

[--- Unable To Translate Graphic ---]

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE**

Volume I

Wednesday, May 7, 1997

8:15 a.m.

Holiday Inn

MILLER REPORTING COMPANY, INC.  
507 C Street, N.E.  
Washington, D.C. 20002  
(202) 546-6666

[--- Unable To Translate Graphic ---]

Goshen Ballroom  
2 Montgomery Village Avenue  
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.  
507 C Street, N.E.  
Washington, D.C. 20002  
(202) 546-6666

[--- Unable To Translate Graphic ---]

PARTICIPANTS

Robert E. Taylor, M.D., Ph.D. Chairperson

Karen Templeton-Somers, Ph.D., Executive Secretary

MEMBERS

Robert A. Branch, M.D., Ph.D.

Gayle A. Brazeau, Ph.D.

Marie Davidian, Ph.D.

Timi I. Edeki, M.D., Ph.D.

Arthur H. Goldberg, Ph.D.

Edgar R. Gonzalez, Ph.D.

Robert Elden Vestal, M.D.

Desmar Walkes, M.D. (Consumer Representative)

Cheryl L. Zimmerman, Ph.D.

FDA

Roger Williams, M.D.

[--- Unable To Translate Graphic ---]

C O N T E N T S

	<u>Page No.</u>
Call to Order: Robert E. Taylor, M.D., Ph.D.	5
Conflict of interest: Karen Templeton-Somers, Ph.D.	7
<b>Office of Pharmaceutical Science</b>	
Overview: Roger Williams, M.D.	9
Office of Testing and Research	
Introduction/Overview: Regulatory Research and Analysis Staff, Division of Testing and Applied Analytical Development: Jim MacGregor, Ph.D.	24
Division of Product Quality Research: Karl Flora, Ph.D.	31
Division of Applied Pharmacology Research: Frank Sistare, Ph.D.	35
Chemistry, Manufacturing, Controls Coordinating Committee (CMC CC): Doug Sporn	39
Eric Sheinin, Ph.D.	45
Biopharmaceutics Coordinating Committee: Roger Williams, M.D.	56
Clinical Pharmacology Section/Medical Policy Coordinating Committee (MPCC): Larry Lesko, Ph.D.	64
<b>Open Public Hearing</b>	77
<b>Committee Discussion</b>	78
<b>Collaborative Efforts</b>	
CDER's Focus on Collaboration: Helen Winkle	132
Collaboration on Drug Development Improvement: Julie Nelson	140

[--- Unable To Translate Graphic ---]

Product Quality Research Initiative:  
Steve Byrn, Ph.D. 148

**Committee Discussion** 160

[--- Unable To Translate Graphic ---]

C O N T E N T S (Continued)

	<u>Page No.</u>
<b>Biopharmaceutics Topics</b>	
Biopharmaceutics Classification System: Update: Ajaz Hussain, Ph.D.	176
Individual Bioequivalence: Update: Mei-Ling Chen, Ph.D.	189
Locally Acting Drug Products: Vinod Shah, Ph.D.	196
Wallace P. Adams, Ph.D.	202
<b>Open Public Hearing</b>	207
<b>Committee Discussion</b>	208

[--- Unable To Translate Graphic ---]

P R O C E E D I N G S

**Call to Order**

DR. TAYLOR: I would like to call the meeting of the Advisory Committee for Pharmaceutical Science of the Center for Drug Evaluation and Research to order.

I am Dr. Robert Taylor. I am Chairman of the Department of Pharmacology at Howard University, and Director of the Clinical Pharmacology Division. I will be chairing the meeting this morning and tomorrow. I will have to leave early in the afternoon, but you will have an Acting Chair at that time.

The first thing I would like to do is to welcome you to Gaithersburg, not to Washington, and to hope that we will have a very productive meeting in understanding the work of CDER.

I would like to move quickly to the introduction of the committee members, and if we would, we could start to my right, the members of the table, as well as the committee. Go ahead and introduce yourself and give your affiliation.

DR. WILLIAMS: I am Roger Williams. I am Deputy Director for Pharmaceutical Science in the Center for Drug Evaluation and Research.

[--- Unable To Translate Graphic ---]

DR. BRAZEAU: Good morning. My name is Gayle Brazeau. I am Associate Professor in the Department of Pharmaceutics at the College of Pharmacy, University of Florida.

DR. VESTAL: I am Bob Vestal, Professor of Medicine and Adjunct Professor of Pharmacology at the University of Washington, and Associate Chief of Staff for Research at the Boise VA Medical Center.

DR. GOLDBERG: I am Arthur Goldberg. I am an independent consultant to the pharmaceutical industry.

DR. TEMPLETON-SOMERS: Karen Somers. I am the Executive Secretary filling in for Kimberly Topper at this meeting.

DR. DAVIDIAN: I am Marie Davidian, Associate Professor, Department of Statistics, North Carolina State University.

DR. WALKES: Desmar Walkes. I am the consumer representative on this committee. I also am a physician and medical director of a private clinic in Texas.

DR. ZIMMERMAN: Cheryl Zimmerman from the University of Minnesota, College of Pharmacy. I am an Associate Professor of Pharmaceutics.

DR. BRANCH: I am Robert Branch from the

[--- Unable To Translate Graphic ---]

University of Pittsburgh and Professor of Medicine and Pharmacology, Director of the Center of Clinical Pharmacology, and also an NIH-funded GCRC at the University of Pittsburgh.

DR. EDEKI: Timi Edeki, University of Honolulu, Louisville, Kentucky.

DR. TAYLOR: Thank you very much.

At this time, we will have a reading of the conflict of interest statement by Dr. Somers.

#### **Conflict of Interest Statement**

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The purpose of this meeting is informational and it will cover a number of broad topics that will require more in-depth discussion at subsequent advisory committee meetings.

Since no questions will be addressed to the committee by the Agency on issues dealing with a specific product, IND, NDA, or form, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research which have been reported by the

[--- Unable To Translate Graphic ---]

participants present no potential for a conflict of interest at this meeting when evaluated against the agenda. However, in the event that the discussions involve any products or firms not on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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.

Thank you.

I do have a couple other announcements. We ask that anybody who speaks, please use their microphone for the benefit of the people in the audience and for the transcriber, and in addition, since we have so many speakers, we do have a timer set up, so for the speakers, there is a black box on the podium which will tell you how many minutes you do have left, and the warning time, time to sum up, it will light up the sum up and then blink when you are starting to go over time, so you will be aware of where time is. Thank you.

DR. TAYLOR: I would like to encourage the

[--- Unable To Translate Graphic ---]

speakers to try to stick to the time that they have been allotted. I am hopeful that we won't have to use the trapdoor technique or the hook to get you to stop, so please try to comply with Dr. Somers' requests.

Are there any other announcements or considerations before we begin the meeting?

If not, then, we will move right into the agenda and have the presentation of the Office of Pharmaceutical Science beginning with Dr. Roger Williams.

### **Office of Pharmaceutical Science**

#### **Overview**

DR. WILLIAMS: Thank you, Dr. Taylor, and I would like to thank the Advisory Committee for coming, in many cases such a long distance, to be here with us today, and giving so much of their valuable time to us.

[Slide.]

In the course of my presentation, I would like to emphasize why I think this committee is so important to the functioning of the Center and the Office of Pharmaceutical Science.

[Slide.]

My task in the 20 or so minutes that I have been allotted is to give an overview of the Center for Drug

[--- Unable To Translate Graphic ---]

Evaluation and Research and the Office of Pharmaceutical Science within the Center.

This particular overhead shows you schematically the Center for Drug Evaluation and Research. As you know, it is one of several product review centers within the Agency here in Rockville. It has a staff of about 1,600 to 1,700, and our Center Director since May of 1994 is Dr. Janet Woodcock.

In November of 1995, Dr. Woodcock created a new structure to the Center that you know about and that appears here on this overhead. It is a complicated structure. There are many aspects to the Center. It has a number of public health responsibilities, the principal, of course, of which is the approval of new drugs for entry into the U.S. market, but it has many other responsibilities, as well. I won't touch on those, but it is a complicated structure, as I say, and it has a matrix component to it that I will show you in just a few overheads.

Now, there are two what we call "super" offices in the Center. The one on the left is the Office of Review Management that is headed by Dr. Mack Lumpkin, and the one on the right is the Office of Pharmaceutical Science, which I direct.

[--- Unable To Translate Graphic ---]

Many of the new drug approvals take place over on the left, in those five Offices of Drug Evaluation with statistical support from the Office of Epidemiology and Biostatistics.

In the middle are some support offices, Office of Management, Compliance, Training and Communications, that work to make sure that the moving parts of the Center, if you will, function effectively and smoothly, and there are many other people who contribute to the success of the Center.

I don't have to tell you that, as always at the Agency and in this Center, it is a time of extraordinary change. Since 1992, we have been under the impact of PDUFA, which charges user fees for the prescription drug approval in the United States, and the success of that program I think has been widely publicized and is apparent to all. I won't talk about it anymore in the course of the meeting, but it is an example of the many changes that the Center is always operating under in response to different societal needs and demands.

Let me now, however, focus over on the right, the Office of Pharmaceutical Science, which has about 500 of the 1,600 or 1,700 or so FTEs.

[--- Unable To Translate Graphic ---]

[Slide.]

Now, this fairly complicated slide is the Office of Pharmaceutical Science. As you can see in the detail of it, it too has many complex moving parts, if you will, and it too also has its matrix structure. Some of the color coding on here, which I won't emphasize, is designed to indicate that matrix structure.

Now, the Office of Pharmaceutical Science has many areas of focus and in the course of this advisory committee, we will be talking about those areas of focus. If I had to summarize briefly, I would say they focus on product quality in general.

So, for the first time since November of 1995, all the product quality functions of the Center have been pulled together under one roof, the Office of Pharmaceutical Science, and I think the power of that decision by Dr. Woodcock is apparent to all, and will continue to be apparent, and it is a topic particularly for this advisory committee.

I will talk to you about the component parts of product quality in just a minute, but I will say that the leadership of some of that aspect of the Center and of the Office of Pharmaceutical Science will be talking to you here

[--- Unable To Translate Graphic ---]

today, Doug Sporn who is head of the Office of Generic Drugs, Eric Sheinin who is head of the Office of New Drug Chemistry, a new creation by Dr. Woodcock that pulled all the Center chemists into one administrative structure.

We have Nancy Sager who is here representing environmental assessments, and there is also a microbiology function that is part of product quality. But it would be a mistake to think that the Office of Pharmaceutical Science is just product quality topics, it also considers pharmacology/toxicology components and it is considers clinical pharmacology, as well.

I am delighted to be able to introduce to you or I will shortly introduce to you Dr. Jim MacGregor, who is an expert pharmacologist/toxicologist and who has recently joined the Agency, I might say within the last few days, to head our Office of Testing and Research, which you see over here on the left, and which will form the principal topic for the first presentation this morning.

In addition, the Office of Pharmaceutical Science is also involved in clinical pharmacology, and Dr. Larry Lesko will be speaking to you with some of his staff in the course of the meeting to talk about that very important topic.

[--- Unable To Translate Graphic ---]

Now, it is clear to the committee and to the public that the constitution of the Advisory Committee for Pharmaceutical Science is carefully selected to represent some of these disciplines, and our goal over the coming years is always to assure that we have the best quality people from the nation to help us in deliberating on some of the important science issues connected with these areas that I just talked about. We have had great success in meeting that objective so far and I expect it to continue in the future.

[Slide.]

Now, let me go on. There is an aspect that we talk about in the Office of Pharmaceutical Science that I would say is maybe our underlying mission statement, if you will, and it is the concept that good science underlies good public policy, which in turn underlies a good review process.

As you can see, it's a cyclical concept where the review generates research questions, which in turn support good policy, et cetera. I won't go into it in more detail than this, but you will see that this theme permeates the structure of the Office of Pharmaceutical Science and some of the new structures and topics that we are building and

[--- Unable To Translate Graphic ---]

that we will discuss with the committee in the course of the next two days.

[Slide.]

Now, my first overhead with the blue boxes showed you the structure of the Center. My next overhead, that was the structural overhead, showed you a detailed view of the Office of Pharmaceutical Science.

This particular overhead shows you another perspective of the same areas, and you can imagine with a very complex structure like the Office of Pharmaceutical Science and the Center, that you can give different pictorial representations of what is going on within the structures.

So, let me look at now from the perspectives that are shown on this particular overhead, and at first I would like to say it is always important to say what is not in the picture. Let me draw your attention to two things that are not in the picture.

First of all, there are approximately 275 million Americans who are not in this picture, but who I would say are the final beneficiaries of all our effort. I have always been delighted that all our advisory committees have a consumer representative on their committees. You know in

[--- Unable To Translate Graphic ---]

this particular committee it is Dr. Walkes, and she has been a very effective representative of the American public in terms of some of the issues that we deal with.

There is another group that is only briefly shown on this particular overhead, and that, of course, is that small group up there that says "Industry," and, of course, we work closely and hopefully effectively with the pharmaceutical industry that generates these marvelous products that have been so useful to patients in the course of this century.

I won't spend any more time on that, but I think we all know what a technological and scientific triumph some of that has been, and I don't want to slight the industry that has made that possible by relegating them to a small set of letters up in the righthand corner of this slide, but it is a Center-centric view of life for the moment, and if you will let me walk through it now, I will explain it in more detail.

You heard me say there is a research to policy to review component to the Center and to the Office of Pharmaceutical Science. Let me start over on the right with those seven boxes that you see there, 1 through 7, which I call the layers of the assessment.

[--- Unable To Translate Graphic ---]

Now, when an application comes in, either a B, new drug application, or a J, abbreviated application, in various ways those disciplines and others, as well, contribute to the assessment of that application.

Depending on how you count, you can say there are different disciplines that contribute to that, but you can see in this particular graphic, I have seven disciplines that contribute to the assessment of a new drug or an abbreviated new drug application.

Now, as you have already heard in my introductory statements, six of those seven disciplines in one way or another are comprised within the Office of Pharmaceutical Science. The only that is not -- and if you will allow me a turf battle on that in the future -- is the Clinical Division where the medical doctors sit in the Center, but even there, I would say they are drawn into the deliberations of this committee in many ways, perhaps principally via the discussions of clinical pharmacology and pharmacology/toxicology.

Now, if you look at those seven layers, I tend in my mind's eye to take the top three layers and say Clinical, Clinical Pharmacology, and Pharmacology/Toxicology have a focus of safety and efficacy of the drug substance.

[--- Unable To Translate Graphic ---]

The bottom four layers again in my mind's eye tend to focus on product quality aspects - CMC, Biopharmaceutics, Microbiology, and Environmental Assessments.

Now, let me go from the righthand part of the slide over here to the left. You will hear in the course of the next two days some very interesting proposals that we have been building over the last year or so that allow the possibility of collaborative enterprise between academia, the Agency, and the pharmaceutical industry, and these two collaborative enterprises for the moment have names like CDDI, Collaboration on Drug Development Improvement, and PQRI, Product Quality Research Initiative.

Now, those are very interesting topics, and I will welcome the committee's comments and suggestions relative to those topics when you hear more about them in the two subsequent presentations that we have scheduled.

You have also seen in your backgrounder for this particular meeting draft proposals that are common on both collaborative enterprises. These are at present planning, preliminary, but we hope over the next several months to implement them in some rational, effective, and appropriate way. So, I would argue that it is very timely moment for the committee to give us comment on these enterprises.

[--- Unable To Translate Graphic ---]

So, I encourage you to listen carefully to the presentations and I welcome any thoughts you may have about them, give us the bad news as well as the good. It is important to hear issues connected with these things, so that we are not surprised later, and I would argue that is one of the main reasons for an advisory committee in a public discussion like this.

Now, moving over to the layer called Policy, and now you can see how those collaborative enterprises, if they work, will support our policy development. I would like to talk a little bit about the policy-generating arms of the Center.

[Slide.]

If you go on to the next overhead, the Center has built a concept that we call Coordinating Committees, and as you can see on this particular overhead, there are a lot of them, perhaps 10 or so. They were an idea perhaps whose time came several years ago. Some people may even say now they are perhaps a little bit out of control, but I think the fact that they exist and the fact that many people are working so hard in connection them documents the need for them.

Now, I won't talk about all these advisory

[--- Unable To Translate Graphic ---]

committees, but I will focus on four of them. These four that I will focus on, which are the Biopharmaceutics Coordinating Committee at the top, Pharmacology/Toxicology Coordinating Committee to the right, CMC, just slightly more to the right clockwise, and the Medical Policy Coordinating Committee, as you can see are the four coordinating committees in the Center that work to develop policy for those particular disciplines, and I would say that is their main focus and reason for being.

When I say "policy" now, I am talking about specifically guidance for industry that helps industry to figure out what it is this black box sitting in Rockville would like in terms of information to support a new drug or an abbreviated new drug application.

[Slide.]

Now, with that brief introduction, let me just show you some of the structures of these committees. I will not spend a long time on these structures because you will be hearing more about them in the course of the morning from the Chair or the Co-Chairs of these coordinating committees.

This is the Chemistry Manufacturing Controls Coordinating Committee. It is one of the granddaddies of the coordinating committees, and I would say the need for it

[--- Unable To Translate Graphic ---]

arose because of several factors, one of which was the importance of making sure that the new drug chemistry function in the Center stayed in tune with the generic drug chemistry function in the Center. That was certainly a powerful impetus for this particular coordinating committee.

I might also say that ICH, the International Conference on Harmonization, was also a reason for the formation of this and some of the other coordinating committees, and you will hear more about the ICH quality topics -- everything here is what I call a quality topic -- forms some of the current activities of the committee when you hear the presentation from its Co-Chairs, Eric Sheinin and Doug Sporn.

Before I go on, I might mention for the benefit of the public, as well as the committee, that these committees are virtual in character. They are staffed by people who either participate in research or who participate in review, and I like to think of them as the middle ground where good scientists who conduct research meet with good scientists who conduct reviews, and they work together to build policy. In the optimal way, that is the way it is supposed to work, and I think you will see in the course of the next two days that, in fact, that is the way it works.

[--- Unable To Translate Graphic ---]

As you can see over here to the left now, we are trying to build these collaborative enterprises where we can draw in the participation of representatives from the pharmaceutical industry, as well as academia, to help that process.

So, I hope you see the vision and I hope you feel comfortable commenting on it in the course of the next two days.

[Slide.]

Let me go on and show you briefly the Biopharmaceutics Coordinating Committee. These two coordinating committees focus on the product quality aspects of policy coming out of the Center for Drug Evaluation and Research. I will be talking to you more about this particular coordinating committee in the course of the morning, so I won't say anything more about it now.

[Slide.]

Let me go on now to the final set of overheads that focus on the Medical Policy Coordinating Committee. Again, I won't dwell on this particular coordinating committee, but you can see its principal leader really is Dr. Bob Temple. I am a co-chair with Bob. I don't have to tell you about Bob's contribution to the new drug approval

[--- Unable To Translate Graphic ---]

process in the United States. It really is his contribution in many ways, and he has been an effective leader of this committee that is focusing on a multitude of topics. It is a very broad-based, wide-ranging committee.

[Slide.]

We won't focus on it too much, but let me show you quickly the other two overheads. This particular subdivision of MPCC focuses on the ICH efficacy topics. I won't spend any time on these either, but you should be aware that this particular committee is working on ICH topics, just like Pharm/Tox is and CMC, and there is a dream connected with ICH that maybe in the course of the next two days we can talk about, that talks about rational policy, not only for the United States, but for other regions of the world that participate in ICH, such as the European Union and Japan.

[Slide.]

Now, the final overhead, again, I won't spend any time on this. I just want to say that Dr. Lesko and others will be talking about some of the activities of this policy-generating arm of MPCC, which is the Clinical Pharmacology Section, and again, of course, we look forward to this particular committee having input onto some of the

[--- Unable To Translate Graphic ---]

documents, not only in the course of the next few days, but in subsequent discussions.

[Slide.]

Now if you go on to the next overhead -- I am watching my time carefully -- let me show you here very briefly there is a cycle of life connected with these guidances and policies and research. If I had to say it now -- and I am using the example of the CMCC Coordinating Committee -- all of these things generate guidances that are used by industry and the reviewers to understand what kind of information is needed in an application and, in some cases, how it should be reviewed.

That comes into the OPS management structure, and then it has to filter out to all those hundreds of reviewers that sit in Rockville and be understood by them and managed effectively by the leadership of OPS in the Center. So, there is a flow of information, if you will.

There is also the concept of updating of a guidance. Guidances have a terrible problem which is, because of the wealth of science, knowledge, and advancement in science, they can become outdated, so there is a concept of updating a guidance which is critical.

You will hear in the course of the next two days

[--- Unable To Translate Graphic ---]

we are already talking about updating guidances that may have been issued a year or two ago. We hopefully want to do that with the participation of this committee and based on good science.

So, there is a lessons learned, and as you can see down at the bottom, I have that lessons learned flowing in connection with the collaborative enterprises, so that you can update.

Now, I don't know what the time of this cycle is, but it is about seven years, which I think has a sort of biblical character to it, if you will. This is a long-term process and it takes a tremendous attention to keep things on track.

Speaking of keeping things on track, I see that my time is over. Let me see what my next overhead is.

[Slide.]

These are what these guidances look like. In February of this year, we published a guidance called Good Guidance Practices. It is in your handout. I encourage the committee to look to it.

I will stop there. Let me just close by saying I think you can see there is a broad process, a broad structure, a broad vision connected with some of our

[--- Unable To Translate Graphic ---]

discussions over the next two days, and I look forward with enthusiasm to what the committee has to say.

Thanks very much, Dr. Taylor.

DR. TAYLOR: Thank you, Dr. Williams.

We will move now to the discussion of the Office of Testing and Research, and Dr. Jim MacGregor will lead that section. As we progress through that section, perhaps he could introduce the subsequent speakers that work in your shop.

### **Office of Testing and Research**

#### **Introduction/Overview**

[Slide.]

DR. MacGREGOR: Thank you. I am very pleased to be here. As Roger said, this is my first week on the job. I have just arrived from my former position in which I was Director of the Toxicology and Metabolism Laboratory in the Biopharmaceutical Development Division at SRI International, which was formerly the Stanford Research Institute.

The focus of that division was on pharmaceutical development particularly preclinical safety studies, formulations, analytical chemistry, and pharmacokinetics and metabolism, so in that position I was involved in many of the activities in which CDER is involved.

