reversibility is a potential marker of response; FEV-1 and peak flow changes are small, and that represents a problem; changes with methacholine and histamine challenge cannot be differentiated, again a problem; and it was also suggested to select the right patients based upon entrance criteria.

[Slide]

Next question, what other in vivo approaches, e.g., surrogate markers, might be sufficiently sensitive and validated to establish in vivo BA and BE for inhaled corticosteroids? The point was raised again that eNO is not at this time accepted as a surrogate marker.

[Slide]

Now, PK or PD studies for systemic exposure of locally acting drugs -- question, are there situations where in vitro data plus systemic PK and systemic PD data can be relied upon to assure local drug delivery for either nasal or inhaled drugs?

Now, go back a few slides where I pointed out that, in fact, one of the earlier comments was that, yes,

there are situations if you possibly use charcoal block or if you had a drug that after oral dosing undergoes high first-pass effect so very little drug is getting into the gut PK data, in fact, may be useful under circumstances to establish local delivery.

When the question was asked in this way, the first bullet, the participants did not have situations that responded to the question. Second bullet, for orally inhaled products, the in vitro and PK assessments are important but not sufficient. Clinical studies for local delivery are needed.

[Slide]

It was stated that the clinical trial could be a bridging study rather than a full-scale study. And, when the nasal dose is increased to increase plasma drug levels for quantitation, the dose should remain within the therapeutic dose range for these drugs.

[Slide]

I would like to acknowledge the following individuals: Dr. Vincent Lee, who was the chairperson of the OIDP subcommittee back in April; the members and invited guests of the OINDP subcommittee; Nancy Chamberlin who also sits here today; and members of the FDA's OINDP technical committee; and the chair and invited guests of the subcommittee meeting back in April.

[Slide]

I know the slide is kind of hard to see, but this indicates the individuals who participated in that meeting.

[Slide]

And, the members of the agency's OINDP technical committee, these are the individuals that really carried the brunt of the development efforts for our draft guidance that has been issued so far. Lastly, I would like to acknowledge the efforts of Dr. Roger Williams who provided the initial impetus for the development of these BA/BE guidances. Thank you.

DR. LAMBORN: Thank you. As I understand it, we have now received a summary of where things stand to date and the major meeting that took place in April. What is the next step, and what is it that we can do to assist today?

DR. ADAMS: As an update of where things stand now, the various issues in this guidance are currently undergoing further consideration and revision based upon public comments that were received to the docket for the nasal BA/BE guidance, as well as discussions that we are having in the working groups. We are doing simulations in some cases, making revisions to the guidance. We have had a number of meetings of our working groups. So, I would say that the process is continuing at this time, Dr. Lamborn, in terms of refining this guidance. Some of the issues on

knottier than others are, more difficult than others are. So, it is a question of how do we feel that these can best be responded to.

In terms of what can the ACPS do to facilitate the process at this time, I would say first to simply be aware of our efforts as we work towards trying to put in place for the first time appropriate BA and BE, but mostly BE issues, approaches for which there are no easy answers. Looking back over a few years, it took us a number of years for albuterol MDI in terms of how to develop appropriate bioequivalence methodology for that, and we finally got there, and that would be reflected in the orally inhaled guidance that is under development. But those types of issues of sensitivity, endpoints, appropriate in vitro testing -- that is another thing that is undergoing revision now. We are looking at the host of in vitro tests that we have asked for in the draft guidance, and trying to refine that for which of those tests are the critical ones needed to establish equivalence of the products and which ones don't we need. So, this effort is continuing.

DR. LAMBORN: Well, I think we have finished the formal presentations for the first section of this afternoon. So, perhaps I could open up the committee to either comment or questions that you might have at this point.

DR. DOULL: Yes, I would like to ask Dr. Harrison or Dr. Adams who also talked about that, about the cascade impactor. You were asking about whether you should analyze all those data in the throat and you showed a slide which showed why that makes a difference. My question is why not just use the Lovelace -- you know, different kind of particle size analyzer rather than the Anderson cascade impactor, one that really gives you the whole spectrum without all the stages? I gather from Carole Evans' presentation that you are looking at alternative particle size analyzers and I guess the question is aren't there some things in there that would eliminate those kind of problems you are talking about with a cascade impactor?

DR. ADAMS: We are aware of the instrument you are talking about but the Anderson cascade impactor or other brands of cascade impactor are a critical element in our in vitro comparisons because that, in fact, measures aerodynamic particle size. Unlike, for instance, laser diffraction or some other instruments, what the cascade impactor does is to measure aerodynamic particle size which is considered to be the best representation for particles going into the lungs --

DR. DOULL: True, but the problem with it is it does it stage, by stage, by stage so that, you know, if it can get around the corner it makes it to the next stage.