[--- Unable To Translate Graphic ---]

As you can imagine, since it is now my third day on the job, I am still in the process myself learning about many of the programs that exist in the Center and in my own division, the Office of Testing and Research, and I am still formulating my own ideas about the importance and direction that the various programs should be taking.

However, I can make a few comments even at this time, one of which is that I believe very strongly in what Roger presented as the OPS paradigm, and that is, namely, the dynamic interaction between basic science research and the review process and the development and application of regulatory policy.

I think if we were to put the mission of the Office of Testing and Research into just a few words, I would say that it is the scientific and laboratory support of the regulatory aspects of CDER.

I think that science, good science, needs to drive regulatory policy and regulatory practice. I think that in order to achieve that, you need to maintain a strong core of first-rate scientists to assure that sound science is the basis of regulations and regulatory practice.

Now, I think one thing you might ask is, in an era of shrinking resources -- and this is one of the things that

[--- Unable To Translate Graphic ---]

I considered strongly when I was considering taking this position and coming here -- how can we really maintain strong science and do the things we need to do in an era of shrinking resources.

I think the answer to that is that it is going to be necessary to be innovative, it is going to be necessary to work through collaborations, it is going to be necessary to leverage resources and use mechanisms, such as consortium efforts between industry groups and the government, and I think that the product quality research initiative, for example, which Roger mentioned earlier and which you will hear more about this morning and this afternoon, is a good example of how these innovative approaches can expand our basic resources.

[Slide.]

If we go to the next overhead, what we would like to do this morning is really just set the stage by introducing you briefly to the Office of Testing and Research, its organization, its major programs, and our general plan for these advisory committee meetings is to also try to select a topic each time we go into a little more depth, and our choice for this session is to focus a little bit more heavily in the area of pharm/tox basic

[--- Unable To Translate Graphic ---]

research.

In order to do that, we will have two presentations tomorrow, one by Frank Sistare on the TG.AC mouse model for carcinogenesis prediction, one by Donna Volpe on the prediction of hematotoxicity using in-vitro technologies.

So, hopefully, by rotating some more in-depth presentations into these advisory committee meetings we can get some more substantive, in-depth response from the review committee on the approaches that we are taking.

[Slide.]

Just to very briefly introduce you to the organization, there are five major activities within the Office of Testing and Research: Regulatory Research and Analysis, which is a relatively small group, three staff; Laboratory of Clinical Pharmacology, about eight staff; the Division of Product Quality Research, a division of approximately 20 people; Division of Applied Pharmacology Research, which is focused on basis pharm/tox research area, again approximately 20 people; and the Division of Testing and Applied Analytical Development, the largest of the groups, approximately 55 individuals divided between St. Louis and Washington area at the moment, but scheduled to

[--- Unable To Translate Graphic ---]

move in the very near future to the Washington area.

We will introduce you briefly to each of these five activities.

If we could go to the next slide, I will introduce the first two, and then we will have the Division Directors talk very briefly about the remaining three.

[Slide.]

The first -- and this is a program that we will probably come back to and focus on a bit more heavily in the next advisory committee meeting, but which we will go very briefly this time -- is the Division of Testing and Applied Analytical Development.

There are really three main activities in this division: one, method validation; the second, reference standard development, physical reference standard maintenance, and then applied analytical development.

This group is involved in the validation of all the new drug chemistry methodologies. It is very active with the USP in maintaining reference standards for all the new drugs, and interacts very closely with the USP in reference standard banks, and also has a significant program in the development of new analytical techniques for product monitoring.

[--- Unable To Translate Graphic ---]

Two examples of that, that I will just cite to give you a flavor of the kind of things they do is the insulin program, which is a major focus of the group, and which is also being developed as a model for other proteinaceous type of molecules and identity and quality monitoring of these types of agents.

They had an active and innovative program in the use of near infrared spectroscopy for rapid monitoring of product quality, uniformity, and content.

We will come back to this division in the future and we will go into a little more depth.

[Slide.]

The second activity that I would like to go over fairly quickly is the Regulatory Research and Analysis Staff. This staff consists of three individuals led by Joe Contrera. I should have mentioned Tom Layloff is the leader of what we call DTAAD, Division of Testing and Applied Analytical Development that I just talked about.

Joe is actually involved in a number of liaison activities in addition to the research and analysis program, but the major focus of the research and analysis programs is to try to use the important and extensive database on preclinical and clinical information that is available

[--- Unable To Translate Graphic ---]

through CDER, probably the only place in the world that such an extensive database is available, and to develop comprehensive databases and use those databases to develop predictive models for predicting human response from laboratory data that is associated with the drug application and review process.

The database focus to date has been mainly in the first two of these areas, carcinogenesis and reproductive and developmental toxicology, but there are active programs already initiated and getting underway in the area of genetic toxicology and metabolite predictivity.

There is also, again coming back to the idea of leveraging resources and developing collaborations, a number of activities that are being undertaken in the area of predictive modeling, to use this pharmaceutical database to develop predictive models through structure activity relationships with existing companies and other institutions that have developed similar databases for other classes of compounds, but to use the extensive pharmaceutical database to develop computerized learning sets for the pharmaceutical database and thereby improve the predictability of these models for the human response. Again, we will come back in a little more depth in subsequent meetings to this are.

[--- Unable To Translate Graphic ---]

I would like to introduce the three people, and in view of the podium setup that we have here, I think I will introduce all three of the individuals and then just let them come one at a time.

These are the Division Directors for the three divisions that we are going to cover in a little bit more depth at this meeting.

The first speaker will be Karl Flora, who is the Director of the Division of Product Quality Research. He will be followed by Frank Sistare, Director of the Division of Applied Pharmacology Research.

Then, Jerry Collins, who was scheduled to speak this morning, unfortunately had to attend a funeral this morning, was unable to attend, but I understand we have made five minutes on the schedule for him tomorrow, so he will present tomorrow afternoon right after lunch.

So, with that introduction, Frank, I would like to call upon you.

I am sorry. Karl is first. Excuse me.

**Division of Product Quality Research**

DR. FLORA: I am going to talk a little bit about the Division of Product Quality Research that you have seen on a couple of the slides.

[--- Unable To Translate Graphic ---]

[Slide.]

The first slide here gives you a schematic of a little bit of what we are all about. The Division of Product Quality Research was created in the reorganization of the Office of Testing and Research, and came about by really the consolidation of the Generic Drugs Laboratory and the chemists from the Division of Research and Testing and Biopharmaceutics Laboratory.

We are about 20 in number and we are trained primarily in analytical chemistry, formulations chemistry, or biopharmaceutics.

The past several months we have been spending a lot of time assessing our resources and developing division programs. After a review of our staff resources and our instrumental capabilities, the following three programs have evolved for the division. It would be the Pre-Formulations Research Program, Formulation Research, and Biopharmaceutics Research.

As you can see, these are rather broad topic areas and are sufficiently broad to really encompass many issues of product quality. For instance, the Pre-Formulation Research team may be involved in the assessment of the physical and chemical characterization of drug substances or

[--- Unable To Translate Graphic ---]

also possibly the chemical characterization of physical and pharm/tox characterization of excipients in vehicles.

In the case of the Formulation Research team, we may be looking at issues of manufacturing research, also formulation development could be included in this area, as well, process control and specification evaluation, looking at those issues that may arise, and also the associated analytical technologies that would necessarily go along with that, whether they be standard technologies, new and novel techniques, or possibly automation or robotics that could be included in that, as well, and also stability in packaging, which stability could obviously be included in either of these two areas, but we have chosen to place it here and address the packaging issue with it, as well.

Finally, the Biopharmaceutics Research area, we would be looking at in-vitro test methods, development and evaluation of those methods, and in-vivo test methods, and also the development of metrics to aid us in the assessment of bioequivalence.

[Slide.]

Our Intramural Research areas were selected, not only to accommodate the intramural resources that we have, but also to align with and facilitate interactions with the

[--- Unable To Translate Graphic ---]

important elements of the Center.

These would include laboratory collaborations with the other organizational elements of the Office of Testing and Research including division applied pharmacology research and the Division of Testing and Applied Analytical Development, and additionally, the Laboratory of Clinical Pharmacology.

Importantly, we need to establish links to relate our research to the policymaking organizations within the OPS, and those primarily being the CMC CC and the BCC that we are concerned with, the Chemistry, Manufacturing, and Controls Coordinating Committee, and the Biopharm Coordinating Committee.

Currently, we have eight staff members from our division as members of either the Coordinating Committee, their technical committees, or their working groups, as members.

Another major effort of our division is the Product Quality Research Initiative, the so-called PQRI. This collaborative enterprise will bring together the FDA, the industry, and academia in hopes of identifying significant research interests of mutual interest that will impact internal policy development through the CCs and also

[--- Unable To Translate Graphic ---]

conceivably result in regulatory relief for the industry with these policy changes in development. We will hear more about the PQRI later this afternoon from Helen Winkle and Steve Byrn.

We have also tried to align our intramural programs with some of the technical committees of the PQRI, in particular, the Drug Substance Technical Committee aligning with the pre-formulation area, the Drug Product Technical Committee aligning with the formulation research team efforts, and also the Biopharm Technical Committee, again all of these of the PQRI aligning with the Biopharmaceutics Research Program here.

I would say that members of the DPQR staff have been very actively involved in promoting and planning the PQRI steering committee and also the technical groups. In this effort, we are continuing to be involved.

Finally, in closing, I would say that we are a very young division, but I think we are off to a good start.

#### **Division of Applied Pharmacology Research**

DR. SISTARE: Good morning. My name is Frank Sistare. I am with the Division of Applied Pharmacology Research.

[Slide.]

[--- Unable To Translate Graphic ---]

The Division of Applied Pharmacology Research is structured around four overlapping, closely interdigitating research teams. Members of our division serve on several teams at a time. In general, research in the Division of Applied Pharmacology Research is oriented toward the evolution of innovative pharm/tox approaches that can bridge preclinical and clinical areas of drug development and review.

We ask two critical questions of such a candidate approach: one, will it be more predictive of human risk; and, two, will it be less costly in time and resources. If so, a research strategy is devised for evaluating its ultimate acceptability into a regulatory guidance that could improve the drug development and review process.

[Slide.]

Now, for each of the four research teams, what I would like to do is highlight an example of one ongoing project in each program area.

The International Committee for Harmonization, that Roger mentioned earlier, has signed a document, ICH document S1B, entitled, "Testing for the Carcinogenicity of Pharmaceuticals." This document allows the use of an alternative short or intermediate term assay to supplement

[--- Unable To Translate Graphic ---]

one standard two-year rodent assay.

In the Carcinogenesis and Molecular Toxicology Program, the newest of the programs in the Division of Applied Pharmacology Research, we are coordinating our efforts with the NIEHS and a consortium of pharmaceutical companies that has been organized under the International Life Sciences Institute to evaluate some proposed promising alternatives.

I am going to be telling you a lot more about this tomorrow, so I am going to cut this short and speak to you about 20 minutes about that tomorrow.

In the Preclinical Chemotherapeutics Evaluation Program, under team leader Donna Volpe, one area of research is directed toward perfecting the use of hematopoietic clonal assays from human bone marrow samples to better predict the starting dose and escalation scheme for clinical trials involving myelotoxic drugs.

Again, because we are taking a little bit closer look at the pharm/tox program, Donna will also be presenting tomorrow, and I won't be saying anything else about this today.

[Slide.]

The Neuropharmacology Research Program is led by

[--- Unable To Translate Graphic ---]

David Lester. In collaboration with colleagues in academia and other government labs, this team has developed some very promising data indicating the strong potential utility for the histological application of magnetic resonance microscopy especially to detect and predict neurotoxicity.

This team seeks to formalize a strategy in concert with our pharm/tox review colleagues to evaluate the full capabilities of this exciting approach with an eye toward evolving new neurotox guidelines.

In the Cardiopulmonary Pharmacology Research Program, under team leader Eugene Herman, this team has developed strong evidence of the utility of Troponin T, for example, as a biomarker for insidious and irreversible drug-induced cardiotoxicities.

This team seeks to further evaluate the utility of this and other biomarkers during initial clinical investigations that can reflect insidious drug-induced cardiac and vascular toxicities and impact on clinical trial safety concerns.

[Slide.]

Finally, I would like to share our thoughts on how we plan to improve on prioritizing research options that we have open to us, and to achieve greater impact with our

[--- Unable To Translate Graphic ---]

research dollars.

As our reviewer colleagues are called upon to develop guidances that will ensure uniformity of policies across the Center, gaps in available scientific information that can be used to justify sound policymaking will surface.

The involvement of research staff on those policy drafting subcommittees of the Pharmacology/Toxicology Coordinating Committee provides a mechanism for identifying specific research priority needs of the Center, and to advance the evolution of regulatory policies.

[Slide.]

This research policy to review paradigm turns full circle, then, as review experience and input is called upon to help us prioritize our CDER research needs and to continue to evolve this regulatory policy.

Formalizing and strengthening these critical linkages with the review components of the Center and enhancing that feedback process is a primary imperative for our division in the coming year.

Thank you.

DR. TAYLOR: Thank you very much. I appreciate the efforts of the speakers to remain on schedule. It looks like you are actually two minutes ahead of schedule. We are

[--- Unable To Translate Graphic ---]

scheduled now for a break at 9:30, and the break will end at 9:50. I would like to encourage you to be back in the room, so that we can begin on time, at 9:50.

[Recess.]

DR. TAYLOR: We would like to reconvene now. We would like to move along with the agenda.

The next topic will be some discussion of the Coordinating Committees that Roger introduced us to just a moment ago. The first presenter is Eric Sheinin and Doug Sporn.

### **Chemistry, Manufacturing, Controls**

#### **Coordinating Committee (CMC CC)**

MR. SPORN: I am Doug. Good morning. Eric and I just want to briefly go over the Chemistry and Manufacturing Controls Coordinating Committee, and one of things Roger didn't tell you is he really invented it and populated the Center with all the committees because I think of the success that they had with the Chemistry and Manufacturing Controls, and it has only been in the last few months that he has stopped chairing that and turned it over to Eric and me.

[Slide.]

I would like first to go back to one of the slides

[--- Unable To Translate Graphic ---]

Roger had showed you earlier. He also didn't tell you that inside the Center, this is referred to Roger's World, and the yellow boxes you see up there are the Divisions of Chemistry in the Office of New Drug Chemistry and the Office of Generic Drugs were under the Director, and so when we talk about CMC, Chemistry and Manufacturing Controls, we are really talking about policy primarily for those groups, but as Roger indicated, we frequently pull down scientists from other parts of Roger's World, as well as from other parts of the Center.

[Slide.]

Now, he also showed you this. This is the Chemistry and Manufacturing Controls Committee. In addition to Eric and I chairing it, the other permanent members are the heads of the Divisions of the Chemistry Review staffs in our two offices, as well as Peter Cooney, who is head of the microbiologist. Then, we have some rotating members, who are the team leaders from our offices, and a number of other people who participate.

Now, I am not going to go through all the boxes other than to say the top boxes, I guess you could say are ongoing, standing technical committees, and Eric is going to talk about these because a number of them deal with ICH

[--- Unable To Translate Graphic ---]

quality topics.

At the bottom, though, we have a number of what we call working groups. These are more finite life working groups. The life goes on for a while, but eventually, they do phase out, and what I am going to do is briefly talk about some of these, in particular, these right here which are called the SUPACs, which stands for Scale Up and Post-Approval Changes. I am going to talk about one of them specifically, but it is a good model for the others.

[Slide.]

Now, the purpose of the SUPACs is basically to maintain the safety and quality of pharmaceuticals, but at the same time, provide a measure of regulatory flexibility for the industry. I think probably most of you know, in the past anyway, almost changes a pharmaceutical manufacturer wanted to make had to be after approval, had to be submitted to the Agency something called a pre-approval supplement.

However, in the regulations there is a section under 314.70, which allows us to use a less burdensome process where we have justification to do that, and that is what SUPAC is all about.

Now, the SUPAC is not a regulation, it is a guidance which represents a communication primarily to

[--- Unable To Translate Graphic ---]

industry. It represents our best judgment. It can be updated. In a sense it is informal and non-binding.

When I say it is non-binding, I really mean it is non-binding on industry. If they choose not to follow what is in the guidance, they are encouraged to call into the Review Division and talk about what they do want to do, and see if we can work out a way that is agreeable to everyone.

It is binding though, however, on our reviewers in Generic Drugs and New Drug Chemistry. That is, if somebody follows a guidance and submits it, and it meets the criteria, it is going to have to be accepted. We can't have reviewers or individual divisions making separate policy.

It is intended to give recommendations to new drug, as well as generic drug, applicants. That is what ANDA up there stands for, Abbreviated New Drug Application, and AADA stands for Abbreviated Antibiotic Drug Application.

[Slide.]

Now, the SUPACs primarily, although not exclusively, deal with four types of changes that can be made: components and composition, site of manufacture, scale of manufacture, and then manufacturing, either equipment or process.

I expect at some point, SUPAC will deal with other

[--- Unable To Translate Graphic ---]

types of changes, but at the time it was felt these were some of the major types that manufacturers have to make and where they wanted regulatory relief.

[Slide.]

What SUPAC specifically does is define levels of changes that a manufacturer might make, and then for each level, it tells what are the recommended CMC tests that should be conducted, also identifies in vitro and in vivo requirements, if there are any, for each of the levels, and then finally, identifies or tells the applicant what sort of documentation does the Agency need to see with respect to these types of tests.

[Slide.]

This is sort of a schematic that says what I just tried to describe. Most of the documents have three levels of change, not always, but most of the time, with the Level 1 being the most basic change, and those types of changes basically are almost non-detectable and are very unlikely to have an impact on performance of the drug product, and this is for immediate release I am talking about now, but again, this concept carries over to other dosage forms.

Generally, Level 1 can be submitted in an annual report, which is the least burdensome, and then we have the

[--- Unable To Translate Graphic ---]

two additional levels, and you get Level 3, that is where we feel the changes would be most significant, and there is a likelihood it could result in a change in performance of the product, which we would want to know about, so the testing requirements at Level 3 would be much more stringent.

[Slide.]

Now, why industry again is interested in this is that in certain circumstances, where they want to change components, composition, site of manufacture, et cetera, they can do that without a pre-approval supplement, and they can submit something we call a CBE, which stands for supplements changes being affected, which means they make the change and immediately notify the Agency.

In other cases, as I indicated a second ago, they can file a change in an annual report. Now, this third bullet really is specific to immediate release products. I am not going to discuss it because I think Dr. Hussain is going to cover it later in the course of the meeting.

[Slide.]

I just wanted to show you briefly what has been worked on or is underway, and it is quite a bit, keeping in mind the same people who are reviewing drug applications are working on this in addition to scientists from Office of

[--- Unable To Translate Graphic ---]

Testing and Research from Larry Lesko's office is, as well.

The SUPAC IR, or immediate release, that is the one that has been out a little out over a year. It has been a great pilot in a way. We have learned a lot from that work that we are putting into the other SUPACs.

SUPAC on semi-solids in modified release are being finalized now. I would say both of those will be out before mid-summer, and industry can implement them. After that, transdermal, which is being actively worked on now, may or may not get out by the end of the year.

BACPAC, which you are going to hear much more about tomorrow, and I would say there is a lot of industry interest in this one, a whole lot, probably more than the other SUPACs combined, and then finally, something new called PAC-SAS, which is Post Approval Changes for Sterile Aqueous Solutions. There will be a workshop or conference I believe in August. FDA and PDA, Parenteral Drug Association, will be putting that on. That will be in Washington.

I also want to make a plug here. We will have industry training at the end of May, I think May 29th. Dr. Vinod Shah is heading that up, and if there is anybody here who is interested in attending that industry training, you

[--- Unable To Translate Graphic ---]

might talk to Vinod while you are here.

Now I am going to ask Eric to come up and tell you a little about the committee does with respect to ICH.

Thank you.

DR. SHEININ: May I have the first overhead.

[Slide.]

I want to go back to an overhead that you have seen previously. This is one Roger showed and Doug also showed it to you. As Doug said, many of these technical committees, these are standing technical committees, are involved not only with some of the SUPAC type work, but they have been heavily involved with the harmonization effort that has been going on through the International Conference on Harmonization.

This involves the U.S., Europe, and Japan, and was indicated earlier, there is three major areas that ICH is working on: efficacy, safety, and quality, as well as a multidisciplinary area. So, we have been involved with many of the quality documents, and I would like to just give you a brief rundown on what these documents are, which ones have been finalized, and what the status is of the two that we are still working on, and then show you how, in the overall scheme of things, these ICH documents and guidances are more

[--- Unable To Translate Graphic ---]

or less interrelated and working in conjunction with our efforts in SUPAC.

There is actually some of our technical committees that have not been involved with ICH, but have been very active, as well, in developing guidances. Part of the next guidance that we are going to be putting out is a guidance on packaging, what sort of information needs to be included in the application when it is discussing the container closure system for a drug. That should be out as a draft guidance, hopefully, within the next month or so.

We have a committee that has been working on guidances on drug master files, and a lot of that information has been guidance to our reviewers on how to approach the review of information in a drug master file, what format the review should take, when is it permissible and under what conditions can a reviewer re-review a DMF, where another reviewer has already reviewed it.

Just to give you an example, many of the drug master files are for the synthesis and manufacture of drug substances, or as they are called today APIs, Active Pharmaceutical Ingredients, and if an API or a drug substance is used for solid oral dosage form, there may be different requirements put on that drug substance if it is

[--- Unable To Translate Graphic ---]

going to be used in a sterile product.

So, under conditions like that, it certainly is permissible, and actually probably would be encouraged, that reviewer of the new drug application for a sterile product take a look at what was in the original review of that drug master file. But generally, we try just to limit our reviews to one, and then when there is deficiencies, somebody will review the response that comes in.

Now, the Stability Technical Committee, they were involved in the first ICH quality document that went all the way through the process to Step 5, where it becomes an official guidance, and that was the Q1A's stability requirements for new drugs that are submitted to the three regions. That actually went to final, Step 5, several years ago. It has not been fully implemented in the United States. There was an agreement at ICH that the implementation date for that guidance, or as ICH calls it, a "guideline," would be January 1st of 1998.

Now, the policy in the U.S. is once a guidance is announced as being available in the Federal Register, in legal terms, it is implemented, it is in effect as opposed to when we publish a new rule or regulation, there can be a delay in when that regulation is implemented.

[--- Unable To Translate Graphic ---]

So, in theory, Q1A has been implemented in the U.S. In actual practice, we are looking to implement this January the 1st. However, on the other side of the coin, as you have already heard this morning, guidances are not binding. They are not binding on the industry, nor are they binding on the Agency.

So, what they do is they provide our best thoughts on guidance as to what a company should do to provide sufficient information when they submit a new drug application.

So, people have been using the conditions that are described in Q1A for some time now. In essence, it will become unofficial as of January 1 of next year.

There is another stability document that is now at Step 4, which means it has been signed off by all the ICH parties and all we are waiting for is to publish its notice of availability in the Federal Register, and at that point, it goes to Step 5.

That is the Q1C document. That is sort of an addendum to Q1A and provides for what sort of stability information and data should be included in the application for a new drug product, a different dosage form of an existing product.

[--- Unable To Translate Graphic ---]

Originally, there were to be several other conditions that were included in that document, other types of changes or, as you have heard, what would be included in a supplemental application, but the ICH parties were not able to harmonize on what those actual requirements should be, so it was kind of a pared-down document. It only talks about new dosage forms.

Kind of related to those two stability documents is one that was worked on by the Photostability Working Group, and the groups up here are technical committees that are standing technical committees.

The ones down here are working groups that are formed for a specific purpose. Once that task has been completed, unless there are other assignments that are given to that working group, it will eventually be abolished and the members of those working groups will either come back and work on other working groups or technical committees or for a while relax and just do reviews.

So, this is the Q1B document on photostability, and the purpose of this document was to provide guidance to the industry on what sort of photochemistry studies should be done on products where the drug substance may be sensitive to light, and it sets forth the conditions, what

[--- Unable To Translate Graphic ---]

sort of lamp should be used what sort of timing there is to examine the photostability of those materials. That is at Step 4 also, and we are waiting to publish its availability.

There is two documents related to analytical methodology, Q2A and Q2B. The Q2A document is essentially a text or a dictionary describing the various parameters that need to be examined when a firm is validating their analytical methodology. It sets forth things, such as accuracy, precision, linearity range, limit of quantitation, limit of detection, et cetera.

There is a second document there, the Q2B, which sets forth guidance on how should a firm go about demonstrating these parameters, demonstrating that the method is suitable and that it works properly. So, it gives guidance on how to accomplish the validation.

Taken together, the two documents kind of mirror and parallel the general Chapter 1225 in the USP, which also provides a discussion of validation of analytical methodology.

The Q2A document went to Step 5 approximately two years ago and has been in effect for that period of time. The Q2B achieved Step 4 last November, along with the other two Step 4 documents that I mentioned.

[--- Unable To Translate Graphic ---]

Then, we have several documents that deal with impurities in the drug substance or drug product. Q3A talks about impurities in drug substances, and sets forth the level at which an impurity needs to be identified and qualified. For most drug substances, the conditions are if it is present in at least a tenth of a percent versus the active ingredient, then, it needs to be identified and qualified. That is a Step 5 document.

The next one related to impurities is Q3B, which deals with impurities in the drug product, and that was a little bit more complicated because of the sense of trying to relate the impurity levels to the maximum daily dose of the drug.

It considers if a drug is going to be used chronically or if it is going to be used for a short period of time, so it has various different levels depending on the maximum daily dosage at which an impurity needs to be identified, which it needs to be qualified, and which it needs to be reported when the analytical data for that drug product are submitted. That is also at Step 4.

Then, we have a committee, Labeling and Nomenclature, who is charged mainly with providing advice and guidance to the reviewers on the trademark or trade name

[--- Unable To Translate Graphic ---]

that the companies submit for their new drug applications, and they also are providing guidance of various types to the industry through a guidance document and through speeches at various meetings.

There is another impurities document right here, Residual Solvents Working Group, Q3C. This ICH document is providing guidance and information on what levels of solvents are permissible in new drug products, and this covers both the drug substance, the excipients or inactive ingredients, and the drug product itself. That is at Step 2, which means it has been signed off initially by the six parties of ICH, and will be published in the Federal Register soon for comment and then further discussion at ICH.

There is the Q5s, which deal with biotech and biological products, and you will hear more about that later in this meeting.

The final document that I just wanted to mention is Q6A, which is guidance to the industry and to the Agency on how you go about setting specifications for new drug substances and new drug products.

The way this document defines specifications is the parameter or characteristic that is being examined, the

[--- Unable To Translate Graphic ---]

analytical test procedure that is used to monitor that parameter, and the acceptance criteria or limits that are associated with each one of those parameters. That is really at Step 1, meaning where it is still undergoing initial discussions, and we hope to get to Step 2 at the next meeting in Brussels.

[Slide.]

This shows some of the way there is interaction between these ICH documents and the various post-approval change documents. Drug substance will be related through the BACPAC, which is going to be starting to be developed very shortly.

The drug product, there is interaction with all of the PACs, SUPAC IR, SUPAC MR, SUPAC SS and TDS, which you have heard about, and whether there may be some other ones coming along, and the PAC SAS interacts back into the drug product.

Here is your Q6A, Q6B is for biologics, and there is some talk eventually of having an AMPAC, which will deal with post-approval changes for analytical methodology and possibly even a PAC-PAC, packaging changes after post-approval for the packaging components.

That kind of a quick overview of what our efforts

[--- Unable To Translate Graphic ---]

have been with ICH and how they interact with some of the other activities of the Center.

Thank you.

DR. WILLIAMS: Thank you, Eric.

My task is to talk to you now about the Biopharmaceutics Coordinating Committee. Before I begin that, I would like to just say a few things to the advisory committee. First of all, somebody reminded me that my ultimate goal as a regulator is to talk about boxes in terms of acronyms, so I never have to use words anymore. I apologize to the committee for the complexity of some of the things we are talking about and the fact that we do end up talking sort of in abbreviations and acronyms.

If you take away one thing from the presentations this morning, I guess it is the message that this is complicated. We are regulating many different dose forms, many different bulk drug substances that range in stability from rock staple to something that has to be kept at minus 70 degrees.

We have to assure continuing quality attributes to shelf life and over time and in the presence of generic substitutions, so I always say the technical challenges associated with product quality are extraordinary, and I

[--- Unable To Translate Graphic ---]

will also say that I think in this country, the industry and the Agency do a remarkable job.

My sense is -- and now I am speaking from my memory as a practicing physician -- is the doctor usually doesn't think too much about product quality, it's a given, it's an assurance. Well, the fact that we have such understanding in this country is related to some of the things you have heard about this morning.

The second thing I would like to say is I would like to remind this committee -- and maybe your historical wisdom is not with it because the composition of the committee has changed -- but, in fact, this committee discussed some of those ICH documents in 1993 and actually endorsed some of the ICH recommendations both for stability in terms of stability conditions, as I recall, as well as that Q3A document for impurities.

That was an experiment where we drew the committee in to these issues, and I think it was a very successful experiment. I might say a word about ICH. ICH is this enterprise involving U.S., Japan, Europe, where 90 percent of the drugs are developed and sold.

It has been working about six and a half years. It has about 40 different guidances that are all designed to

[--- Unable To Translate Graphic ---]

tell sponsors in those three regions how to submit an application, what kind of information do you need to submit in an application for a new drug.

Now, when all is said and done, ICH may even begin working on what we call the Common Technical Document, which would be a single application with a sort of common content and format structure to it, that could be submitted to those regulatory regions.

Now, if you think about the wonder of that in terms of payoff, it would really be extraordinary in terms of avoid duplicative testing, avoiding unnecessary expense, getting better products, lowering the cost of products to the world community.

So, ICH is not a small effort. I think it has been an extraordinary effort, and as you can see from Eric's talk, we have participated very actively in that, including this committee.

### **Biopharmaceutics Coordinating Committee**

Let me go on to the Biopharmaceutics Coordinating Committee and you can show the first overhead, again talking probably in acronyms and boxes.

[Slide.]

I might remind this committee that in a way when

[--- Unable To Translate Graphic ---]

it started out -- and this committee began I believe in 1991 as the Generic Drugs Advisory Committee -- it really focused on biopharmaceutics, and that focused then on one aspect, if you will, of product quality.

You can see we have extended it now by some of our discussions to the world of CMC, and we look forward to the further discussions in the future in the areas of clinical pharmacology and pharmacology/toxicology, which take us a little bit out of the realm of product quality.

There are many aspects to product quality we could talk about, but if I wanted to talk about a core issue that we are always struggling with, it is the issue of sameness. When they give me some kind of award, I want them to tattoo sameness on some part of my body, because it is what we struggle with all the time in the Center.

You will hear it when we talk about BACPAC. The question is, is the drug substance staying the same in terms of its quality attributes that Eric talked about in the presence of change.

A lot of what we talk about the biopharmaceutics is, is the performance of the product staying the same in the presence of change. Now, of course, with the generic issues, that is a key debating point for this country ever

[--- Unable To Translate Graphic ---]

since the passage of Hatch-Waxman in 1984, are the generics the same as the reference listed drug.

Now, the debate about sameness is a CMC debate that I would describe in terms of pharmaceutical equivalence. You will hear in the course of the advisory committee meeting over the next couple of days when we talk about these biologic molecules, the biotech products which are sweeping in to us a great rate, there is a question of sameness in the presence of change. It is a very challenging question when you think about the complexity of some of these molecules.

I call that a pharmaceutical CMC question. In addition, we talk about bioequivalence, performance of the drug product, and when we talk about that aspect of it, we talk about it in terms of biopharmaceutics, bioavailability, bioequivalence, and dissolution.

Now, all of these questions are not routine, humdrum questions of science. I think you have seen from some of the discussions before this committee that they are highly technical and highly difficult, and I would argue the general challenge of establishing sameness is a very deep and difficult scientific challenge.

It relates to metrics, it relates to statistics,

[--- Unable To Translate Graphic ---]

and it is an ongoing debate in our Center, and well as this country, that will continue, and I expect we will continue to bring before this committee, issues of sameness both for the drug substance and the drug product.

Now, this particular set of charts shows you some of the topics that we are struggling with in the area of biopharmaceutics. There are some general core topics that we have been debating for many years and have discussed before this advisory committee. I will just draw the attention of the committee to some of them.

At the righthand corner, you see the individual bioequivalence topic. That is a hot topic, I think it was an interesting scientific topic. You will hear more about it from the chairs of the working group, Dr. Chen and Dr. Patnaik, in the course of the presentation.

As you know, we had a very hard, tough discussion of it before this committee last August. I will always emphasize, even though it was hard and tough, it was a very helpful discussion and some of the recommendations that came from the committee last August, you will see have been taken up in our further recommendations via the guidance that we are preparing.

Also, in the upper left, you see the

[--- Unable To Translate Graphic ---]

biopharmaceutics classification system topic, again, a very exciting topic that we will discuss later on in the course of the next two days.

I won't talk about some of these other ones except with the understanding that in the future, we intend to come before this advisory committee to talk about some of the science underlying some of these topics, and I think you will always find the science interesting and challenging.

[Slide.]

If I had now to do what Eric did, you know, you show all the boxes with the names in them, but really, what are they doing? This is a perhaps better picture that sort of says what are they doing.

Over on the left, we talk about the issue of bioavailability and bioequivalence. The United States, FDA, and this society has a very evolved regulatory and science understanding of what we expect from the drug product and the drug substance over time/

For the drug product performance, these were embodied in our 1977 regulations for bioavailability and bioequivalence. I would say we ask the innovator product, which becomes the reference listed drug, to show stable performance characteristics that are documented through

[--- Unable To Translate Graphic ---]

bioavailability.

Then, after that we expect both that listed drug, during the time it is in the marketplace, as well as its generic equivalence, to also show bioequivalence. So, when we talk about biopharmaceutics and product quality, we are focusing on bioavailability and bioequivalence.

Now, our approaches to documenting bioavailability and bioequivalence relate to blood level studies, pharmacokinetics. I am pleased to say that in 90-plus percent of the cases, we can look at a blood level study and rely on it to document BA/BE.

For certain drugs that right now we are calling "locally acting drug products," you don't get a useful measurement of bioavailability/bioequivalence by looking at the blood level. These are what we call the locally acting drug products, which include inhalation drug products, topical products, some oral products, and some otics and ophthalmics.

You will hear more about some of our challenges in the area of locally acting drug products in the course of the committee meeting, and I don't have to remind this committee that we have brought some of our key issues to the committee in the past to talk about the science aspects of

[--- Unable To Translate Graphic ---]

documenting BA/BE for some of these locally acting drug products.

If we can't use PK and PD, we can use comparative clinical trials to document bioavailability and bioequivalence, and you can see we are thinking about the biopharmaceutic drug classification system -- and you will hear more about it in the course of the meeting -- as a way to say perhaps for some drug substances and drug products, we don't have to do these very expensive in-vivo studies.

So, we kind of look at the BCS classification system as I call it a pointer to say for these drugs, you have to do this, for some of these drug substances and drug products, you don't have to do this, you can do this.

Now, this is an overview. We always have our metrics questions, which you can see is a working group, and then we have our statistical approaches of the metrics, so there is a very logical thought connected with how these working groups interrelate, how they interact, how the whole picture forms based on the general discussion.

Over here are some isolated topics that we will probably be discussing before the committee and actually, in some cases, have discussed before the committee in the past.

[Slide.]

[--- Unable To Translate Graphic ---]

So that is a quick overview of the Biopharmaceutics Coordinating Committee. Again, the overall goal is a set of guidance documents that will tell industry how we would like to see information, how we set regulations standards, what kind of review we will conduct on the information we receive with the goal of being transparent, open, and letting industry know what we need to do to meet these regulatory and statutory requirements.

Now, if I had to kind of put it into some kind of picture that says what do we do and when do we do it, there is this IND process that you see up at the top, Phases I, II, and III of the drug development process, where my metaphor for it is that it is during this period of time that the pharmaceutical sponsor builds a drug product, and that the drug product contains the active substance that Eric talked about, and in association with that effort, you develop the specifications of the drug substance in the drug product.

Now, I don't want to underemphasize how important I think it is, the fact that we ask that the manufacturer of that drug product meet those specifications during its period in the market and during its shelf life is what gives us the assurance of the quality of that product.

[--- Unable To Translate Graphic ---]

Now, we ask that somehow the performance of the product be related to the clinical trial material on which safety and efficacy are based, so there is a logical connection with how we do it. We have all got to agree on it. That is what some of the discussions in front of this advisory committee are all about, and some of our further public discussions and workshops and seminars, and other things.

So, I hope you see there is kind of a logic to what happens in the IND phase relative to the drug product and relative to the documentation of safety and efficacy.

There is a brief interregnum, if you will, prior to approval between the filing of the NDA and before approval, where a product undergoes an inspection. I emphasize that is important because it is critical that the scientists in the Center stay in tune with the field personnel who subsequently inspect to these products.

So, the Agency has a very evolved mechanism that it is not just building a good product, building the specifications of the product, but also manufacturing to those specifications and notifying the field inspector if it starts to fail those specifications.

So, you know, this isn't easy. It is something

[--- Unable To Translate Graphic ---]

that has been built up over many years, but it leads to these high-quality products that we have in the United States.

After approval, we then get into full-scale production. That is when we deal with the world of the PAC, and as you all know, our pharmaceutical manufacturing in this country and elsewhere is associated with change. There are always changes, and it is that concept of change and the desire for stability and quality attributes that has led us to this PAC approach that you heard Doug and Eric talk about.

Change is inevitable and in an era of global consolidation it is increasing, so we are seeing many, many changes in the manufacture of the drug product.

Bioavailability and bioequivalence extends in all directions, and I don't think I need to say much more about it. I think you see the picture. When you hear a lot of our topics in the course of the day, this is what we are talking about. Actually, I think the science of it is quite exciting.

I will turn it back to the Chair. Thank you.

DR. TAYLOR: Thank you, Roger.

Next, we will have some discussion of the Clinical

[--- Unable To Translate Graphic ---]

Pharmacology Section/Medical Policy Coordinating Committee  
by Larry Lesko.

**Clinical Pharmacology Section/Medical  
Policy Coordinating Committee (MPCC)**

DR. LESKO: Thank you, Dr. Taylor, and good  
morning, everybody.

[Slide.]

As you look the program, I think you can see that  
the goal of this morning's session is to lay some  
groundwork, groundwork that provides the context for, not  
only discussions in the rest of the day today and also  
tomorrow on the various topics that are part of the Office  
of Pharmaceutical Sciences, but also some groundwork for  
future meetings the advisory committee to get into some of  
these topics in much more detail where we bring some of the  
issues forward for discussion.

[Slide.]

To continue with the theme of the morning, we are  
going counterclockwise around the CDER Coordinating  
Committees and moving from CMC to Biopharmaceutics. We are  
now down at 6 o'clock, going to look at Medical Policy  
Coordinating Committee, and specifically, a corner of the  
Medical Policy Coordinating Committee called the Clinical

[--- Unable To Translate Graphic ---]

Pharmacology Section.

[Slide.]

Now, consistent with previous discussions of the mission of the Office of Pharmaceutical Sciences, the area of clinical pharmacology follows a very similar suit to both CMC and Biopharmaceutics in that we try to link the review disciplines that are part of OPS back to policy-generating organizations, like our Coordinating Committees, and also back to the research base for some of our policymaking.

So, for medical policy, then, we are focusing on the review discipline of clinical pharmacology, and where research comes into play in the working groups of medical policy, we look forward to the CDDI collaborative initiative for generating some of the research information that become part of the policymaking under MPCC.

[Slide.]

Now, the issues for the committee today, as I say, are really to provide some background and relationships, not only with the Medical Policy Coordinating Committee, Clin Pharm Section, but also for the Office of Clinical Pharmacology and Biopharmaceutics, which drives a lot of the efforts under MPCC in the area of clinical pharmacology.

So, my goal here today is to provide the context,

[--- Unable To Translate Graphic ---]

and I think we can move then from the context to some very specific issues, and we will begin to do that tomorrow, at 1 o'clock or thereabout tomorrow afternoon we get into some specific guidance or science related issues in clinical pharmacology, and you will be hearing a little about the core information in clinical pharmacology and biopharmaceutics needed for drug approval, the area of drug interactions, PK/PD, and then finally you will hear something about the labeling of drug products in the Clinical Pharmacology Section.

All of these initiatives represent potential topics, and I anticipate topics for our next advisory committee that will be coming up later this year, I believe.

[Slide.]

I want to go back to the organizational slide that Roger had shown earlier, and bring your attention back to the Office of Pharmaceutical Sciences and specifically, under OPS, the Office of Clinical Pharmacology and Biopharmaceutics.

As its name implies, it has two responsibilities in the review management part of the Center. It reviews Section 6 of applications that contain, not only the biopharmaceutics information that comes out of drug

[--- Unable To Translate Graphic ---]

development, but also the clinical pharmacology information.

So, in a sense, we have a dual role. In the area of biopharmaceutics, as you heard with the Biopharm Coordinating Committee, we coordinate our policy development within the office, through BCC, with the Office of Generic Drugs and specifically, the Division of Bioequivalence. We share many of the same interests and same scientific topics in the area of dissolution, bioavailability, and bioequivalence.

On the other hand, clinical pharmacology is defined in many different ways, but many think of it as a bridge science, a science that links the basic science of drug development with the eventual therapeutic use of that drug.

So, by virtue of its definition as a bridge science, when we set up the Clinical Pharmacology Section of the MPCC, we recognized and acknowledged that this committee, this group has to function as the science functions and we drew in representation from the Office of Review Management to staff the Clinical Pharmacology Section.

So, this section then represents an interdisciplinary group composed of individuals from the

[--- Unable To Translate Graphic ---]

Office of Clinical Pharmacology and Biopharmaceutics and representation from the different Office of Drug Evaluations under the Office of Review Management. So, MPCC is a nice link, if you will, between the so-called "super" offices within CDER, and it gives us a forum and an opportunity to be consistent in the way we approach some of the clinical pharmacology topics.

The members of the Clinical Pharmacology Section were selected specifically with skill sets in mind, in particular their knowledge and experience in clinical pharmacology and their understanding of drug development with regard to this particular discipline.

[Slide.]

Now, focusing on the office a little bit, I think this will give you a sense of the matrix aspects of the Center. When we talk about Clin Pharm, Bio Pharm, and we look at the types of studies that come in, in an application, the types of studies that come out of the different early phases of drug development, I have separated them into those I have indicated in red, which I would refer to as the biopharmaceutics components of Section 6 of the application, and then down here, in the black print, are those that we might label clinical pharmacology.

[--- Unable To Translate Graphic ---]

We attempt to distinguish the studies and the topics by virtue of what we are asking in terms of questions. Generally, these topics are asking questions about the drug or the drug delivery system, and that sort of links to Roger's view of product quality issues in the BCC.

On the other hand, these topics are I would say studies and questions that relate to the performance of the drug substance, once it gets out of the dosage form, what happens to it. That is to say, the pharmacokinetics, the pharmacodynamics, and the link of those disciplines to the eventual area of therapeutics.

So, in terms of matrix in the Center, the BCC then sort of links the product quality, biopharmaceutics issues within these two offices. In contrast, the Medical Policy Coordinating Committee, the Clin Pharm Section, matrix in this fashion, linking PK/PD and the other aspects of early clinical trials with the later clinical trials in Phase III and confirmatory studies that are reviewed over in the Office of Review Management. In many ways, in drug development, these form the basis for the design of these studies that occur in Phase III, so it is a natural link, if you will, between our office and ORM.

[Slide.]

[--- Unable To Translate Graphic ---]

Now, getting to the Clin Pharm Section specifically, we have again our home is the Medical Policy Coordinating Committee. We have our section with the representation from the Office of Drug Evaluations, 1 through 5, and then down below are the initial six working groups that are formed under Clin Pharm Section.

So, the Medical Policy Coordinating Committee, like other coordinating committees, consists of a series of working groups whose prime objective is to develop the guidances for the industry that pertain to drug development.

Now, in that portfolio of studies that represent clinical pharmacology, the ones that we selected based on our impressions of need are, first, in the area of disease states, renal studies and hepatic studies.

Then, in the area of drug interactions, we have an in-vitro drug metabolism interaction guidance that was recently released by the Center, and we are currently working on a companion to that which emphasizes the in-vivo drug metabolism interaction aspects of drug development, and in particular, the predictability of these results from the in-vitro studies.

[Slide.]

Finally, over on the right are two working groups

[--- Unable To Translate Graphic ---]

that are focusing on an area I would call "pharmacometrics." The first is looking at a guidance dealing with population PK/PD, and the second, with a topic of PK/PD or dose response.