What you need is something that isn't stage by stage but that is continuous deposition depending on the particle size mass and how far it travels. The Lovelace particle size analyzer does precisely that and, therefore, would not have that problem you are talking about with the stage thing.

I assume, because you do have activity, that it is going to look at alternative methodology for particle size and that that would be something that the subcommittee would get involved in.

I have one other question, and that has to do with Dr. Hansen's presentation. He gives some nice description about the tox qualifications to be used for leachates and so on, but he mentions in here the genotoxic and the non-genotoxic leachables. Everything else has a threshold, either implied or indicated, and I wonder if he is going to have a threshold for genotoxic leachables.

DR. HANSEN: No, there was not an intention to have a threshold for genotoxic leachables but for standard non-genotoxic leachables only.

DR. DOULL: That, of course, is a big issue in toxicology but there are some people, Gary Williams for example, who just published a paper in which he shows thresholds for four genotoxic -- four very potent genotoxic agents. So, you know, the argument that there might be thresholds for the genotoxics just like we have for all the

non-genotoxics is, I think, getting to the point where we should give that some consideration. It would facilitate what you are talking about for the tox protocol in here if, in fact, you had thresholds.

DR. VENITZ: I have a question about the progress as well, and I would like to compliment the industry for getting together and putting together a database that I am pretty sure is very valuable.

My question is for Dr. Adams. Wally, to what extent are you going to incorporate data-driven specifications?

DR. ADAMS: Dr. Venitz, data-driven in the sense of what, in vitro, in vivo correlation?

DR. VENITZ: In the sense that they are coming out right now from the database that the industry is analyzing, and they find that some of those specifications would basically fail 95 percent of their products. Is that going to be considered when you review or revise the current guidance?

DR. ADAMS: Are you referring to the CMC specifications?

DR. VENITZ: Yes. Are you going to answer this?

[Laughter]

DR. POOCHIKIAN: Thanks for the question. As I indicated on numerous occasions, most of our current

proposal, which is in the draft guidances are the result of approved applications. Does that answer the question?

DR. LAMBORN: So, you are saying that most approved products would, in fact, meet these specifications?

DR. POOCHIKIAN: That is what I am saying.

DR. LAMBORN: Thank you.

DR. BOEHLERT: I have a question then for the consortium people because you presented some data that said that 68 percent of all products show results outside one limit and, in another case, a very high number of products would not comply. Is that based on products that you all would feel are acceptable in the marketplace, or were there products in there perhaps that might be deemed unacceptable and should be outside the limits?

DR. LAMBORN: Would someone from the consortium care to respond to that?

DR. OLSSON: The products in the database are from all over the world so they include commercial products on the market in the U.S., commercial products in the rest of the world, and a lot of them are late development products. It is our opinion that these have been submitted to the database by ethical companies. So, we have no real fear that these do not represent the actual capabilities of the various technologies that they represent.

DR. LAMBORN: I think the question was not whether

somebody was fudging the data but simply whether or not these were approved products, and that these represented tests on approved products.

DR. BOEHLERT: Yes, exactly.

DR. OLSSON: And I repeat that a number of them are from approved products in the U.S., a number of them are from approved products in the rest of the world, and a number of them are products which are in the late development phase and which are intended to be approved.

DR. EVANS: Please correct me if I am wrong, but just to elaborate a little more, the figure presented earlier where we had a 68 percent failure rate based on any values being outside of plus/minus 25 percent, that was based on the database of 60 total products. Of those 60 total products, 6 were U.S. commercial products. Looking at the database, 4 out of those 6 would have failed that plus/minus 25 percent requirement. Does that clarify it for you?

DR. RODRIGUEZ-HORNEDO: I will follow-up that same theme, do you have any idea of how those limits correlate with the therapeutic outcomes? So, if the confidence limits should be widened, what are going to be out endpoints?

DR. OLSSON: That is an extremely complex question, as I am sure you know. First of all, because we are dealing here with a number of different molecules it

would be really surprising if you would have the same relation for different molecules. So, I think that in order to circumvent this extreme difficulty we are talking now not really about in vivo relevant measures but, rather, about achievable technical quality and the products are then validated by the clinical studies that are performed.

DR. LAMBORN: Other questions? Comments?

DR. BLOOM: In your presentation you comment that a single content uniformity specification is not suitable. Have you thought about measuring content uniformity according to the specific drug? Maybe I missed it but nobody addressed that content uniformity should be done or shouldn't be done in terms of a specific drug.