[Slide.]

Now, what does the Clin Pharm Section do? I mean what was the purpose of it? Well, our goals in setting up the Clin Pharm Section was again to coordinate our activities with the Office of Drug Evaluation. So, what we have asked the Clin Pharm Section to do is to provide oversight to these working groups.

In particular, we want to assure that good science is part of these guidance initiatives and also that they have relevance to the clinical use of the drug therapeutics.

Next, we have asked the Clin Pharm Section to recommend the needs that they see for new policy or new guidance development initiatives, in other words, to make suggestions that we could consider for future and subsequent working groups.

Finally, because these guidances not only impact the way we review our work in the Office of Pharmaceutical Sciences and OCPB, but also I think the Office of Review Management, the Clin Pharm Section has the responsibility to

[--- Unable To Translate Graphic ---]

facilitate communication during the guidance development process between OPS and the Office of Review Management, so they act like emissaries, if you will, to the respective Office of Drug Evaluations to keep them up to date on what we are doing, to get their input, and to eventually facilitate the implementation of these guidances.

[Slide.]

Now, the section is new, and we originally proposed this section back in July of last summer to the Medical Policy Coordinating Committee, and it was approved and we moved forward in August 1996 with the membership and the duties of the Clin Pharm Section. We had our first meeting of our Clin Pharm Section earlier this year, and went over the goals of this section and what our plans were for the first six working groups that I already showed on the slide.

We have already utilized the Clin Pharm Section in one of our lead guidance projects, which is the renal guidance, and the group was very instrumental in providing their scientific expertise into the development of a draft guidance for renal studies and also for soliciting the comments from the different Office of Drug Evaluations to allow us to update that draft as we move forward in the

[--- Unable To Translate Graphic ---]

process.

So, we did that recently at our second meeting of the group, and we plan to meet on a quarterly basis and focus, one by one, on the individual guidances.

[Slide.]

Now, how does this all sort of flow together and where does the advisory committee come in? Well, this is something I have called "Path to a Guidance," and it is really a path that comes out of the Good Guidance Practices that were published in the Federal Register back in February of this year.

As you can see, the path is again fairly tedious in the sense of doing due diligence, and as we move along the path, we try to look into our own database in terms of learning and looking at what the issues are in the respective areas of clinical pharmacology.

The committee in the past has recommended that we do this almost on every occasion to learn what are the questions and what are the things we want to know. The working groups really come in here. There is a lot of internal discussion of the working groups. When you see a draft guidance before the committee, it usually is the result of many, many months of discussion and debate, and in

[--- Unable To Translate Graphic ---]

many cases, unresolved issues that come before the committee.

Over here is the public input component of guidance development. The expert meeting helps us frame issues. The advisory committee oftentimes deals with specific questions that we bring before it, and then the trade and professional organizations come into play. As you can see, the path is again a well-structured one, defined not only in our Good Guidance Practice, but also in a CDER map or standard operating procedures for doing this sort of activity.

[Slide.]

Now, I mentioned the expert meeting, and this represents a typical agenda for a Clin Pharm topic from an expert meeting. An expert meeting is one where we invite a number of academicians, people from industry, to help us, not write a guidance or not get into the guidance per se, but rather to sort of say what are the questions, what are the issues, what do we need to deal with in the guidance. That is the purpose of the expert meeting.

We had one recently for our renal study initiative in February of '97, and there are four bullets up here. The first of them really gets into the issue of when are studies

[--- Unable To Translate Graphic ---]

not needed. So, in a sense, I would say most of our initiatives are designed to not only look at what is, but also what should be. So, we ask the question when are studies not needed.

We also get into the broad area of study design. We get into the area of data analyses. Finally, all of our initiatives will have a component that deals with labeling, such that the design data analysis leads us into some language for the labeling, which eventually ends up in the product insert. So, we are trying to develop consistency, if you will, in each of these initiatives with common links.

[Slide.]

Now, I mentioned the renal guidance, and I am using it as an example of process and how the science plays into the guidance development, and taking those broad issues that I mentioned as part of our expert meeting, the next step was for the working group to begin to develop and write the guidance.

You can see that the guidance looks something like this. This is a table of contents, and the guidance will be composed of the same sections that we talked about in the previous slide in terms of framing issues, so when the document is eventually done, it will deal with when studies

[--- Unable To Translate Graphic ---]

are needed or not needed, again, the study design.

You can see the expansion of that topic in terms of the sections of the guidance, the data analysis dealing with parameter estimation and how that links to dosing recommendations for the package insert, and then finally, how does all of the information and studies in drug development lead to language in the labeling for individualization of dose.

So, if we are talking about renal, this is what it would look like. If we are talking about hepatic, it would have the same flow, and so on, and so forth.

[Slide.]

Finally, with those six working groups, this slide gives you a view of where we are with the individual guidance efforts. This one up here is the in-vitro drug metabolism, drug interaction guidance that Dr. Collins headed up, and that was under construction for a long time from October '94 all the way to April '97, almost a three-year period, and that was signed off and released by the Center very recently.

I have been talking about the renal guidance as a prototype for the initiatives under the Clin Pharm Section, and as you can see, we are pretty far along with this

[--- Unable To Translate Graphic ---]

process. We are right about at this point having had the expert meeting and now putting pencil to paper and writing the guidance.

Out here is the advisory committee, and you can see that we are getting ready to bring some of these issues to the advisory committee as we move forward.

Coming behind the renal guidance in terms of their rate of progress are the ones on the population PK, PK/PD, hepatic, and then finally our most recent initiation of the In-Vivo Drug Metabolism/Drug Interaction Working Group.

So, as we move down the path, we can look forward to seeing some of these things in terms of the issues that we want input on and that we will bring forth to the committee.

Now, tomorrow, we will give sort of a preview of some of this. I think we will be talking about PK/PD, we will be talking about the drug metabolism, and also the labeling initiative which isn't on this particular slide, and another topic that we are very interested in getting input on, and that is the core information needed for the Clin Pharm/Bio Pharm component of Drug Development.

I think that is it. Thanks.

DR. TAYLOR: Thank you.

[--- Unable To Translate Graphic ---]

### **Open Public Hearing**

We had an opportunity here for a fairly extensive discussion of the kinds of issues that come up in the Office of Pharmaceutical Sciences and the various committees that apply to the office.

The time has come now for us to have an opportunity for the public to make comment on what we have heard this morning. I don't believe we have individuals that indicated that they were going to make public comment, but if you would like to make public comment on these issues that we have discussed, would you come to the mike, identify yourself and make that comment at this time.

[No response.]

### **Committee Discussion**

DR. TAYLOR: There being no public comment, I would like to now focus on the committee to discuss the issues that were raised in the morning session here, and the committee discussion can begin now. Any discussion by the committee? Yes.

DR. BRAZEAU: I have some questions and some suggestions. One of the concerns I have with the new structure I am seeing here is communication between the various groups, and the question I have is what methods have

[--- Unable To Translate Graphic ---]

been developed to assume that there is communication.

For example, I am a little bothered, and maybe I don't understand, why Laboratory for the Office of Clinical Pharmacology is separate from the other Clinical Pharmacology. That is one thing that became obvious as I was reading through it last night. So, I am not sure how the left hand and the right hand is going to know what each other is doing. So, that is one of my first questions.

DR. TAYLOR: You say separate from the other?

DR. BRAZEAU: Yes. It seemed that there was an Office of the Laboratory for Clinical Pharmacology, which was separate from the Office of Clinical Pharmacology.

DR. ZIMMERMAN: So, the Laboratory for Clinical Pharmacology is in the Office of OTR, and then there is actually another office that is Clinical Pharmacology and Biopharmaceutics. So, we had discussed this. We didn't understand why, if they have gone through this reorganization, it seems to me that we don't understand why they are not together essentially.

DR. TAYLOR: Were there other comments or questions that you want to raise?

DR. BRAZEAU: Yes, there are some other things, too.

[--- Unable To Translate Graphic ---]

DR. TAYLOR: Do you want to have Roger explain that to us after that?

DR. ZIMMERMAN: Sure.

DR. BRAZEAU: The other thing, as I was looking at the CMC Coordinating Committee, and I was looking at some of the working groups versus some of the committees they had, I guess I am thinking a little ahead of things. A lot of the working groups that they have are dealing with issues that they have to deal with on a day-to-day, but I am wondering about -- they have I believe it is a working group that is looking at liposomes and complexing agents or complexing agents and liposomes -- and I am wondering should that working group be a committee, because I think we are going to see more and more of these type of projects, and the second issue, I am wondering if they should be dividing this into different types, because we have liposomes, we have complexing agents, then, we have microspheres, nanoparticles, and all those different types of dosage forms are being formulated.

I am wondering if the Agency might try to be more proactive -- and they extremely are proactive right now -- but to try to anticipate the kind of things they are going to see down the road related to these other type of dosage

[--- Unable To Translate Graphic ---]

forms.

The other thing that I didn't see, that I might suggest they might have a working group at this stage, is as we go into the area of gene delivery in the literature, the scientific literature is just filled with all different types of gene delivery, and particularly some of these nonviral vectors that are being looked at, like the cationic liposomes.

I think it would be useful for the Agency to have a working group that would start to get at least ahead of what they might see in the future. We are talking about things to enhance delivery of plasmids, and I think it would be useful if at least some group was there to be aware of it, because eventually, there are going to be products on the road that are going to use some of these nonviral vectors, and I would hate the Agency to be behind the eight ball.

DR. TAYLOR: Roger, would you like to comment?

DR. WILLIAMS: Yes. Thank you, Dr. Taylor. I hope it is all right with the Chair if other people from the Agency could supplement whatever else I might say because certainly there are people here who are more knowledgeable than I am. I would encourage people in back of me to raise

[--- Unable To Translate Graphic ---]

their hand if it is all right with you, and add to what I am saying.

DR. TAYLOR: Sure. The only admonition is that they use the mike and they identify themselves.

DR. WILLIAMS: Okay. I will just touch on -- maybe I will answer the first and third comments, and I will leave it to somebody else to comment on liposomes and complexing agents.

First of all, I think the first question is a terrific question and the whole issue of communication and coordination, as you can see, it is something we have struggled with mightily ever since we were put into our new structure in October of 1995.

I don't want to scare Jim MacGregor because he just walked in the door three days ago, but you could imagine as a structure, blowing apart the Office of Testing and Research and putting each of the clumps with the Review Divisions. Now, I hope that model is clear.

I could take the group of Karl Flora's and move it in connection with the chemists in the Center, and I think you suggested that for Clinical Pharmacology, you could move that group with Larry in the Office of Clinical Pharmacology and Biopharmaceutics.

[--- Unable To Translate Graphic ---]

I might mention that in some areas of the Center, that model exists. For example, in the Division of Antiviral Drug Products, they have a research unit that is in close proximity both in terms of space and management to the review process. It is a great model. We happen to choose the other model because we thought that there was a value to having the research scientists working together as a group.

I might say that whichever model you choose, you impose challenges with it, so, you know, without being facetious, I might say if somebody saw the clinical pharmacologists working in association with Larry and OCPB, somebody would say, well, why didn't you move them with OTR where they would be, you know, closer to their kind.

I don't have an answer here, and all I can say is you try one model and see if it works; if it doesn't work very well, you try another model.

Should I pause there?

DR. TAYLOR: Is there rebuttal?

DR. ZIMMERMAN: Just an additional question. So what you are telling us, then, is that all the research in this is done in OTR, and the other three offices are review offices, are considered to be review offices, is that what

[--- Unable To Translate Graphic ---]

you are saying?

DR. WILLIAMS: Yes, Dr. Zimmerman, but I wouldn't say it is quite so bright line. I think people in the review offices do research, and some of the people in research build policy, and also can conduct review, so I think there is kind of a healthy interaction here if we can promote it. But for the most part, what you said is accurate.

Should I go on to the third question?

DR. TAYLOR: Any other comment in regard to the Clinical Pharmacology coordination?

DR. BRAZEAU: Well, I think the critical issue is that there is going to be good lines of communication, and I don't know if these groups routinely get together on a quarterly basis, so they know what each other is doing, because I could see things getting lost somewhere. That would be one of my concerns.

DR. WILLIAMS: I think it is a very good point. You know, people sometimes laugh at me for all these boxes, but what I would say the boxes do is they create a group of people who are identifiably the ones you communicate with.

Sometimes I imagine what would the Agency be like without all its structure, and you just have 10,000 people

[--- Unable To Translate Graphic ---]

milling around trying to figure out who to talk to, and some people say that's what we are like anyway, but the reality is I think these structures that we have talked about so much more create an environment so people know who they need to talk to, and one of our biggest challenges is achieving what Dr. Brazeau talked about.

DR. TAYLOR: There is a comment from the audience.

DR. LESKO: Larry Lesko from OCPB. I wanted to address the communication topic that came up by Dr. Zimmerman and Dr. Brazeau, and point out that we acknowledge the challenge of that communication, but I think in some ways it is working well.

Dr. Collins runs the Laboratory of Clinical Pharmacology and reviews all of the briefings that come out of our office along with the others in the office, as well, and participates in our briefings of the NDAs when we review the science that is contained in our section.

So, one level of communication is at that level, where he brings a lot of his knowledge from drug metabolism, drug interactions, and what is going on in the laboratory to apply it and communicate it with the office in the review process.

The other flow of information between the Office

[--- Unable To Translate Graphic ---]

and Laboratory of Clinical Pharmacology is that the laboratory collaborates, as Roger mentioned, in our office. People have a certain degree of time that they spend on research that is relevant to the regulatory review process, but a lot of that is collaborations with the Laboratory of Clinical Pharmacology.

In the past, we have had a small number of people actually go to the laboratory and collaborate on research projects, and much of that work actually not only result in publications, but also underpin some of the elements of that in-vitro drug metabolism, drug interaction guidance.

So, when the interaction works in that sense, it is very useful to us.

DR. TAYLOR: Thank you. Any other comment on the issue of coordination of Clinical Pharmacology?

Okay. Will you move to comment on I guess the third item?

DR. VESTAL: Actually, Dr. Taylor, this might relate to that. It is a question I had about the effect of this new section of Clinical Pharmacology and how it fits into the review process.

I think this may just be my lack of understanding of the process, but I am wondering whether the section of

[--- Unable To Translate Graphic ---]

Clinical Pharmacology actually participates in the review of NDAs and ANDAs, or does it just focus primarily on policy, guidance development, and so on, and if it is involved in the review process, as a new structure, how has it affected the time required for processing applications.

DR. LESKO: Those are all good questions. I will try to answer them, and I don't know if I will remember each of them, but the Clin Pharm Section, as I showed it, is made up of individuals who have what I would call oversight for the specific working groups that are very topic oriented.

The individuals in the Clin Pharm Section, particularly from the Office of Drug Evaluation, are all medical officers that conduct primary reviews of NDAs and in particular the clinical trial sections of NDAs, so they have hands-on experience.

It is almost as if the short-term efforts of the individuals involved with the Clin Pharm Section are for the review process, but the longer term investment of time is for the development of policy, so people wear dual hats in the Clin Pharm Section, functioning both as reviewers and as members of the section to develop policy.

Does that make sense?

DR. VESTAL: Maybe. Does that mean that

[--- Unable To Translate Graphic ---]

individuals have two bosses, as it were, that is, are they both in the Office of Review Management and the Office of Pharmaceutical Science?

DR. LESKO: The makeup of the group, if they are from the Office of Drug Evaluation, they have one boss, with is in the ORM stream or the Office of Review Management. When we bring people from different disciplines together in a working group, it becomes basically kind of a matrix organization at that point with not so much of a boss as much as a leader of the working group.

When the working group is done or the guidance project is done, the individuals return to their home base, which is in the respective offices.

DR. VESTAL: So, can I just ask, then, what determines -- I mean there is some review process that takes place in the Office of Pharmaceutical Science, and does that mean the need for review in the Office of Pharmaceutical Science is determined by a primary reviewer under ORM, is that what happens, or does every NDA get seen by people in the Office of Pharmaceutical Science?

DR. LESKO: When the NDA comes in, when all the volumes come in, it is really broken up into disciplines, so a section of the NDA would come to our office, for example,

[--- Unable To Translate Graphic ---]

and a section would go to the medical officers, and a section to Chemistry, et cetera. Our section is labeled Section 6, and it contains all the Clin Pharm/Bio Pharm studies, and that is what we focus on.

Now, the efforts of individuals, not only in our office, but in many of the offices in the Office of Pharmaceutical Sciences are sort of set up as a priority by the deadline to review the NDA, so that the main goal of individuals in the review offices is to meet the deadlines for review of that application.

Now, within the context of that driver of people's time is the time that they have to spend on the working groups on the Clin Pharm Section and on policy development, so it becomes a sense of priorities, then, in the individual's mind, for example, if they can participate in a working group, if they can lead a working groups. It is a given that they have a review responsibility that they have to meet and deadline to meet, as well.

DR. BRAZEAU: Now, this is where maybe I am a bit confused. Some of the proposed guidances to date, do they come from either working groups or do they come from the committees? Did I see them from both areas?

DR. LESKO: The way it would work is the working

[--- Unable To Translate Graphic ---]

group produces a guidance. It is a draft guidance which is then reviewed in the affected offices. So, for example, a renal disease guidance, renal disease studies, that would be reviewed in our office since we review that part of the application when it comes in, and it would also be reviewed by medical officers who have input into the final labeling of the product.

So, when we finish that guidance, it will be distributed both within the Office of Clinical Pharmacology and Biopharmaceutics and also the Office of Drug Evaluation, and that is like a comment period.

Those comments are brought in to the working group who revise the guidance, and then it is moved up through the Medical Policy Coordinating Committee. I would say the final signoff on the guidance would be the responsibility of the chairs of MPCC, which would be Roger Williams and Bob Temple.

DR. TAYLOR: Dr. Williams.

DR. WILLIAMS: Dr. Taylor, let me just add to what Larry said, because the reality is the way life works in the Center is review comes first and that is our first priority, particularly under the mandate of PADUFA, the Prescription Drug User Fee Act.

[--- Unable To Translate Graphic ---]

There has been a revolution in the Center in terms of meeting those review performance goals, which is six months for a priority review and 12 months for a standard review. Everything we have been talking about so far this morning is what I call future investment, and it comes after we meet those review commitments. So, a lot of what you see here are people working overtime, you know, beyond their usual hours, to make all this policy and research possible.

The other thing I might add is the review process is a matrix process, so many review disciplines contribute to that review of a new drug as it goes out the door.

DR. TAYLOR: How often do various components that are similar get together to discuss that review of, say, an individual application, or is it just signed off and sent to the next level?

DR. WILLIAMS: No, I think there is good communication within an Office of Review Management office and the divisions that, you know, lead to a final assessment of a new drug application. A lot of that is handled by project managers who work very closely with the review staff to make sure that their reviews are done on time and that they communicate well.

There are a lot of internal meetings with a

[--- Unable To Translate Graphic ---]

sponsor on a particular application, so that as you get to the final approval letter with the labeling, it is a highly coordinated activity actually, but is an activity we haven't talked much about today, because, you know, this is more a policy aspect for this particular committee to focus on.

DR. TAYLOR: I think it is important because the statement you just made is that review comes first and everything else is just value added, as I sort of think about it. So, I guess I do have some concern that the policy aspect becomes secondary almost, but in my mind, it is critical to the development of efficient operations within the office along the lines that have been already discussed, like future therapies.

I do think you need to develop some strategies to tease out where you ought to be going before you get there.

DR. VESTAL: I would just like to add that I think that Roger and his staff should be congratulated on taking on these very important policy issues and the development of what I think is a ramped-up effort to produce guidance documents.

I believe that this is going to help create a more level playing field, so that companies at various levels of size and experience can go through the development process

[--- Unable To Translate Graphic ---]

of their products in as an efficient manner as possible. So, I think this effort is really something to be strongly endorsed by this committee.

I guess I am somewhat concerned that it sounds like it is almost an after-hours sort of activity, and it may be that we have a problem with availability of resources.

DR. WALKES: Mr. Chairman.

DR. TAYLOR: Yes.

DR. WALKES: I heard through the discussion this morning the talk that once a guidance is implemented, that the reviewer is obliged to follow the guidance. As we all know, there may be times when a reviewer may have a question or not feel that something exactly meets the standard, there may be some doubt.

What happens in that instance, do you get together and talk about it, and then does the policy that generally applies in other instances, does that take precedence over the guidance?

DR. TAYLOR: Dr. Williams.

DR. WILLIAMS: Again, that is an excellent question, and I would say -- it is a complicated question. I mean we have this kind of boiler plate statement that says

[--- Unable To Translate Graphic ---]

guidances aren't binding on us or the reviewer, and I think the intent underlying that approach is that guidances are sort of best practices, but we don't want to bind anybody if they have an alternate approach.

So, we always say to a sponsor if you have a better way or an alternate way, come in and tell us about it and we are glad to hear it.

Now, what does a guidance do for a reviewer? I think there is an intent of the guidance to bring us all in line in terms of what we recommend to industry or what we say in our review, but we don't want to deny our scientific review staff the possibility of having a better question, recognizing that a guidance can't cover every possibility.

They may have a better thought, a better question, a better approach, and they should be able to deviate from a guidance, but we don't want to make that kind of standard practice, otherwise, the guidance has no meaning, and it wasn't worth building in the first place.

So, there are words in this Good Guidance Practice that say a reviewer can build an alternate approach with supervisory concurrence, and I would like to think that the Center would build the mechanism to capture those very thoughtful contributions from the reviewer and use them in

[--- Unable To Translate Graphic ---]

updating a guidance later on, to say, well, it was necessary.

DR. WALKES: You said that your function basically is ensuring sameness, and we look to rely upon that when we are using the products that are approved.

So, getting back to the guidance, because we talked a lot about that. There was a Q3A guidance that was talked about by Doug Sporn, who was talking about -- or maybe it was Dr. Sheinin who was talking about impurities in drug substances, and that one-tenth of a percent that was identified, and that sort of thing.

So, if we are looking at, not necessarily stuff that is done here in this country, but suppose we start taking in more products from abroad, what happens with those guidances, I mean is one-tenth of a percent acceptable, has somebody decided that that is okay, or are going to find down the line like we did with the recent release on generic Premarin that we need to revisit that issue totally because there is a substance that we see here that may be more important than we originally thought?

So, then, do we have to look at more clinical trials when we are dealing with those things that we are looking to bring into our market that aren't produced here?

[--- Unable To Translate Graphic ---]

DR. TAYLOR: Roger.

DR. WILLIAMS: Would it be all right to ask Eric to respond?

DR. TAYLOR: Sure.

DR. SHEININ: Eric Sheinin, Office of New Drug Chemistry. The guidances apply to any product that an applicant or sponsor wants to market in the U.S. It doesn't matter where the product originates. We do have some foreign applicants who manufacture totally in other countries and then just import the finished drug product and distribute it here.

There are also many, many situations where the active pharmaceutical ingredient is manufactured out of the United States and then is shipped into the U.S. for eventual formulation into a drug product. Again, everything in the guidances apply to those materials, as well. So, Q3A, which deals with the drug substance, would into that category.

We heard somewhere on the order of 70 to 80 percent of the APIs are manufactured outside of the U.S. these days. This applies, not only for generics, but for the new drugs, as well. A very high percentage of those actives come from out of the U.S.

The guidances, well, the same standards have to be

[--- Unable To Translate Graphic ---]

met. Now, there may be some instances where an impurity that is present lower than a tenth of a percent is critical. The discussions that went into the Q3A, there were pharm/tox -- I guess we could call them consultants or advisers -- who made up part of the expert working group. That is how the ICH operates.

The committees that put together the guidances are called expert working groups, and they had input from pharm/tox experts in all three regions as that guidance was developed, and based on their input, it was felt that a tenth of a percent should cover almost all of the instances where an impurity might have a pharmacological or physiological effect on somebody taking that drug product down the road.

If there are cases where one would suspect that, say, a 0.01 percent of an impurity could be a problem, those would be dealt with on a case-by-case basis. We certainly are always free to ask for additional information, ask for a company to go down to a lower level and provide us information.

Some of that type of sense that there might be a problem would be picked up or hopefully would be picked up during the clinical trials and during the pharm/tox studies

[--- Unable To Translate Graphic ---]

that are done even before the IND stages.

Hopefully, during the Phase III IND trials, the formulation is essentially the same as what is going to be approved in the drug application when it comes in, so that it would be using the same quality of material, same quality of active ingredient, same quality of drug product.

That is one way that where an impurity is identified, that it is qualified, that it was used in the clinical trials and there were no unexpected or unwanted physiological effects. So, if there was an impurity that was below that level and was suspected from those studies that there might have to be tighter control, it certainly could be asked for.

DR. TAYLOR: Dr. Walkes?

DR. WALKES: I think the question was well answered.

DR. TAYLOR: Good. Dr. Edeki.

DR. EDEKI: I would like to congratulate the Office of Pharmaceutical Science for all these innovative changes that are going on. I realize it to be very difficult to have a perfect system, and I am sure that with time, the present setup will also undergo some further refinement.

[--- Unable To Translate Graphic ---]

I just have a quick question. Because of people participating in various working groups and various committees, when you hold meetings, is it always possible to have most of the members participating in those meetings? Do you have quorum all the time, anything like that?

DR. WILLIAMS: It is always a challenge.

DR. TAYLOR: Yes.

DR. WILLIAMS: Just a couple of comments. I wanted to come back to a question of Dr. Walkes, because I thought it merited some attention, because it has been a topic for this committee in the past, which is the Premarin decision.

You all know that we circulated to you some of the public statements from the Agency in that regard. We did not intend to discuss it at this meeting, and I don't think we will discuss it. I think if we had intended to discuss it, we would have had to put it in the notice, and I am not sure there is any point in discussing it in front of this committee because, as you can see, the Center has issued a final scientific conclusion in the matter.

But I will say conceptually, your question went right to the heart of the question, which is -- and it is a pharmaceutical equivalence question -- what are the active

[--- Unable To Translate Graphic ---]

ingredients, what are impurities, can you full characterize the product, and moving past Premarin for a minute, these are questions that we will continue to struggle with, with complex biologic mixtures, certain biotechnology products, herbal products. I mean sad to say, these issues will be with us for many years, just as Premarin was.

DR. TAYLOR: Thank you. Before we move on to the next question that was generated, any other comment on guidances or coordination of the clinical pharmacology groups?

DR. BRANCH: Can I make one comment?

DR. TAYLOR: Yes.

DR. BRANCH: I am a newcomer to the committee, so it has been an interesting experience hearing about the details of the changes that are taking place. A comment I would make is that it is interesting how international harmonization is leading to the development of guidances which, as I see it, as being the fundamental driving force for change for a radical restructuring within the Agency. I would have to congratulate the Agency in responding to this whole changing perception of the relationship between regulators and industry.

I think that what I am hearing coming through from

[--- Unable To Translate Graphic ---]

the various subsections is the process of developing guidances is really focusing attention on not only what is known, but what isn't known, and as each guidance is developed, areas that are uncertainties are being identified.

It would seem to me that there is a tremendous congruency of motivation in both industry, as well as the Agency, to try and resolve some of these questions. I guess my question relates to potential for creating funding to address the issues of paying for the Agency time in creating these guidances, for paying for research that is focused on answering the questions that are raised by guidances, which would be to industry's benefit.

I would like to surface an idea that the PADUFA approach, which has been restricted to regulation, could be considered to be extended to supporting research that focuses on resolving guidances, because I think it is to everybody's best interest to that effect.

Is there any potential or any suggestions of how such an approach might be raised or is this unrealistic?

DR. TAYLOR: Who would like to tackle that one?  
Roger, you are elected.

DR. WILLIAMS: I put this under the "R" category.

[--- Unable To Translate Graphic ---]

There is some difficulty discussing it in front of this committee, and there is some difficulty discussing it from our FDA staff, because I think the general rule is, you know, we are not here to plead for resources. But at the same time, I think it is a key question, you know, it is a resource question that has to be answered societally.

I might mention that other societies have a different view of agencies, you know, where they are really supposed to just do an assessment and get it out the door.

Our Agency for I think good public health reasons has always thought it had a broader mandate. You may know that our current lead commissioner is Dr. Friedman. He has had a strong interest in Agency research and policy, and he recently commissioned a committee to look at how we do research and how we generate resources for it.

I don't think there are easy answers. I think probably this committee could talk for a couple more days about it. I think it is a question that needs to be asked by our society and addressed by our Congress.

DR. BRANCH: Maybe restructuring the question, is there a way that this committee could support or initiate or help direct an initiative towards that effect? Does this committee have any role within that purview? I am not quite

[--- Unable To Translate Graphic ---]

sure what this committee really has a role for. I am trying to work out why -- it seems to me that this is a committee in transition. It started off with one role, and this a show and tell exercise where you are really redefining what you are asking us to do.

So, my question to you is, is this something that you would like us to try and take on?

DR. WILLIAMS: You know, that thought crossed my mind this morning, as well. I mean we are setting up these collaborative enterprises, and I think it would take a lot more thought and discussion in the Agency, but I could easily imagine this committee providing some oversight to those collaborative enterprises, if nothing else, by listening to some of the science that would be generated out of there, and saying how does this translate into good policy.

So, it could either be done generally or it could be done on a case-by-case basis.

DR. TAYLOR: Any other comment? Dr. Vestal.

DR. VESTAL: I think one thing we can do is endorse the collaborative efforts, and that is what you are doing, Dr. Branch, with your comment and question. I think that this is a very healthy thing for the Agency to be doing

[--- Unable To Translate Graphic ---]

because these kinds of collaborations at least in principle should lead to the more efficient use of time and resources in order to answer important questions that are relevant to regulatory matters and the science that underlies them.

I think these kinds of collaborations have the potential to diminish what I perceive to have been a traditional kind of adversarial relationship between the industry and the Agency.

So, I think that this is a very positive thing that is beginning to take place on a broader scale.

DR. TAYLOR: Dr. Brazeau.

DR. BRAZEAU: I think we are probably going to be hearing more about some of their collaborative efforts this afternoon, but I think a role of this committee could be two things. One would be to help the Agency prioritize what should be perhaps some of the more pertinent issues to develop collaborative issues research with, and second of all, maybe help in that decision of where do we go, what do we focus our time and efforts on, and second of all, then to look at what comes back in that science, you know, we want to make sure that the best science gets done that is possible. I think that is where this committee can play a role in conjunction with other advisory committees.

[--- Unable To Translate Graphic ---]

DR. TAYLOR: I look forward to this afternoon's discussion. I think we need to have the benefit of that to see what the thinking is first, and then we can critique that based on that data.

Dr. Williams.

DR. WILLIAMS: Just a further comment, you know, things kind of hit my mind, and the cost savings here can really be extraordinary. I have heard some estimates related to Q1A, this ICH stability document, that a global company that was developing a stability program in Japan, U.S. and the 15 member states of Europe had seen their stability program costs go down from about \$1.25 million for a particular drug to about \$125,000. It was a 90 percent cut, because you have to think about each country was sort of asking for a different set of stability conditions and, you know, test procedures, and the harmonization of that had extraordinary payoff.

DR. TAYLOR: I think we need to move on to some of the other topics that were introduced. The other topic was development of working groups that had vision, looking at specific kinds of things, liposome and other complexing agent technologies, and the other comment was on gene delivery systems.

[--- Unable To Translate Graphic ---]

DR. BRAZEAU: I just wanted to kind of maybe clarify what I said or what I meant to say, is that I think there is working group, I believe on complexing agents and liposomes, and I guess my concern is, is this working group too broad, or more importantly, is it the time to start developing a guidance with respect to some of these particulate dosage forms that we are going to see.

I don't know what the status is. It seems to me you are going to see more of these in the future when you are delivering peptides and proteins, and maybe that is a guidance that needs to start on its way. I don't know if there is one, but it seems to me it is something that the Agency might want to consider.

DR. SHEININ: I can address that somewhat. The Liposome and Complexing Agents Working Group actually within the last couple of months has been divided into two working groups. Originally, it was set up and there was one chair of the working group. He left the Agency to I believe return to academia. It is still listed as one working group, but there are two subgroups under that.

It is a very good question you have, should it perhaps be a technical committee, a standing committee, because there may be long-term implications there, and I

[--- Unable To Translate Graphic ---]

think it is a very good suggestion. The CMC Coordinating Committee meets once a month, and I think that is something we ought to consider at our next meeting.

As you said, there may be or certainly will be other types of dosage forms that would fall sort of related into that same category. The main charge of that working group, in fact, is to develop guidances, and originally, I guess we had thought there could be one guidance, now our thoughts were that there would be a separate guidance, and we even considered at some point do we need to have a separate working group looking at complexing agents that are used in radiopharmaceuticals, and we felt at this point we really did not need to break that out as a separate category, but it is something I think we really do need to consider.

Most of our technical committees, as I indicated during my presentation, they are standing committees, and traditionally, one of their major charges in the past was to develop and maintain guidances or, as they used to be called, guidelines. There is a fine legal distinction between a guideline and a guidance. We don't need to get into that, but we don't have guidelines anymore, we have guidances.

[--- Unable To Translate Graphic ---]

Along with the developing of those guidances, they are also charged with responding to inquiries from the outside in areas that relate to their expertise for the technical committee. In our technical committees, we have them set up now, so that the membership rotates. Each person in theory serves a two-year term, and we are trying to stagger them, so that there is not a wholesale reshuffling of the committee.

There is a chair and a vice chair, so one person could serve for six years, it could be on the committee for two, a two-year term as vice chair, and a two-year term as chair, and then they would rotate off and perhaps go on to other things or return to only doing reviews for a while. As Roger indicated, getting the reviews done in a timely manner is our number one priority, and the reason we are able to function and develop these guidances is through a lot of hard work by a lot of dedicated individuals who are willing to put in that extra time that it requires and to work harder to get their reviews done, as well.

Now, perhaps the Liposome and Complexing Group, maybe that might be considered a candidate to be a subcommittee of the Drug Product Committee, because what we are talking about is the drug product, and as an example of

[--- Unable To Translate Graphic ---]

a subcommittee or a working group being part of another committee, the BACPAC guidance is going to be developed by a working group that is taken from members of the Drug Substance Technical Committee.

So, it is a very good suggestion. I think it is something that we will definitely consider at our next meeting.

DR. BRAZEAU: I think what you are going to find out is that these issues of manufacturing of some of these particulate dosage forms, the manufacturing issues are going to be so complex that I think the industry is going to be looking to guidance to try to deal with some of these, because when we talk about the manufacturing, there is going to be a whole different or a whole set of parameters that we haven't had to consider with some of the other traditional dosage forms.

DR. SHEININ: It is very insightful. I thank you.

I would like to add one thing to something that came up a little earlier, about the communication. When we went through this reorganization, the Center has coined a new term, and it is called co-location. The chemists and the biopharmaceutists and statisticians are co-located with the review division, so there is constant day-to-day contact

[--- Unable To Translate Graphic ---]

between the reviewers that are assigned to a specific application, and they do have periodic meetings.

Some of the review divisions have their teams get together once a week to discuss where they are and what problems they are facing. So, I think the Agency and the Center are well aware of how important it is to have good communication.

DR. TAYLOR: Yes, Dr. Davidian.

DR. DAVIDIAN: Seeing you brought up the membership of statisticians, I would like to get a little more clarification on that since I am the lone statistician on this committee. I was just curious as to what is the representation on the various working groups, and so on, of statisticians, and are all those statisticians members of the Office of Epidemiology and Biostatistics, and how does that all work, and just some clarification in the interests, I guess, of communication, and as Dr. Brazeau said, good science. As a statistician, I feel there should be a statistician involved in everything.

DR. TAYLOR: Dr. Williams.

DR. WILLIAMS: Dr. Taylor, we are fortunate to have in our audience the person who can directly answer that question, Dr. Stella Machado, who is head of something

[--- Unable To Translate Graphic ---]

called Quantitative Methods and Research, which is the Office of Epidemiology and Biostatistics. She gives us statistical support, and, Stella, this is a chance for you to tell us about your effort.

DR. MACHADO: Thank you, Dr. Davidian, for asking the question. My unit has seven people, and we are actually in the Office of Review Management in the Office of Epidemiology and Biostatistics, but most of our function is actually to support the Office of Testing and Research, Clinical Pharm and Biopharmaceutics, and Generic Drugs. We don't support Chemistry.

In terms of statistical support on the various committees, we, in fact, have members, perhaps one statistician, occasionally two, on as many committees as we can. I can give three examples that come to mind, is Population Pharmacokinetics, Population PK/PD, and individual Bioequivalence, and are having some involvement with Drug Interactions.

So, we do the best we can. We also have a heavy workload, too.

Thank you.

DR. DAVIDIAN: Since Roger had brought up the issue of resources, I was wondering if, Stella, you felt

[--- Unable To Translate Graphic ---]

that you had adequate ability to give the statistical support that you think is needed.

DR. MACHADO: At the moment, I think we are doing quite fine, but the workload just recently increased, and so a week ago I would perhaps have said yes, we have enough resources. This week, I am inclined to say perhaps in the future we may need an extra person or two.

DR. TAYLOR: Any other comments? I have a question. It is just out of interest. I know from time to time you meet with sponsors in the Review Branch to look at specific items as they develop their applications.

Is that just with people from the Review Branch, the Clinical Review Branch, or is it with people from the Office of Pharmaceutical Sciences, as well? Since they are going to end up reviewing it, if the review people, clinical people make recommendations, you need to make sure that the people who are going to review it also sort of agree with that.

DR. WILLIAMS: First of all, I will remind the committee that we actually have two review streams represented here. Doug Sporn represents the generic drug review stream. He might want to comment in part to that question. Then, we also have the new drug review stream,

[--- Unable To Translate Graphic ---]

and I would say Eric and Larry are our principal representatives to that, so maybe, if it is all right, they could reach respond to that question.

DR. SHEININ: There is a lot of communication that goes on, and as I indicated, the chemists are co-located with the rest of the office, with the rest of the people involved in the review of a new drug application.

The clinicians and the pharmacologists who review the pharm/tox data in an application are actually part of ORM. When there are questions for the individual applicant, we talk about applicants for NDAs and ANDAs, sponsors for INDS.

So, when there is a need for whatever reason to have a meeting with a sponsor or an applicant, depending on what the issues are, all of the review team may be present or only a part of the review team may be present, and some of it depends on the way each of the clinical divisions operate.

Some of the clinical divisions, whatever the type of meeting that is being held, that division director wants all disciplines represented, and there is pluses or minuses that you can look at for that philosophy.

It is good to have everybody there, so all members

[--- Unable To Translate Graphic ---]

of the team know what is going on. On the other hand, when the discussion goes off to some level up here, on to a clinical issue, and speaking from the chemistry end, we are lost.

In some ways, it is not that valuable and not that good of a use of our time, but on the other hand, at times when they are talking up here, a chemistry question materializes, and it is good to have the person who is most familiar with the chemistry portion of the application present.

So, the bottom line is there is a lot of interaction that goes on, and sponsors and applicants are coming in for meetings periodically. We recommend highly end of Phase II meetings, and many of the clinical divisions there have all the disciplines together.

The chemists feel quite often we would like to have our own end of Phase II meeting for a couple of reasons. One, we think we have an hour or a two-hour meeting, there really is not enough time to get into the chemistry issues to great detail, like we would really like to. The more that can be discussed and resolved early in the IND process, the more complete, the more accurate and the fewer questions there will be when the NDA comes in.

[--- Unable To Translate Graphic ---]

So, sometimes the chemists will go to the big end of Phase II meeting, and then we will have another one later on. Quite often the companies are not really ready at the big end of Phase II meeting to talk about the chemistry issues, because aspects of manufacturing and testing, and the other parts of the CMC section are still being evolved and improved upon when they are in Phase II.

We try to have a pre-NDA meeting, and again, chemistry can be a large portion of that where we finalize how that company should approach the CMC section of the NDA. We even highly recommend, especially for companies that have not gone through the process in the past, that they come in for pre-IND meetings before they even submit the IND, and we can talk about what their plans are for developing the chemistry section, how are they going to plan their stability studies, what about the manufacturing, what sites are being used, and things like that.

So, there is a constant communication, and meetings are taking place, at times, it almost seems to the detriment of getting the review completed because you are going to so many meetings, but it really is a large portion of the review process.

I am encouraged to hear that the committee is

[--- Unable To Translate Graphic ---]

bringing this up as an issue.

DR. TAYLOR: Any further committee discussion of the issues that have had on the table so far?

DR. BRAZEAU: I just wanted to follow up and see what the results were of some other area, developing or emerging therapies and some of the rule of the institute, for example, I mentioned gene delivery. I don't know if Roger got a chance to address that one, or he said he was going to address the first and third, and that was my third.

DR. TAYLOR: Before we get into that, I guess I goofed. Dr. Lesko, did you have a comment that you wanted to make relative to the previous issue? I am sorry. You switched microphones on me.

DR. LESKO: I did. I have to get consistent here on our policies or something. After all of that, I don't have much more to add to what Eric said, but I would just add to it that philosophically or functionally, in the office of Clin Pharm, we emphasize early involvement in interactions with the firms because we feel much of the value of the types of studies that we review when it comes in, are really if they are done in real-time with the interaction with how does this information impact the next phase of drug development.

[--- Unable To Translate Graphic ---]

Once we get into the NDA, it is kind of history at that point, and we are just really assessing something for its face value, so our preference is to really urge the early interactions where I think the staff in our office can really set the expectations about the information we require and maybe even get into the areas of how most efficiently that information could be gathered rather than leaving it up in the air as sort of a guessing game as to what the office needs for their part of their assessment.

Along with all the meetings Eric mentioned, many of them are kind of formal meetings in the whole process, and I would venture to say any one that he mentioned, the pre-IND meeting, the end of Phase II meeting, pre-NDA meeting are formal meetings for the most part that our discipline is represented, as well as chemistry and then the clinical component of the Center, but I think we can go much more beyond that, and we have begun to have office-specific meetings with companies now, and that has been very productive, where we can focus specifically on early clinical studies and the value that they can bring to the subsequent studies in Phase II and Phase III.

DR. TAYLOR: Very good. Dr. Goldberg?

DR. GOLDBERG: Could I say something, Gayle,

[--- Unable To Translate Graphic ---]

before we get into genes? That is, that I see a tremendous difference in feelings in the industry and people I come in contact with towards the Agency and their ability to work together and to change things from an adversarial position to one of working together for the public good, and I think the Agency is to be strongly commended for that.

If I look at the number of problems that the industry has with pre-approval inspections, for example, the number of problems still stand very high in terms of CGMP and compliance issues, and I think what we are doing here goes a long way to the science, but we also have to do a lot in terms of technologies and CGMP in the same sort of format that we are doing on this.

DR. TAYLOR: Okay. Now, I think we can move to the next topic. Gayle, do you want to kind of restate your question?

DR. BRAZEAU: It was not a question, it was more a suggestion. I think what the Agency needs to do is start looking at and having either a working group on some of these nonviral mechanisms for gene delivery, and particularly some of the things like the cationic liposomes that you are seeing in the literature.

There is a wealth of information on gene delivery,

[--- Unable To Translate Graphic ---]

and I would not be surprised if there is going to be some of the products that are going to be coming down the road, and I would hate the Agency to be behind the eight ball, so that was my suggestion to maybe start having a working group look at some of these other delivery agents that you are going to see for like plasmids and other forms of DNA.

DR. TAYLOR: I guess as a corollary to that, has the Agency had an opportunity to review any of that type of technology currently.

DR. WILLIAMS: I should tell this committee, and perhaps they should feel some relief when they hear this, is that a lot of these topics are taken up by the Center for Biologic Evaluation and Research, and they have their own advisory committee, which I think is called the Biologic Response Modifier Committee.

I think they have issued guidelines recently on gene therapy and all its aspects. That sister center is very active in terms of how they work with industry, because so many of the things over there are cutting edge, and they represent a challenge, just like Dr. Brazeau was talking about.

I should also say that in the course of this meeting, you will hear that there are areas of overlap

[--- Unable To Translate Graphic ---]

between the two centers. CDER regulates biotechnology products, and there are certain classification criteria as to when we see it versus when CBER sees it.

For example, we tend to regulate the hormone products, like insulin and growth hormone, and I think we regulate synthetic drugs that are produced via molecular biology techniques, and there are some other criteria, as well, but don't quote me.

So, that overlap is a critical point. Some of the topics will be discussed before this committee, and we might have a duplicate discussion in front of the CBER committee, where we might invite some membership from this committee to attend. It goes back to this communication and coordination that was one of the first questions, and have to be very sure we stay in tune with CBER on some of these topics.

DR. TAYLOR: Very good. Any other discussion of any topic? Dr. Vestal.