DR. POOCHIKIAN: Is this a question for us or for the panel?

DR. LAMBORN: I think you all should start.

DR. POOCHIKIAN: Okay. As I indicated in my presentation, there were different views. From a clinical perspective, the clinicians on the subcommittee were of the opinion that a standardized approach is the way to go because it will help physicians prescribing, and also from the patient perspective. But there were also, as I indicated, other views that different standards may be applied also depending on, for example, the type of the drug and the population that we are dealing with. So, those were

various options. So, it was a mixed approach. Some people felt standardized is the preferred way to go but, at the same time, there were members who thought that different standards also can be applied. Now, what is the best way? That is why we have subcommittees and committees seeking advice.

DR. LAMBORN: This is an example of where I am not clear what happens next. I mean, you clearly had a discussion. The subcommittee discussed it. Some people felt one way, some people felt another. You have a number of thoughtful comments in here. Will there be further discussion? Other individuals involved? How will it move forward to a next step from these different viewpoints?

DR. POOCHIKIAN: That is a very different question that we are wrestling with at the agency. As Dr. Adams indicated, we are considering all the comments through the public comments and also through the subcommittee reports and, hopefully, from this meeting to go back and discuss internally not only from the CMC perspective but also from the clinical perspective to see what the best approach is, whether to go with one standardized approach, or more than one, or be somewhere in the middle, and be flexible, putting in some criteria to clarify under what criteria what can be applied. What Dr. Hauck was presenting will do away, in many aspects, with some of the issues that we are discussing

because his point was if we define the patient risk and a couple of criteria, what probability of the population should be within that limit. Then, the applicant can define the producer risk in terms of the sampling and in terms of number of tiers. So, if somebody has a high quality drug product, then he or she has a different option to take as opposed to somebody else with regard to the samples to meet that criteria. So, that is a third option that was presented, and we are looking into it seriously too.

DR. LAMBORN: But that also could still leave you with multiple standards depending on the application for the drug in terms of relative risk that, for instance, you would accept for different patient populations.

DR. POOCHIKIAN: Even in that scenario, that is possible also, to branch into two tiers.

DR. LAMBORN: Other questions, comments from the committee? There is obviously a lot of work and a lot of thought that has gone into this from a lot of people, and I think you have obviously impressed the committee. They are just trying to absorb all the information that they have received. So, I think maybe the best thing to do is to go ahead and take our break now. I think this was scheduled to be a 15-minute break. So, let's reconvene at 3:00 p.m.

[Brief recess]

DR. LAMBORN: Just a couple of issues. First for

clarification for committee members, you received a copy of minutes from the April 26 meeting in your original packet, and then you received a new copy here. There is no difference. They were not official yet when they were sent out to us first so they were listed as "draft" but they are the same thing as we have received.

The other is that when we finish the formal meeting this afternoon, if the committee members would sort of gather around; we have a couple of housekeeping items to deal with.

I think we are going to turn to the nonclinical studies subcommittee.

Subcommittee Report - Nonclinical Studies

DR. DOULL: Thank you, Dr. Lamborn.

[Slide]

We are delighted to have this opportunity to update the full committee on the activity of your nonclinical studies subcommittee of this advisory committee.

[Slide]

This subcommittee, like many Food and Drug committees, has two functions, one scientific and one collaborative. The two functions here, the scientific function is to provide advice on improved scientific approaches to nonclinical drug development and regulation. And, the second function then is to foster collaboration

among FDA, industry, academia and the public.

[Slide]

Our specific objectives here -- first the scientific objective: We are seeking ways, approaches and mechanisms that will improve nonclinical information for effective drug development. We are seeking ways, approaches, mechanisms to improve the predictivity of nonclinical tests for human outcomes and, finally, seeking approaches and mechanisms to improve linkages between the nonclinical studies and the clinical studies.

Then the other, the collaborative effort is to facilitate a collaborative approach to advancing the science and regulation of drug developments.

[Slide]

This slide shows the list of the groups that are collaborating, and you can see that from Food and Drug we have CDER and CBER; NCTR, which is the lab in Arkansas. We have industry collaborations from PhRMA and from BIO. Academia, we have several academicians on the committee and we seek collaboration with academia, and we have some strong links with NIH.