DR. VESTAL: I guess I have the least understanding or feel for how the OTR functions and whether it is involved in the review process or monitoring in some way, or whether it is entirely research, and I guess the related question is does that segment of the organization really have sufficient resources in terms of personnel, and

[--- Unable To Translate Graphic ---]

so on, to really make a dent in this.

I envision departments of pharmaceutical and medicinal chemistry around the country devoting lots and lots of resources, and graduate students and postdoctoral fellows to this kind of work, and it is just not exactly clear to me what kind of -- I think I understand what Jerry Collins' group does because I am pretty familiar with that kind of research, but I don't have a good feel for the other sections, and the presentations were so brief that I couldn't get a feel for it.

DR. TAYLOR: Who would like to comment on that? Roger, would you?

DR. WILLIAMS: Maybe I could say a few words, and then I would encourage anybody from OTR sitting in back of me to also speak up.

I think the leadership of OTR over the last 18 months has done a terrific job of bringing themselves in line with the rest of OPS and the Center in terms of what needs to get done, and you can see there are five areas of focus that Jim MacGregor talked about.

I think these linkages between policy and review, and the external world, that we are working so hard to build, are just critical to make sure that OTR functions

[--- Unable To Translate Graphic ---]

effectively, and it goes back to the communication and coordination that Dr. Brazeau talked about.

There are other things to mention. I mean we are trying to build linkages to our professional societies, for example, AAPS and ASCPT, and the pharm/tox societies, the Society of Toxicology and other societies that I don't know as well because I am not in that area.

The relevance of this activity, I would say has to be continually scrutinized in an era of resource reduction, and I would say everything we do has to be value-added, and it is a challenge because, as you all know, research has a longer time frame and, you know, you may find that to embark people on a program that takes two or three years, and in the meantime, the setting and everything has changed, the focus of the Agency has changed maybe because of some societal issue.

I would say these collaborative groups that we are talking about are designed to make sure that we stay in touch with reality, if you will.

Can you have -- and I am answering a multitude of questions here, obviously, Bob -- but can you have researchers who do review? Sure, but, you know, it goes back to that magic clinical pharmacologist we always talked

[--- Unable To Translate Graphic ---]

about who did research, teaching, and public service. I mean at a certain point in time, you have to focus or you are going to lose the value of that person, but it is something we all struggle with, and people on this committee I am sure struggle with it as much as we do.

Whether we do a good job, I would say is a very proper area for this committee to give oversight to.

DR. TAYLOR: Yes.

DR. MacGREGOR: Jim MacGregor from the Office of Testing and Research. I think these are excellent questions and obviously, they are questions I am beginning to address myself.

Certainly, there are many examples of people from the research groups interfacing with reviews and their expertise being used in reviews. I think that was one of your first questions, but I think the more basic question that you raise really is the role of research and science, and as I said in my introduction, in an era of shrinking resources, how do you really maintain a core.

My personal feeling at this point is that if you don't have a scientific base, you are really not going to have very good regulatory practice. If you look at the rate at which science is expanding, I don't consider myself that

[--- Unable To Translate Graphic ---]

old an individual, but in my own lifetime, it was not even known that DNA was the genetic material, and now we are talking about how do we deal with delivery, gene therapy products, and so on.

So, science is moving very, very rapidly.

Yesterday, I attended a CDER review on the career track for reviewers and how can people just review for their entire career and advance through the system. If that is successful and you keep those people happy, you are going to have people in a review track that are in the most senior positions in the review side, that haven't been in or seen laboratory in 20 years.

Somehow you need to have a scientific core and you have to interface it with the regulatory practice or you are very rapidly going to be behind times.

Now, I absolutely agree with the implication of your comment that it is really not possible to maintain the breadth of scientific expertise within CDER that is going to be able to respond to every scientific question that arises in a review. That simply is not feasible. So, the question is what do you really need, and that is question obviously that I am going to need to grapple with, but I gave you some of my early, early thinking in the introduction.

[--- Unable To Translate Graphic ---]

I think you have to have a corps of people who really understand and participate in science. I think this is true both in the biology and the chemistry side. If you have chemistry reviewers out who have not had hands-on experience with how certain classes of molecule are separated, and then they get a review application from an applicant, and they haven't really worked with these kind of things, they are not going to be able to look at potential impurities and decide was this really the best separation technology, because this is changing all the time, new technologies are being developed.

So, the key is to decide how much scientific corps do you need, so you have people who are involved in science, how do you keep them interfacing with the regulatory practice, which is critical, a communication issue, and I think part of the solution has to be leveraging, as I think you have to expand the consortium efforts, you have to develop ways of working with industry consortia, and so on, and I think to define really what are the important scientific questions and needs, and to work together in a collaborative way to get at that.

We will hear more about the Product Quality Research Initiative, which is an early effort and a model to

[--- Unable To Translate Graphic ---]

get at this. I don't know if Karl might want to say a few words about that, but I think that type of model and other similar models may be the answer, partial answer to the resource issues.

DR. TAYLOR: Dr. Brazeau.

DR. BRAZEAU: I just have a brief comment. I think the thing that you are discussing goes back to an idea of culture, and it is the same thing we are facing in academics, is this idea of there is bounds between teaching and research, you know, can you be a teacher without being a researcher, and I think the best reviewers are those that are still going to have a good, sound scientific background, so that means it is going to be a culture.

You know, part of the expectation is that you keep up and current with the science, because you are not going to be able to deal with some of these review questions that will come down the pike as we get new products.

So, I think the Agency needs, in its culture, to develop in the reviewers still that keen level of science, but given that, they need to be involved with some science either through these working groups or through their actual getting a chance to get involved with some projects.

DR. TAYLOR: Thank you.

[--- Unable To Translate Graphic ---]

DR. FLORA: Karl Flora, DPQR, part of OTR.

I have just one comment to relate to that. We have individuals in our group that are involved with the technical committees of the CMC CC and the BCC. Also, we hope to include more reviewers in research.

We have about five right now in our small division that are working in that area, and we have three members of our research group that are doing reviews, so hopefully, those things will be more integrated throughout the OTR.

DR. TAYLOR: Yes, Dr. Zimmerman.

DR. ZIMMERMAN: Along the lines of keeping the reviewers up on science, does the FDA have sabbaticals for its people where one could send them -- I am talking about sort of the academic mode here where after you put in your seven years you get to have a sabbatical and go retool yourself for your next seven years.

To me, that sounds like something that would be a reasonable way to help your reviewers and your scientists keep up or retool themselves, or gain certain skills that might be of use.

DR. WILLIAMS: We do have the sabbatical concept for certain categories, and I would welcome any further comments, if I don't have this quite right, from people in

[--- Unable To Translate Graphic ---]

back of me. But, for example, the Senior Executive Service Program allows the possibility of a sabbatical, but I think realistically, it almost never occurs, I mean because our resources are so constrained and everybody, you know, you need to get those widgets out the door.

We do have the concept of professional development, so, for example, a reviewer could spend, say, half a day a week doing something of interest, and, of course, there is a tremendous wealth of opportunities here in the Washington area for doing that kind of research.

But we also think the opportunity to participate in these coordinating committees and in the research effort, that you heard in OTR and perhaps in these collaborative groups, will also add opportunity for the reviewer to keep them with us. You know, I think if a reviewer just ends up doing reviewing, it can be very, you know, not the most exciting opportunity.

DR. TAYLOR: Dr. Zimmerman.

DR. ZIMMERMAN: Our deans in our colleges also say that the sabbaticals are a resource issue, so I have heard that argument before. As we talk this afternoon about some of the collaborative initiatives, perhaps as part of the collaborative initiatives that one takes up with the

[--- Unable To Translate Graphic ---]

academic and the industrial institutions, particularly the academic institutions, there might be opportunities for some of your scientists to spend time at some of the collaborating institutions for, you know, not one day a week, but maybe three months or something.

DR. GONZALEZ: If I could briefly comment, because I think that is very important that we talk about sabbaticals. Many sabbaticals may be actually better, more appropriate, because it allows us in academia to interface with the reviewers from the FDA and kind of dispel the mystique of the black box and at the same allow individuals to share ideas that go both ways.

It improves our scientific approach and it also improves the review process, as Dr. Brazeau was mentioning, because it keeps everybody current. Sometimes what happens is there is an information and technology lag, technology moves so far ahead, yet, even in academia, we are slow to change. Industry is moving very fast, and the review process is lagging even further behind. I think a mini-sabbatical would help this.

DR. BRAZEAU: I would add that I think that mini-sabbatical could go both ways. I mean I know that there are faculty members that have gone to other branch

[--- Unable To Translate Graphic ---]

agencies, so bring someone from the outside to the FDA for three months. I think you would find that they could provide their expertise, you know, on a one-to-one basis.

So, I see it going both ways, and that is I think a key issue to your collaborative projects in the future, because those individuals can also help you to maybe outline the kind of areas that you should be looking for or starting to investigate.

DR. TAYLOR: I will say that these kind of things I think occur already in certain of the offices. I know at Howard we have graduate students, for example, that are working out in Laurel in the Toxicological Research Center out there. In fact, Frank Sistare has given lectures in our toxicology course. So, I think there are a lot of informal arrangements that already exist that are not generally known to the public. You may correct me if I am wrong, Roger.

MR. SPORN: Could I mention that I think everyone is in violent agreement that the reviewers ought to have access to universities and have an opportunity to reengineer themselves, so to speak, but the reality is, based on our statute, Eric's staff and my staff, Larry's, we all have a regulatory basic requirement to get reviews out by a certain period of time, and I don't get letters from Congress or

[--- Unable To Translate Graphic ---]

industry saying what have you done in research. I get letters from Congress saying why isn't my application out.

So, it is a constant struggle to give the reviewers that sort of opportunity, which they really do need, and meeting out commitments to industry.

You may recall that the Office of Generic Drugs some time ago did have a contract with the University of Maryland School of Pharmacy, and that worked very well. We were close enough to the university that people go up on weekends or maybe one day a week, and do some research, as well as people from the university coming in and talking to our staff, but those were in days when the budget was in a little better shape, and they are gone now.

I think our staff would certainly welcome people from academia coming in and spending time in FDA. If they could take a sabbatical from the university where they are and come onboard, it would probably expose a lot more of our reviewers to new ideas and concepts.

I know, speaking for my office, the chances that I could let someone go on even a three-month sabbatical right now, any of my reviewers, is very, very unlikely unless Dr. Williams or Dr. Woodcock provided the funding.

DR. TAYLOR: Dr. Zimmerman.

[--- Unable To Translate Graphic ---]

DR. ZIMMERMAN: I don't get letters from the legislators of the State of Minnesota asking me what I have done in research lately either. They ask me how many pharmacy students have I trained this year, and when I leave, somebody has to do my teaching for me and run my graduate students for me, and we don't have a lot of slack time at the university either, unlike what some people might think.

But if you are committed to maintaining your scientific edge, then, sitting in your office doing reviews or whatever you are doing, teaching the pharmacy students or whatever, day in and day out, you are not going to be able to maintain your edge.

I am glad that there was a collaborative interaction with the University of Maryland which was good for the Agency and good for the University of Maryland, but this certainly has to be, I would think, expanded to other areas, as well.

DR. TAYLOR: Larry.

DR. LESKO: This is such a critical area, and I think we recognize that within the Agency, and Doug mentioned some of the challenges, and I think we have the same challenge. We don't get the letters that Doug gets,

[--- Unable To Translate Graphic ---]

but what we have tried to do in the office, particularly this past year, is really bring the expertise and bring the sabbatical type of thing into the Agency.

Over the past year, we have actively tried to bring in people on a regular basis, so we have, for example, Dr. Venitz is coming from the Medical College of Virginia two days a month, spends time working with working groups, individual reviewers.

Beginning in October this year, we have Dr. Terry Blaschki from Stanford coming for a five-month sabbatical at FDA, and he will work within OPS in the office, and he is Professor of Medicine, Clinical Pharmacology.

So, it is these sorts of things, along with short courses, where we bring in the experts on a particular area. For example, Dr. Shiew-Mei Huang, who will speak tomorrow, has organized a series of courses over the past year in drug interactions, mechanisms of drug interactions, and brought in really the world's experts in this field to bring the office up to date in terms of the emerging science.

So, I share the concerns of releasing resources, so one way we have dealt with that is to bring it internal and treat it as an in-house need.

DR. TAYLOR: I think our time has run out that we

[--- Unable To Translate Graphic ---]

have got to discuss this. I am going to give Roger the last word this morning.

DR. BRAZEAU: But I think I have to say this.

DR. TAYLOR: Make it real short.

DR. BRAZEAU: Okay. I think that you also have to remember there is technology. You don't have to bring them to the FDA. The FDA has in its abilities things to do teleconferencing, so that could also save funding and get good interaction with scientists.

DR. WILLIAMS: A 30-second last word.

DR. TAYLOR: Yes.

DR. WILLIAMS: First of all, an excellent discussion this morning, very helpful to us as we move forward. I want to come back to something Bob Branch said, which is what is the role and responsibility of this committee.

If you compare it to our advisory committees, I would say this is a very different committee. The other advisory committees tend to focus on specific product approvals, and this committee, I would say is a general science committee, and it also serves the needs of some of the disciplines in the Center as opposed to the product review people.

[--- Unable To Translate Graphic ---]

I would argue this committee is a critical thing as we move forward into the future. It gives a focus and attention to parts of the Center that didn't get a lot of focus and attention in the past.

So, even though the glare of publicity may not always be with this committee, and sometimes that is very fortunate, I still think calm deliberation of some of our science issues will always be valuable.

DR. TAYLOR: Thank you very much.

With that, we will end the morning session. We will be adjourned until 1:30, at which time we will reconvene. Thank you.

[Whereupon, at 12:05 p.m., the proceedings were recessed, to be resumed at 1:30 p.m.]

[--- Unable To Translate Graphic ---]

AFTERNOON PROCEEDINGS

[1:35 p.m.]

DR. TAYLOR: The afternoon session will involve some discussion of collaborative efforts with the Office of Pharmaceutical Sciences. Before we begin that session, and while you are making your way to your seats, we would like to make another announcement for the speakers' benefit.

DR. TEMPLETON-SOMERS: This is just to inform any of the speakers who weren't here this morning that we are running a timer on you, and so you have a green light that is visible when you have plenty of time left, the yellow light when it is almost time to quit, and then it will blink red at you quite ominously when you are over time. So, we appreciate that. Thanks.

DR. TAYLOR: At this time I would like to turn the Chair's duties over to Dr. Marie Davidian for the afternoon session since I have a previous commitment mid-afternoon. So, Dr. Davidian.

DR. DAVIDIAN: Thank you, Dr. Taylor.

If the red light continues to blink and you don't get off, the Acting Chair will leap to her feet and shriek. I am sure that none of you want to witness that spectacle. Keep to the schedule.

[--- Unable To Translate Graphic ---]

I believe we have one committee member who arrived late, so if he wouldn't mind introducing himself.

DR. GONZALEZ: I am Edgar Gonzalez from the Medical College of Virginia. I have been on the committee for two years I think now. I am sorry I was late, got hung up in traffic.

DR. DAVIDIAN: A good excuse.

DR. GONZALEZ: But true.

DR. DAVIDIAN: I guess we should get started then. Our first speaker, Helen Winkle.

### **Collaborative Efforts**

#### **CDER's Focus on Collaboration**

MS. WINKLE: I see my role here today -- I thought my role was going to be to sort of introduce you all to the whole idea of CDER's collaborative enterprises, as Roger refers to them, but you all have already started talking about it, so I don't probably see this more as an introduction, but more as sort of helping you have an idea of what we are thinking about, the directions that we are going and stuff, and giving you more perspective in order to ask questions and see what you may feel like you can contribute.

[Slide.]

[--- Unable To Translate Graphic ---]

Basically, I think that we have talked a little here today about some of the two, shall I say two collaborative enterprises that we have started, and I want to reiterate what Roger said. These are preliminary, we have been working on them for some time, but they still are in the building stages.

We have the PQRI and the CDDI, and PQRI, as was said before, stands for Product Quality Research Initiative, and the CDDI stands for the Collaboration on Drug Development and Improvement.

Again, I am just going to sort of give CDER's overview and then Julie Nelson, who is from Georgetown, is going to talk a little bit more about CDDI, and Steve Byrn from Purdue will talk a little bit more about PQRI and what we are doing with some of the committees.

[Slide.]

The first question you might ask is what is collaboration, and basically, what we are talking about here is the process for industry, academia, and FDA to discuss and make some decisions on focused research and policy development projects, and these projects are going to be designed to meet growing challenges associated with both drug development and drug evaluation.

[--- Unable To Translate Graphic ---]

We see a lot of regulatory research coming out of this. This research can lead to support guidance that will help enhance the whole drug development process, and will also facilitate how we do evaluations or reviews in the Center.

You know, we hope to be able to reduce some of the reliance on anecdotal type of information. We also would hope through some of this regulatory research to actually increase reliance on less burdensome type tests in development and what we look at, at review.

The whole idea of collaboration is not new to FDA. There have been several other collaborative efforts in FDA, not in CDER, but in the Center for Food Safety and Applied Nutrition. We have had what they call the Moffitt [ph] Center, which is the National Center for Food Safety and Technology, and there they combined industry, academia, and FDA in doing various research looking at food safety, et cetera.

They also have a new center that they are starting at the University of Maryland, the Joint Institute for Food Safety and Applied Nutrition, so again, this is not the first time that the Agency has gotten involved in collaboration, but obviously, it won't be the last, because

[--- Unable To Translate Graphic ---]

CDER is moving that way, too.

[Slide.]

The second question that you may want to ask is why would we collaborate, and I think both Jim MacGregor and Roger have hit on the main thing, and this is to leverage some of the resources. We are in a time where resources are becoming more and more difficult to come by, and this gives us an opportunity to utilize resources both in industry and academia along side by side partner with FDA, and get the best utilization of all the resources.

We also want to continue to emphasize the importance of research in reaching policy, and I think we have actually sort of had some discussion here already on this. It is a very important factor that we are hoping to achieve through these collaborations.

Also, we feel that it is a really good idea to get industry, who is definitely affected by this policy, involved in the creation of the policy itself.

[Slide.]

Roger has already showed this slide, but I think it is real important to show it again, to show where the consortium or the collaborative enterprises fit into the whole scheme of what CDER is doing.

[--- Unable To Translate Graphic ---]

Roger talked about the paradigm in OPS of research to policy to review, and this is an important part of the paradigm upfront where we have the two consortiums. We see this as very important in the whole development of research.

[Slide.]

I am going to talk just a little bit, very little on PQRI and CDDI, and what we have been doing. Again, Steven and Julie will talk more in these areas. PQRI efforts really started back in December 1995, and they sort of started up from what we had done with the SUPAC. We had had development of the SUPAC policies.

We have done some research with the University of Maryland. We had applied that research into developing the policy that is going into SUPAC. We saw this as a very good way to work. So, we started talking. We set up a steering committee with several of the trade associations. We had several meetings throughout 1996.

We decided that it would be good to set up some technical committees, we have talked about that, and we have moved forward and to the point where, in March of 1997, Roger came before this sort of ad-hoc, if I want to call it, steering committee and said, well, do you all buy off on this, and should we move forward, and the steering committee

[--- Unable To Translate Graphic ---]

unanimously said yes, let's go ahead with it.

So, this is where we are at right now with PQRI, and we are moving ahead.

[Slide.]

Just so you will have a feel before I go ahead with who the steering committee was, you will see the names here. I won't go through all of them, but you will see they are from the major trade associations along with Roger and several others in FDA who have been working side by side with Roger to make this a reality.

Basically, the people that should get the notoriety for really doing what has been done are Karl Flora and Ajaz Hussain.

[Slide.]

Here, I have the proposed structure for PQRI, and I think it is a very interesting model to look at. As you can see, we have a steering committee, which is composed of FDA, industry, and academia. Under that is the technical committees, and Steve is going to talk a lot about the type of work that the technical committees are doing, but we see these committees contributing proposed ideas for research, and then they will go to the steering committee.

We will look at those along with what policies can

[--- Unable To Translate Graphic ---]

be developed and make some decisions through the steering committee and the directions that we want to go. We are still looking at ways that we can figure out mechanisms, then, for getting that research to reality.

We see some contracts possibly, we see some collaborations, such as cooperative agreements, with industry. We see a variety of ways to get this research done, but those decisions then will be made by the technical committees.

One thing else I want to mention on this slide is the Training and Evaluation Committee. I know Dr. Zimmerman brought up the fact of the sabbaticals, and it was interesting, we were talking yesterday about the whole concept of PQRI and talking about maybe there were possibilities for collaboration or even what you might want to call sabbaticals under the auspices of the enterprise.

[Slide.]

I think the most important thing about PQRI is to recognize what the steps are, and I think I made the comment that the steering committee was sort of ad hoc, and we are really in the process of trying to formalize that committee, and we have been looking at a variety of models on how we could do this.

[--- Unable To Translate Graphic ---]

We looked at another advisory committee to possibly run the whole steering committee. We have sort of come to a model that we think is going to work well, and that is just sort of partner with AAPS in developing the steering committee, the whole umbrella under which we can work the PQRI, and we see this as a really good model because it brings lots of people to the table.

I mean we still have a steering committee, but it avails us of everyone who is a member of AAPS, as well as others. Also, as I said, it gives us a lot of other openings, such as training openings, sabbaticals, et cetera, et cetera.

We also need to start identifying some of those projects that we want to work on, some of the research that we want to work on, and this has been one of the things we have sort of been waiting for the formalization of the committee to do, so we can figure out what projects we want to get started on.

I think once we get some of these projects going and some recognition of what we are doing, and people can see sort of the bang for the buck, I think that PQRI will really take off and I think the whole concept will sell well.

[--- Unable To Translate Graphic ---]

We have, as I mentioned, the working groups. They need to initiate some more research. There is already some proposals on the table. We will look at those in the whole context of recommendations as far as the process goes.

[Slide.]

As I have already mentioned, the other collaborative enterprise we are looking at is CDDI. The is again the Collaboration on Drug Development Improvement. I won't talk much about this because Julie has quite a bit she wants talk about, and she has been part of the activity.

But basically, we have several centers in FDA, CDER and CBER, the biologics area, along with Georgetown and Pharma and others, looking at a collaboration, and this collaboration, unlike PQRI, will be directed at research for safety and efficacy. Obviously, Product Quality is looking at the product quality side of the coin.

So, there will be two separate consortiums, but both with the same idea and the same focus or direction that they wanted to go.

The next steps as far as CDDI is concerned is they are going to try and finalize their collaboration, their direction, and they are meeting in June to do that. I also failed to mention that PQRI also is meeting again in June,

[--- Unable To Translate Graphic ---]

June 16th, and we will then follow up on that.

This is really a quick overview, but at least, as I said, it gives you a little perspective as to some of the direction that we are going in, and Julie and Steve will add a lot more to that.

I am going to hand it over to Julie Nelson from Georgetown.

### **Collaboration on Drug Development Improvement**

MS. NELSON: Good afternoon, everyone, members of the advisory committee. It is a pleasure for me to be here this afternoon to describe for you, I think an exciting newly developing collaboration among FDA, the pharmaceutical industry, and academic scientists.

I am a surrogate this afternoon. Ray Woosley, my chairman, was originally scheduled, so I am here in his stead. I work in the Center for Drug Development Science at Georgetown University.

[Slide.]

The initiative, as Helen mentioned earlier, is called CDDI, and she gave you just a brief, I think, beginning on it, and I will take you through a little bit of the background, because I think it is important for us to understand how it came about.

[--- Unable To Translate Graphic ---]

[Slide.]

It seems to be sort of common opinion today, I think about in most constituencies, that modern drug development takes too long and costs too much money. There is some basis in fact for these sentiments.

The Center for the Study of Drug Development at Tufts shows us data and also we have some data from the PMA annual survey showing that we can see the geometrical increase in R&D expenditures from over the last 20 years, let's say, in both the NIH and from the U.S. pharmaceutical companies.

As of 1991, the graph shows -- you can see that industry has surpassed NIH at this time in their R&D expenditures, and has reached \$12.6 billion. Is that too much cost? I am not sure I know the answer, but it is a lot of resources being spent, and I think maybe we ought to consider how we are utilizing them and consider possibly taking some other approaches.

The data, as I mentioned from Tufts, shows us the time that it takes on average to develop drugs, and we are running around the area now of around eight years, it looks from their data, from IND to approval, approximately six years of that being the actual drug development time.

[--- Unable To Translate Graphic ---]

I think most scientists in industry and the FDA and in academia agree that there are probably many ways we could shorten that time. CDDI is really geared to target itself at that derivation of knowledge base and how we do it.

[Slide.]

So, given this state of development, I would say, or drug development, in June of 1996, many people participated in a conference that was jointly sponsored by the Food and Drug Law Institute, Georgetown Center for Drug Development Science, and the FDA, to examine the reasons for the long development times and the high costs with the intent of determining opportunities for improvement.

Leaders in drug development, regulation, and science management presented information on the bottlenecks and the barriers to efficient and informative drug development programs. Throughout the program, much information was presented, but in the end, there was still an incomplete understanding by presenters and participants as to why the time and cost is so high.

There was an expert panel that reviewed the presentations at the end of the meeting, and they concluded basically that there was definitely a need for further

[--- Unable To Translate Graphic ---]

investigation, and they also proposed a cooperative program to investigate and advance the solutions in several drug development areas, which was received I think positively by the audience, as well as the endorsement of the entire panel.

So, subsequently, the panel and other conference participants agreed to proceed to create the collaboration.

[Slide.]

Individuals from the FDA, industry, and academia, over the summer of 1996, had many dialogues I would say informally, as Helen was describing earlier, about how this collaboration could be set up and how it should be structured, how it could be organized, but basically, the collaborators came from all sectors, from both Centers of the FDA, CDER and CBER initially, although we may also have participants from CDRH, too, eventually, industry as represented from members in Pharma and Bio, and academia as represented initially by Georgetown University, and on the steering committee will be having participation from the Sloan School of Management of MIT.

[Slide.]

The process to date has been somewhat similar to PQRI. As you will see, we have had several I would say

[--- Unable To Translate Graphic ---]

ad-hoc meeting, but serious in intent, to try to understand how we will establish this collaboration.

The first official meeting was in September of '96, and members of at that time the ad hoc steering committee from the participating organizations met for a full day to discuss the need and the mechanisms to which this could occur, and also I think, as Helen mentioned, to agree whether they felt it should go forward. They all did.

A second meeting was held in December to discuss further the goals and objectives and mechanisms again of CDDI. In January, the first draft concept paper about this organization was I would say released publicly. That is sort of loosely stated, but it had been released publicly. It is a work in progress, and I think you all have a copy of that actually in your binder.

Helen mentioned in June, on June 20th, there will be a meeting of what we call the issues identification meeting, and I will talk about that a little bit further, but this has been basically the process as it has occurred.

[Slide.]

The steering committee and the support staff, which we are calling the secretariat, for lack of another term at the moment, have worked to establish and state some

[--- Unable To Translate Graphic ---]

of the purposes, objectives of CDDI, and I will reflect those for you today.

The purpose of CDDI is to substantially improve the development of pharmaceuticals, including biopharmaceuticals.

[Slide.]

The scope of its work will comprise areas of preclinical and clinical testing phases in the development of pharmaceuticals, including the post-approval phase. Development science and science management methodologies will both be considered.

[Slide.]

The goals of CDDI, I think are succinct and quite clear, and hopefully quantitative. That is, CDDI will study and advance current and new approaches to substantially improve the efficiency of drug development and assessment processes by the following three means: reducing unnecessary studies and activities; increasing useful information about drugs as they are developed and brought to the public; and improving resource utilization by shortening development times.

[Slide.]

Progress to date. I mentioned that we had an

[--- Unable To Translate Graphic ---]

ad-hoc organization essentially put together to initial the process, and that has resulted in an organization which has been set up to oversee and complete the establishment or creation of CDDI.

[Slide.]

It looks like this, which is again very similar to PQRI. I think we find this model to be very effective. We have a steering committee, a technical advisory committee, and working groups which will focus on specific areas of development of the efficacy and safety knowledge base on new drugs.

[Slide.]

The steering committee function at this time is specified to really be that of providing general direction and oversight to CDDI and to review and approve technical committee proposals. They have many other functions that they are filling in for, as well, but for now this is their official capacity.

The steering committee is made up at this point of members or I should say the directors of CBER and CDER, senior executives from Pharma and Bio industries, and also some expert academicians in drug development and science management.

[--- Unable To Translate Graphic ---]

[Slide.]

Progress to date in furthering the process is we are working now to establish procedures to recruit and engage participants in activities to specifically identify the issues and information and research needs. Bullets 2 and 3 will come later. We haven't reached those points yet.

[Slide.]

CDDI is envisioned at this point to work in this way. The issues identification meeting will take place in June, and at that meeting we will have senior members of the FDA, academia, and industry at that meeting, and they will collaborate during a one-day meeting in these six areas, which have been identified as a result of the Georgetown conference and subsequent discussions with the steering committee.

At that meeting, the teams or the group will attempt to begin to identify specific areas for which proposals would be created to engage in research or investigations that hopefully would result in recommendations to fit into I guess, if you will, the diagram, as Helen showed you, where the efficacy and safety issues would hopefully be feeding into FDA's Medical Policy and Coordinating Committees.

[--- Unable To Translate Graphic ---]

[Slide.]

Subsequent to the issues identification meeting, the technical committees will take over. They also will contain members of the FDA, academia, and industry. They will work further on defining the problems and creating working groups to specifically address them.

[Slide.]

The working groups, members again from FDA, academia, and industry, will actually get down to the work of executing the projects, utilizing resources from academia, industry, and the Agency.

[Slide.]

I think one of the goals of the steering committee and those participating in the collaborative program is going to be very specific, actionable, measurable results hopefully. They will be realistic and very time-sensitive.

[Slide.]

Our next steps is that the issues teams and the technical advisory committee will prepare their concept papers on specific issues, and hopefully, those will then result in working groups being established to address them.

One last, but not least, but quite important item, that the steering committee and the secretariat, together

[--- Unable To Translate Graphic ---]

actually, will continue to work to seek sources of funding to hopefully support I think this exciting and very promising project.

Thank you.

### **Product Quality Research Initiative**

DR. BYRN: Thank you. As the previous speaker said, I am going to talk about some of the specific activities of the technical groups in PQRI. I want to thank Ajaz Hussain for being nice enough to send me some of his slides, so that I would include those.

[Slide.]

What we are going to talk about -- you have already seen this diagram -- we are going to talk about the technical committees in the PQRI, the Product Quality Research Initiative.

There are five technical committees. Two of these are similar to the CDDI, and I am going to give you a quick overview of those. The Drug Product Technical Committee is going to be the first one because this is the committee that developed SUPAC, and so has a track record and has been successful.

I am going to explain more about the Drug Substance Technical Committee, because this is one of the

[--- Unable To Translate Graphic ---]

new ones that actually is intimately related to BACPAC, and the Biopharm Technical Committee is also an ongoing activity with Gordon Amidon.

The technical committees are going to, and in the process of, forming working programs groups which will develop the research programs that we have, and I will try to give you a flavor for some of the projects that are under discussion right at this time.

[Slide.]

Each technical committee developed a proposed hypothesis. This is the committee for the drug product. Now, we are talking about everything that happens to the drug after it is approved as a drug substance, meets analytical and all specifications.

This is the committee. Larry Augsburger is the academic link to this committee, and he is at the University of Maryland and headed the program on SUPAC, and the hypothesis that this committee -- and you will see each of these committees has a hypothesis -- the hypothesis is that adherence to established product specifications are sufficient to approve drug products that undergo pre- and post-approval changes in: manufacturing scale, site, equipment, and process; composition and components; and

[--- Unable To Translate Graphic ---]

packaging.

Now, this is a rather broad hypothesis and we are not really expecting that all these hypotheses will be approved, but this, of course, is the most general one, and that is sort of the rationale for developing these hypotheses was to take the broadest and most general, and work from that point.

[Slide.]

Now, in order to test this hypothesis, we developed a number of demonstration projects, and this is drug product again, so we are continuing on with SUPAC-IR. As was shown in the triangle that Doug Sporn showed you, there is a Level 2 and 3 SUPAC-IR, and this hypothesis simply says that the current product specifications are sufficient to approve Level 2 and 3 site changes. We don't know whether that is possible, but that would be a research project. Then, the same hypothesis follows for manufacturing changes.

[Slide.]

Now, this is some of the new technology that we are building on based on the SUPAC project, and this can give you a flavor for a project that could be quite worthwhile for industry.

[--- Unable To Translate Graphic ---]

One of the major problems right now is to ensure blend homogeneity in making of the drug product. You blend the drug substance, the pure drug, with various components, and there are a number of tests that are done to ensure homogeneity. Almost all these tests involve using what is called a thief or a device that you stick into the mixer and pull out a sample.

You then transport that sample to the analytical lab where some kind of measurement of homogeneity is made. During these processes, most people in the field feel that desegregation, demixing of the sample can occur, and major errors are uncovered and major problems result from this.

A lot of analytical effort is spent on this. This demonstration project would relieve all of those problems from industry by developing a new technology called near-IR, which can shoot a beam of near-IR-like into the mixture and analyze its homogeneity directly without going through this process.

If this project worked, this would result in very significant savings to the industry in their sampling, analytical, and testing activities. So this would be one of the new technologies. Here is another new technology that would allow a changing in, for example, barrier technology,

[--- Unable To Translate Graphic ---]

if the product met specifications. In other words, at present, if any manufacturing method is changed, you have to get approval. This would allow changes and then allow them to be reported in an annual report.

[Slide.]

Here are two more demonstration projects. Here is one that would allow approval of different technical grades or sources of excipients in a drug product, and here would be a statement that would essentially ratify the first bullet, that any excipient that meets the USP/MF monograph would be approved.

This would allow changes in excipients. There is some question as to whether this would work out, but this is the kind of thing that needs to be investigated.

[Slide.]

The second committee that I want to talk about is the Drug Substance. This is the drug prior to mixing in the product. This is the pure chemical entity, the drug substance itself. There is a lot of pressure on the Agency and interest in from the manufacturers to reduce regulatory burdens in this area.

They are under tremendous pressure to produce the drug substance sooner and to scale up faster. This results

[--- Unable To Translate Graphic ---]

in a process that is often not efficient, and then once it is locked in, it is very difficult to change it. So, there is tremendous interest in reducing regulatory burdens and allowing changes in the process.

There is also interest in shifting some of the regulatory requirements to industry, as you will see later on, and just what I said, there is a general perception that the present regulations, which lock in a process, are a barrier to new technology, in other words, a new dryer, a new method becomes available, that cannot be used because the present process is essentially locked in once the NDA is filed.

[Slide.]

So, the hypothesis that we are working on, this should be Drug Substance Technical Committee, is the same thing as the drug product. Adherence to final drug substance specifications should be sufficient to approve drug substances that undergo pre- and post-approval, changes in manufacturing, scale, site, equipment, controls, and process, route of synthesis, packaging and supplier of the drug substance.

Now, we already know from BACPAC that even the most aggressive groups in industry would not completely

[--- Unable To Translate Graphic ---]

agree with this hypothesis, and that will become apparent as we talk about it further.

However, this is a lot of interest in developing a way to change certain things. For example, if you have a 15-step synthesis to change something in Step 5 of that 15-step synthesis without having to get approval from the Agency prior to making that change, so there is a lot of interest in relaxing the requirements early in the drug substance synthesis.

This committee includes a number of people who -- well, at least Karl Flora, who you have already heard from, Kasturi Srinivasachar, who will be here tomorrow, and myself, as well as several other industry representatives.

[Slide.]

Now, one of the problems that you get into in the drug substance area is what is the meaning of the specifications. There is a lot of concern about the meaning of drug substance specifications and whether or not they truly can ensure equivalence of drug substances of sameness, and so this sub-hypothesis really deals with specifications which also fall into the International Harmonization Program that Eric Sheinin had talked about this morning, the Q68 document, and what we are saying here is that drug substance

[--- Unable To Translate Graphic ---]

specifications can be established which will ensure equivalence among various suppliers.

For example, there are some drug substances that the only specification is melting point. We are fairly sure that that is not going to assure equivalence among different manufacturers throughout the world, maybe 20 different manufacturers, so what we are saying here is that we can get specifications that will ensure equivalence.

This is an issue that might bear some discussion, and we spent probably an hour discussing this. Specifications should be based on those for the bulk substance of the currently marketed product. This says that in order to get these specifications, you would have to look at the innovator product in the case of a generic substitution or all current marketed products if there are generics already on the market.

A key issue is this whole issue of physical-chemical properties, which we are not going to go into in detail at this time, but relate to the polymorphism, the flow properties, how the substance behaves as a material.

[Slide.]

These are the two issues that are raised when you

[--- Unable To Translate Graphic ---]

start talking about equivalent or same drug substance, and this was already raised this morning, the issue of impurities. If you are going to say that two drug substances are the same, you need to evaluate the impurity profile and make sure that the substances have essentially the same impurity limits, and the number that we have taken right now or the idea, at least in present discussions, is that no level of impurities outside the ICH limits, which is a tenth of a percent, would be allowed.

But this general statement and this thinking, which is going to have to be evaluated in PQRI, and maybe by this committee also, the general question is when we approve a new drug substance that has different impurities, we are in effect allowing different impurities to be disseminated to the public.

They are going to be below a tenth of a percent by taking this statement. Is this something that is acceptable to the public? This is an issue that PQRI is going to have to deal with. Then, for drug substances intended for solid oral dosage forms, these are some of the issues that we are going to have to deal with related to the solid product: what crystal form it is in, its particle size, and so on.

[Slide.]

[--- Unable To Translate Graphic ---]

Here are some of the novel approaches again aimed at trying to provide relief to the industry. These relate again to lessening the number of tests that have to be done on a drug substance - could you carry out what is called parametric release, which would be tests that are essentially carried out by computer, no individual analytical tests, but simply on-line computerized tests, could you release a drug substance based on those? Could you test only every third lot of a drug substance, could you could do sunset testing, where you would test for a certain parameter for 20 lots, and then not carry out that test any further? That is another set of research projects that we will be carrying out or are interested in.

[Slide.]

Now, in general, in these research projects, this is sort of a general idea in the drug substance of how we are going to do, might approach these projects. One would be a data mining/survey type approach where we would survey the industry and try to gain as much information as we can find out prior to doing any work.

The AATS-FDA workshops have been very successful and it would be appropriate to have workshops on occasion. It is clear that in some cases, we would need to do some

[--- Unable To Translate Graphic ---]

research projects on model compounds to test certain of these ideas, and in cases like particle size, which I haven't talked very much about, and other analytical methods, there may be a way to carry out or gain a lot of information by working with vendors that provide certain kinds of equipment in order to take advantage of their work that they have already done.

So, we are going to use a multifaceted approach to carry out these projects.

[Slide.]

I think we can go ahead and skip these and go to the next slide.

[Slide.]

Okay. This is the Biopharm Technical Committee. The main contact on this committee is Gordon Amidon and then Ajaz and Hank Malinowski, and three experts in the field, and this continues the same kind of hypothesis. These two hypotheses would state that in-vitro tests are sufficient to ensure bioequivalence of highly permeable drugs, and then here is another hypothesis related to NSADs.

[Slide.]

There are then two other committees, the Novel Approach Committee and the Science Management Committee.

[--- Unable To Translate Graphic ---]

The Novel Approach Committee is really almost everybody on the Over Review Committee, and this includes the four generic trade associations, PDA Pharma, and the FDA.

These are quite interesting ideas. One is to move away from the current PAS process to a five-year recertification approach with a mechanism to allow necessary changes during the no-submission period.

A second idea is to recognize a company's good performance record and implementing changes by relaxing the filing requirements from PASs to CBEs or annual reports.

[Slide.]

Then, there is a Training Committee that has already been mentioned. These are the members, and Gary Hollenbeck from the University of Maryland is the contact on that committee, and they would be involved in efficient implementation of new regulatory policies and maybe some of the other activities that have been suggested this morning.

[Slide.]

The last slide is the Science Management Committee. This overlaps with CDDI, and these may be the same committees. This includes Tom Allen from MIT, who is co-director of the POPI Program on the pharmaceutical industry and MIT, and Ajaz, and Chuck Hoiberg, who is here,

[--- Unable To Translate Graphic ---]

as well as Ken Loving from the University of Maryland.

This committee would then address the goal of whether to address the management of the science and technical aspects of the drug development process to ensure timely availability of the information, and basically would handle all the science from our view, on our side, would handle all the scientific studies that I have discussed and how they would be merged into a final document.

So, in conclusion, we are going to have a meeting as was said on the 16th of June where we are going to continue to develop these projects. There is a lot of interest among the committees in some of the projects, and any feedback that you would like to provide us would be helpful, and I think I should stop at that point.

#### **Committee Discussion**

DR. DAVIDIAN: Thank you. Now, committee discussion. Dr. Brazeau.

DR. BRAZEAU: I have two questions for Julie Nelson and one question for Steve Byrn.

In the CDDI, I was wondering if the steering committee should have membership of a representative from AAPS, because I didn't seem to see any, and I thought that might be useful to have or if they have thought about that.

[--- Unable To Translate Graphic ---]

Second of all, how is the selection of senior scientists from the industry or academic arena chosen? They say they are senior scientists on certain issues identification. How is that process achieved? Those are the two questions for Julie.

MS. NELSON: I expected that question. I am glad you asked it. I knew that was going to be one of them in terms of understanding how the individuals who are participating have been selected at this time.

All the participating member organizations, as you saw on my overhead, have within their organization held discussions, I will say, because I certainly wasn't part of the process, but to identify I think the appropriate people that they felt should participate, and at this point, that is the process as it has been undertaken. I think there probably will have to be a more formalized mechanism defined as CDDI's formal organization goes forward, and we would be interested in your thoughts, recommendations, things like that.

I don't think AAPS was an organization that we so far had identified as being the linking body, but maybe there is one, technical organizations or suggestions could be made there for sure.

[--- Unable To Translate Graphic ---]

DR. DAVIDIAN: Dr. Taylor, since he has to leave.

DR. TAYLOR: Two questions. One is will participation in the CDDI be limited to just a single academic institution, and if so, what is the justification for that, and secondly, how does the CDDI differ from an idea that was promulgated a few years ago, called the CERT, Center for Education and Research and Therapeutics, I think it was called?

MS. NELSON: Well, if Ray were here, he would love to answer that question obviously, because that is a project that has been near and dear to his heart.

It has never been the intention that CDDI would only have one or even two academic institutions representing it. We have two at the moment only on the steering committee, but that is hopefully going to be expanded as we get dissemination of the information out more and we get some I guess more awareness, if you will, by some others in academia, but no, the answer is no, never was meant to be that way.

We just were part of the originating body, I think, at Georgetown, and Tom Allen and the group at Sloan School of Management also participated in the Georgetown Conference, and I think that is really basically how those

[--- Unable To Translate Graphic ---]

two institutions got onto the steering committee, but as it goes forward in the technical committee -- we haven't even really decided how long a member is going to exist on the steering committee yet. There is a lot of organizational formality that hasn't been finalized.

The CERT, I can't speak extremely fluently on it, but is really an organization that is designed and meant to look more at the back side of the drug development as a process. In other words, after the initial approval of a new chemical entity, as I understand it, really, CDDI is meant to look at the forward side in the upfront development stages prior to being released to the public for use. But Ray would love to give you further information on CERT, I am sure.

DR. DAVIDIAN: Dr. Edeki.

DR. EDEKI: I think any form of collaboration between the FDA, on one hand, and academic centers and industry, on the other hand, should be highly commended, but my question is in regards to the CDDI, how was it initiated, was it from the FDA, or it was just from the academic center, or it just started as a loose organization? Also, is there a funding involved, has it been funded at this point in time, they are just volunteers, the participants?

[--- Unable To Translate Graphic ---]

MS. NELSON: Somehow I always like to answer the second question first, I don't know why, but the funding so far has been voluntary by the participating organizations. What resources have been utilized have been voluntarily donated, I guess is the way to say it.

We do not have any official funding although that is actually quite correct, Pharma has actually given a small grant for the initial operational and formation funding stages, which we will use for some travel expenses for some people to come to participate in the early development stages, so that is actually an official designation of some funds, but other than that, we do not have official funding.

And your first question was?

DR. EDEKI: How was the idea initiated?

MS. NELSON: Actually, I tried to explain it really came as an offshoot of the Georgetown Conference, which was entitled Drug Development, Where Does the Time Go?