[Slide]

This is the membership. In addition to Dr. MacGregor and myself, as you can see, we have David Essayan; Daniel Casciano, who is the new head at NCTR and is a new

member of the committee and hasn't been to a meeting yet; Jack Reynolds from PhRMA; John Cavagnaro from BIO. Ray Tennant is also a relatively new member. He has been to a meeting or two but he is from the Triangle; he is from NIH but he represents that. Jay Goodman is a toxicologist from Michigan State University; Jack Dean is from Sanofi. He is also a toxicologist. Both Jack Dean and Gloria Anderson, who is here today, are both members of this committee and they are also members of our committee.

[Slide]

We have had two meetings. The first meeting was an educational meeting for all of us to get up speed in areas of genomics and imaging, and we had experts from all of these different areas who came and talked to us about what is happening in those fields. We had experts come and talk to us about potential biomarkers of toxicity, and noninvasive or the imaging techniques that one can use in nonclinical studies.

After that meeting, we then focused in more sharply on areas that we thought would be profitable for our subcommittee to focus on, and we have identified two of these, and they are listed here. We thought there is sufficient information, and we have made sufficient progress in finding biomarkers of cardiac toxicity and that that would be a good area to work on. Second would be a similar

situation for biomarkers of vasculitis.

Now, of the imaging, we looked at MRI and PET scan and decided that the PET scan was furthest along. However, we intend to get into that group but we haven't quite decided exactly how we are going to do that. So, that is not as fully organized as those other two groups.

[Slide]

This is the role of this subcommittee. Our task is to identify and recommend areas in which we would focus. As I have already indicated, we are going to focus on biomarkers at least for the beginning. Our task then is to identify experts in the focus areas to form working groups, to identify people that could serve in this, and then to encourage nominations and those nominations would come from any place that is likely to be able to provide good nominations. That would include the Federal Register announcements. It would include FDA and stakeholder announcements with all of their groups. We have used the professional societies. We have sent letters to them and we have also talked to a number of those. What the expert working groups actually will do is to identify opportunities for collaboration and to define the objectives of those different expert working groups.

So, the role of our subcommittee is really kind of an oversight or a steering committee approach to get the

expert groups up and going, and then to keep track of what is happening with each of the expert groups. Once they get the activities going, begin to plan workshops and so on, then our task will be to encourage that and facilitate those as they are developed by the expert groups and the subcommittee.

[Slide]

Well, where are we at? Having identified the areas in which we are going to focus, biomarkers for cardiac toxicity, biomarkers for vasculitis, we have initiated the process to develop nominations. The Federal Register notice was published on July 26. As I have indicated, we have sent letters to all the scientific societies that we thought would have an interest in this activity. FDA has made all kinds of official announcements, and we have had a number of informal contacts. Members of the subcommittee and others have been helping us recruit good candidates. Jay Goodman and I and Dr. MacGregor were out at the Tox Forum and that is the kind of meeting where you go around and solicit all your colleagues to get nominations, and we did that.

[Slide]

The status we are at then is that the deadline for nomination submission was 9/29, and we received 26 nominations, very good nominations. We are now in the process of approval to get those expert groups established,

and we are doing that through the channels that are involved in getting that done. So, right now we are in the process of waiting for the members of the expert groups to be assembled or announced, and once that is done, then hopefully in January we will be able to have those expert groups meet, and we thought we would meet initially with the subcommittee and try and identify exactly what we hope will come out of those expert group meetings. The recommendations from the expert groups would come back to the subcommittee and eventually then we will be bringing those to this committee.

I have given you kind of a sketchy history of where we are at. This is a brand-new committee and a very brand-new area and a very exciting and challenging area, and we are very hopeful that we will be able to bring you some very significant recommendations and workshop plans. Thank you.

DR. LAMBORN: Dr. MacGregor, did you have additional comments?

DR. MACGREGOR: I don't think I have specific comments. I would be happy to answer questions or expand on any area that you would like.

DR. LAMBORN: I think then we are open to discussion by the committee. Questions? I certainly agree that it sounds like an exciting and challenging additional

area, and one well worth starting to work on.

DR. DOULL: I think the main difficulty -- there are all kinds of possibilities for biomarkers and, I must say, that we heard dozens of suggestions so that the difficulty was really figuring out which of those suggestions are far enough along that they could be implemented and really be useful for nonclinical studies, and could be linked to the clinical studies. So, I hope we have picked the right two to start with, and possibly an imaging one if we can get that up and going. But at least that is our plan for now.

DR. LAMBORN: Are there any other topics for this afternoon that committee members or FDA wishes to make?

[No response]

Then, I think we should consider that we are adjourned. We will meet again tomorrow, same location. Thank you all.

[Whereupon, at 3:15 p.m., the proceedings were adjourned, to reconvene on Thursday, November 16, 2000]

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