There was a panel of individuals who represented academia, the FDA, and the pharmaceutical industry, and they concluded after reviewing the presentations that really a collaboration to address these issues should be formed. The FDA was, as I said, a participant in that panel and in the meeting, as well, so I think everyone enthusiastically

[--- Unable To Translate Graphic ---]

embraced the idea and from that point on, the FDA has been a significant driver to help the process flourish and continue.

DR. VESTAL: I would just mention that I think it probably is not essential that professional societies have a formal role in this, but I think they would be very interested in the outcomes, the presentation of results, and to be kept informed, and certainly the American Society for Clinical Pharmacology, as well as AAPS, would be very interested in this whole project.

In terms of funding, it seems to me that this is very nice in concept, but without resources it is not going to accomplish anything, and since both industry and the public will benefit, it seems to me that there ought to be some very serious efforts to identify joint funding from Pharma and from the FDA or conceivably even NIH.

MS. NELSON: I guess that wasn't a question. I will just agree with you.

DR. VESTAL: Not really a question, more of a comment.

MS. NELSON: A good comment. I agree with that.

DR. DAVIDIAN: Dr. Zimmerman.

DR. ZIMMERMAN: I guess a question or the comments

[--- Unable To Translate Graphic ---]

I would like to make is that in terms of dissemination of information about these initiatives, if I as an academician was not sitting on this committee, I wouldn't know anything about it, about the CDDI or the PQRI, and the question is, if this is actually going to be a collaboration where academicians and the regulatory agencies and industry are going to be working together, then, there is going to have to be a formalized, for example, request for proposals or requests for applications, such as the NIH has when it is developing contractual agreements, they have the RFPs.

Certainly, this initiative, these research initiatives have to be disseminated beyond the East Coast to all of the other institutions that certainly can contribute to many of these initiatives. So, I think that when one is talking about dissemination of information, there is going to have to be a formalized mechanism, such as an announcement, a quarterly announcement or monthly announcement of things that are available, because this certainly has not been widely disseminated.

The second point I would like to make is that if you are really thinking of these collaborative efforts, then, I think that they have to be subject to peer review in the sense that any research projects are subject to peer

[--- Unable To Translate Graphic ---]

review.

It is like opening a can of worms. Now, you are going to get into the peer review issue, but I guess that is my comment, is that if that is what you mean to do, is to have these collaborative research efforts, then, they are going to have to be dealt with in the way that other federally funded research efforts are dealt with.

DR. DAVIDIAN: Fair comment, I think.

Dr. Vestal.

DR. VESTAL: I will just second that comment, and it applies to the product quality research initiative, as well. The process has to be open, but certainly the effort to get these initiatives started and organized and to develop a research agenda, I think as Dr. Edeki said, to be highly commended.

DR. DAVIDIAN: Dr. Branch.

DR. BRANCH: As an attendee of that conference that was where did all the time go, it was notable that although it was widely advertised, there were only three academic institutions that bothered to attend it.

I think the idea is laudable of getting academia, industry, and the FDA together, but the brief of each is very, very different, and finding a common ground and

[--- Unable To Translate Graphic ---]

finding funding that people will actually agree that it is common enough to put some funding into it is a somewhat different issue.

I think industry has clearly got one agenda, FDA is trying to meet industry's needs for the second, and I can see why that there has been an extensive series of discussions between them. I am just intrigued by the idea of where does academia fit. I am not convinced that it has shown any leadership within this area at all or has contributed very much.

I think there is one notable lack in your equation, and that is fitting the NIH into the backdrop of this, and I think there is a major problem of how clinical pharmacology sponsored at NIH and the role of NIGMS towards industry, but I think at the macro level, there is a lot of pressure that Congress brings to bear on the NIH to say it should be supporting work that ends up by contributing to drug development, and it has done so through a variety of mechanisms.

I would strongly recommend that the political pressures that are brought to bear within this area actually start to go from small businesses to large businesses. I think it is very feasible, but I think it is a much larger

[--- Unable To Translate Graphic ---]

size of the picture.

The NIH does not have the structure or the ability really to respond to the need that is identified here, but I don't see why it shouldn't. Has anything been thought about within your committee structure in terms of creating a proposal that is realistic, considering who to lobby? The industry has got one of the biggest lobbies capabilities in the country, actually using this to sponsor the idea of leverage that no one group alone can do what you are suggesting.

Is there any movement in that area, do either you or Roger know of any of that or thought about it?

DR. DAVIDIAN: Dr. Byrn, would you like to respond?

DR. BYRN: Yes. I have so many ideas on this I could give another 15-minute discussion on that. I think it might be easier to frame this whole discussion by talking about PQRI than it would be CDDI, because PQRI has several ongoing features that we could look at to understand what is happening.

The PQRI, both SUPAC and the Biopharm programs were funded, as Doug Sporn mentioned this morning, by the FDA. The SUPAC program was funded at the University of

[--- Unable To Translate Graphic ---]

Maryland, and the Biopharm program was funded at both Michigan and Uppsala, the University of Uppsala, so these were ongoing programs that had gone through an announcement, a request for proposals, and so on.

Our program, Purdue's program, which came in as a drug substance, we have two sources of support. We have an NSF pharmaceutical processing center, which is a peer-reviewed university industrial center, and we also have a program called CAPM, Consortium for Advancement of Pharmaceutical Manufacturing, which is funded solely from industry to do advanced manufacturing research.

So, those are sort of the backdrop that were brought together to start forming PQRI. Now, as I understand it -- and I agree with Cheryl -- we need to have peer review in this, so it is not going to go without peer review.

As I understand it, the next step for PQRI is to involve AAPS, and I believe a meeting is scheduled to start to involve AAPS in the organization.

Also, I have a fairly strong feeling, having been a medicinal chemist, and still am a medicinal chemist, and worked with NIH, NIH is probably not the right organization to fund this kind of research. NIH has very little

[--- Unable To Translate Graphic ---]

knowledge in the product quality end, and that is all I am talking about, material science, engineering, and those kind of fundamental studies.

It has been historically NIH has not been strong in this area, they don't have strong review panels in this area. My vision is to have the FDA -- what I would like to see happen is that the FDA would form an institute like the NIH that would fund research on product quality. After all, FDA is the federal agency that is most concerned with product quality, they have the most knowledge about product quality, they work on it every day both through recalls and through NDAs.

So, my argument is that we should, all of us should try to get the FDA funding to set up a peer-reviewed program with a study section or two initially that would fund projects in this area.

I think it is very interesting that the Government spend so much money on molecular biological research, and so little money on product quality research.

Let me just go on briefly a little bit. I am talking more about product quality now, because I know more about it. The area of material science, the fundamental area of material science is exploding in both engineering,

[--- Unable To Translate Graphic ---]

physics, and chemistry programs throughout the country.

Rice University has renamed their Chemistry Department, Material Science, and this is the fundamental area that underlies product quality, the knowledge of how solids, materials behave, whether they are solids or in solution, how they interact with each other, what happens when they bind to each other, and so we have a fundamental knowledge base, and this has historically been supported by NSF.

So, we have that base that we could bring to bear, so I think that really all the pieces are in place, that if we got an agency, the FDA in my argument, that had the funding, we could advance this field significantly and address some of these problems.

DR. BRANCH: I think the same argument can be raised on the clinical aspect in terms of the CERT concept, which is after the drug is approved, but how can that be promoted and how can the quality of utilization be enhanced, which is what Ray would have talked to if he had been here, but having a CERT at Pittsburgh, we have the same issue.

I think that the whole issue of being able to translate the clinical pharmacology ideas would be also enhanced by creating a research arm to the FDA. I think

[--- Unable To Translate Graphic ---]

that is a very good idea.

DR. DAVIDIAN: Dr. Zimmerman.

DR. ZIMMERMAN: I just wanted to comment about something that actually NIGMS did try not too long ago. They put out a request for applications, which essentially is requesting investigator-initiated grant proposals, the title of which I believe was Prediction of Oral Drug Bioavailability.

This essentially came out of a workshop that the NIGMS had put together, that had people from academics and from the industry, and the industry made it very clear that they felt that this was within the purview of NIGMS, and I think NIGMS agreed with that.

So, they put out an RFA on prediction of oral drug bioavailability, but many, many people who answered that RFA with an RO1 could not get out a study section, because the study sections were constituted in such a way that the people who were reviewing it did not view this as an important issue, and, you know, many of the study sections were oriented towards molecular biology and these other very fundamental and not unimportant things, but certainly not in an applications area.

So, my view is that NIH may try or may be

[--- Unable To Translate Graphic ---]

interested in this, but unless they change their study sections or whatever, these proposals won't get out of study section, and then the Institute can't do anything because they can't fund anything that hasn't been approved by the study sections.

Again, perhaps FDA is the place where this kind of work has to be done.

DR. BYRN: That is my view, my impression also, and I don't see why there couldn't be in this scenario two study sections, one that handled the products and one that handled clinical.

DR. DAVIDIAN: I think we have time for maybe one or two more comments, and then we will break.

Dr. Brazeau and then Dr. Williams.

DR. BRAZEAU: Steve, I have a question. What would be the mechanism for the PDQI about prioritizing which of the demonstration projects that you showed? You showed us a number of those.

DR. BYRN: Again, I think this would have to be done by peer review either through the AAPS or through a study section, whether it would be a request for proposals sent out, I don't know whether Ajaz, but that is basically I think what their thinking is. There would be some mechanism

[--- Unable To Translate Graphic ---]

set up either by working with AAPS or through a peer review committee to review the proposals.

DR. DAVIDIAN: I think Dr. Williams will have the last word.

DR. WILLIAMS: First of all, let me say it has been wonderful hearing the committee discuss this because I think you have brought a freshness to some of our thinking where we have been struggling with some of these issues ourselves over the last 18 months.

I could imagine coming back again before this committee, say at the fall meeting, where we would continue to present the evolution of these projects with you.

Just to add a little bit to some of the -- and I would hope if the committee felt comfortable, they would come back during some of the subsequent discussion times and talk about some of these things again, it is very hopeful to us.

Just to recall, one of the motivations in back of some of the scale-up workshops that led to the SUPACs and the University of Maryland project was to get publicly available data and information, because we all respect the fact that industry sometimes spends great sums of money for information, and it is things they don't want to share

[--- Unable To Translate Graphic ---]

publicly, and yet industry, at the same time, has been very willing to come before us and share information, and we certainly appreciate that, but I think the concept of a true publicly available discussion and set of information is just enormously valuable to us.

I think in all these discussions we have had about these collaborations, there has been an intent to be transparent about it, and as you know, we have a lot of mechanisms in this country that allow transparency.

For example, let's say we create these proposals that we are working on now. Well, those can go in the Federal Register, and we can ask for comment on them. We can put minutes of our meeting on the Internet. There is just an endless variety of ways that we can be transparent now, and I am delighted of it. I think that is the way to work.

I think Bob and others mentioned the concept of membership, and membership is a critical issue for us because no matter how you set it up, there are always going to be people there who say I am not in the picture, and how to solve that problem I would very much welcome the committee's thoughts on.

I can tell you ICH has struggled with this

[--- Unable To Translate Graphic ---]

problem. There is an aspect of ICH where it was really people who focused on new drug development, NME development, and ultimately, that has caused ICH problems in terms of excluding all pharmaceutical manufacturers and people who aren't members of trade associations.

So, the only hope I have is that given the value of this, that we can solve these problems, and I think our society does have mechanisms that allow the solution. This committee is one of them. So, I think it is a very exciting discussion.

DR. DAVIDIAN: I propose we take a sort of accelerated break and reconvene at 3 o'clock for the biopharmaceutics topics, so if everyone could get back promptly at 3 o'clock.

[Recess.]

DR. DAVIDIAN: If everyone would take their seats, we can get started again. Despite the absence of a few stray committee members, we will go ahead and get started with the presentation.

This session is on Biopharmaceutics Topics, and we have three presentations, by Dr. Hussain, Dr. Chen, I believe will giving the second one, and Dr. Adams.

### **Biopharmaceutics Topics**

[--- Unable To Translate Graphic ---]

## **Biopharmaceutics Classification System: Update**

DR. HUSSAIN: Thank you and good afternoon.

[Slide.]

My topic is a progress report on the biopharmaceutic classification system.

[Slide.]

The transparencies that I will be using are in the handout that you have, but I will not be using all of those, especially because I don't want somebody to jump in this room. But let me get started.

In a sense, the biopharmaceutic classification system was developed as a result of research at FDA, Medical Product Agency, Uppsala, Sweden, University of Michigan, and Maryland. There have been several public presentations including the presentation to the former Generic Drug Advisory Committee and application SUPAC-IR.

I gave a brief presentation on this topic at the last Advisory Committee for Pharmaceutical Science meeting in August. We have sort of drafted a draft guidance and we are still making a number of presentations, the last one being the AAPS/CRS/FDA workshop in April. We have a brief presentation here.

Other presentations include the European

[--- Unable To Translate Graphic ---]

Federation for Pharmaceutical Sciences, Drug Absorption Conference in Scotland in June coming up. We are setting up an expert panel to resolve some of the issues that remain and will come back to the Advisory Committee with a more detailed presentation at the next meeting.

[Slide.]

At the last meeting, Dr. Williams introduced this topic and talked about the pre-1962 bio-problems and the AA, or nonbio-problem, drugs. I gave a brief theoretical foundation of the classification system, talked about the class boundaries with some examples.

I also laid out what the concerns were for the group when we got started discussing these and these were essentially taken from what we have, the regulations, 320.33, and these are based on the therapeutic index, physicochemical and pharmacokinetics, and also outlined what our objectives were.

There were some comments at the end of that meeting. Dr. Goldberg had questions regarding what would be the definition of wide and narrow therapeutic-range drugs. Dr. Vestal said what sort of experimental validation would we be providing for this, and then some issues of subject-by-formulation interactions, could we do that in

[--- Unable To Translate Graphic ---]

vitro.

Dr. Benet pointed out that propranolol is probably not a good example and he pointed out that oleic acid and other excipients can interfere with metabolism and we do need to consider that.

[Slide.]

I would like to take a few minutes to just walk you through the origins of our current bioequivalence requirements. The 1974 Drug Bioequivalence Study Panel recommendations were the key starting point for what we have today as our bioequivalence requirements.

This committee made several recommendations starting out saying that, at that point, the current regulations were not sufficient to insure bioequivalence and that we do need to proceed and develop methods for in vivo bioequivalence assessment, need for defining drugs which are problem drugs and non-problem drugs from a bioequivalence perspective and essentially started the concept of AA drugs in the Orange Book that we are familiar with.

This committee also recommended that bioequivalence was not necessary for all drugs or all drug products and a classification system needs to be developed.

In 1977, the bioequivalence requirements or

[--- Unable To Translate Graphic ---]

regulations were finalized and a list of criteria and evidence needed to assess actual or potential bioequivalence problems were sort of published or included in the regulation. These are now under 21 CFR 320.33

The Orange Book was published with a list of AA drugs and, in 1981 through 1984, here is where we had the paper NDA process accepted.

[Slide.]

Essentially, that led to our current bioequivalence requirements which requires bioequivalence by means of in vivo methods for almost all drug products containing solid drug or undissolved drug.

However, the regulations do recognize that, for certain products -- one example is a solution, an oral solution, elixir, syrup, tincture or similar other solubilized dosage form may not require an in vivo bioequivalence or bioavailability method if the active is in the same concentration and there are no inactive ingredients present that may significantly affect absorption of the active.

That is how we currently regulate solubilized or solution systems without a bioequivalence study.

[Slide.]

[--- Unable To Translate Graphic ---]

Clearly, the way we regulate drugs right now, solid dosage forms require bioequivalence studies. Essentially, dissolution has been recognized as the primary factor that affects bioavailability and bioequivalence. Dissolution technology has gone through phases of acceptance and then lack of confidence in those test methods that we currently use.

Right now, for immediate release dosage forms, dissolution testing is mainly used as a quality assurance or a product release specification, not for bioequivalence. But it can be used for bioequivalence if you demonstrate in vitro/in vivo correlation.

As you know, it is quite difficult to demonstrate that for immediate release products. We have several examples of in vitro/in vivo correlations on the extended release products but not the immediate release products.

So the Biopharmaceutic Classification System comes out as a tool which is based on drug solubility and permeability and product dissolution characteristics for identifying when an in vitro/in vivo correlation may be expected and also it recommends appropriate dissolution test methods and indicates when in vivo bioequivalence assessment may not be necessary.

[--- Unable To Translate Graphic ---]

[Slide.]

The Biopharmaceutic Classification draft guidance has two objectives. One is to recommend a class of immediate release solid oral dosage forms for which bioequivalence may be assessed based on dissolution tests in vitro and to recommend methods to permit classification according to dosage form dissolution, solubility and permeability characteristics of the drug.

[Slide.]

In June of '96, a working group under the direction of the Biopharm Coordinating Committee was formed consisting of the following members: Lydia Kaus from the Office of Clinical Pharmacology of Biopharmaceutics; Ko-Yu Lo representing the New Drug Chemistry; Ram Mhatre, OGD, Biopharm, Bioequivalence Division; Vinod Shah representing OPS; Donna Volpe and I are from the Office of Testing and Research.

We spent several months discussing the Biopharmaceutic Classification System. You will recall, the SUPAC-IR application of the Biopharmaceutic Classification System was done with a different group. So, essentially, this group was starting from scratch looking at the data again, rethinking the Biopharmaceutic Classification System,

[--- Unable To Translate Graphic ---]

going through the process of rehashing things again.

Also, the responsibilities for different parts of the guidance were distributed as follows: Lydia focusing on permeability methods in humans, fraction of those absorbed versus effective permeability relationship and a computer simulation study.

Ko-Yu Lo focused her attention on solubility determination; Ram Mhatre, permeability in animals; Dr. Shah is linking the classification system to his guidance on dissolution which was recently released; Dr. Volpe is focusing on permeability assessment methods using cell and tissue culture; and I was sort of coordinating all the efforts and spending most of my time getting the experimental evidence for rapid dissolution class which we will talk about in a minute.

[Slide.]

The progress has been as follows: we have reevaluated what was called the Biopharmaceutic Drug Classification System and renamed it Biopharmaceutic Classification System. Although dropping D might be minor, but it really puts dissolution back up front and says we do need to look at dissolution, solubility and permeability all taken together.

[--- Unable To Translate Graphic ---]

We have sort of applied a rapid and slow dissolution class to this.

Also, the group has come to a consensus that a rapidly dissolving, highly soluble, highly permeable class can behave as a solution, as an aqueous solution, and be a candidate for bioequivalence by in vitro methods. The experimental evidence that we are collecting is coming from NDA, ANDA and our research database. There is also a computer simulation study to address this.

There are a number of issues that remain to be resolved with permeability methods and there are some special considerations that we will talk about.

[Slide.]

With regard to permeability determination, we have retained the definition of permeability as it was applied in SUPAC-IR essentially saying that highly permeable drugs have extent of absorption greater than 90 percent. That is an extended sort of definition but, obviously, permeability is a rate factor and we will address that as we go along.

For methods that are applicable for permeability determination, we believe several different methods are possible; human pharmacokinetic studies, animal experiments, in-situ rat perfusion, for example, and KAO2 and other

[--- Unable To Translate Graphic ---]

cell-culture systems are all possible.

However, at this time, we didn't have enough information and data to say here is a boundary, if you use a KAO2 cell-culture system, if your permeability value is this, that will be high. We are unable to say that at this time and we are essentially saying that any method that does not directly estimate the extent of drug absorption in humans will need to be justified and the ability to predict the extent of absorption in the human is demonstrated.

So, essentially, a validation of any other appropriate method will be possible. Also, impact of absorption mechanism and free system metabolism would need to be considered when selecting the appropriate experimental method for estimating permeability.

The issues we hope to discuss with an expert panel soon is our method selection, standardization, use of "internal standards," can we include internal standards in a permeability experiment to reduce variability and maybe get a better estimate of permeability that way and also some sort of predictive ability in error analysis of these methods.

So this issue remains to be resolved as we go forward.

[--- Unable To Translate Graphic ---]

[Slide.]

Let me focus the rest of the presentation on how we are getting information and data support for our what we might want to call the "New AA Drug Class." There are two founding stones here. One is the 21 CFR which provides a criteria for bio-problems based on clinical, physico-chemical and pharmacokinetics, and we have the USP experience.

This is a direct quote from USP which says that "There are no medically significant bioequivalence problems with articles where 75 percent of an article dissolved in water or acid at 37 degrees in 45 minutes in the official basket or paddle apparatus operated at the usual speed, that is, USP First Case."

We quickly realized that these two were not sufficient, the science has progressed so much that this would not be enough. That is where the Biopharmaceutic Classification System comes in. We build on the experience here to move forward.

For example, just recently, propantheline bromide was an AA drug and was changed to BB drug where the reason was we notice bioequivalence problems. It meets this requirement. It is an AA drug.

[--- Unable To Translate Graphic ---]

[Slide.]

Here is an example where these two were insufficient to protect a problem situation, whereas, if you look at propantheline bromide under the biopharmaceutic class, it would not be classified as a new AA drug.

Also, what I have specifically done is I am looking for exceptions and failures. We have found a couple of failures and will be doing more detailed analysis and presenting whether we can move forward in this direction and have no problems with failures.

Also, Medical Product Agency in Sweden, Germany, and Canada, our colleagues in other agencies are also helping us out looking for examples where a drug might fail bioequivalence and still be classified as New AA, which we hope we won't have any.

[Slide.]

Just to show you a flavor of one example what we think will happen. Here is a plot, sort of a vision plot here. On the x axis we have ratio, test-to-ratio of percent dissolved at 10 minutes in vitro, and AUC and Cmax ratios, and here are our current goalpost for bioequivalence.

What we feel will happen for highly soluble, highly permeable drugs, which also dissolve rapidly, is the

[--- Unable To Translate Graphic ---]

end of the curve and the Cmax may remain within the goalpost for a significant change in dissolution. Dissolution is rapid enough.

For example, if you take the reference which dissolves 85 percent in 15 minutes, and in solution, solution obviously 100 percent has been dissolved, the starting point is here, and as we go forward, that is, we are slowing down the rate of dissolution in vitro, and we will still be within this, and if that is so, then gastric emptying is very controlling here.

[Slide.]

Here is an example of dissolutions in vitro under what we call rapid dissolution for a drug metoprolol, and here is the current USP and product release specification, and this is where the pharmaceutical rapid dissolution boundary is. Obviously, some products which are on the market will not meet that, but most will.

[Slide.]

If you go back and link the in vitro dissolution to in vitro bioequivalence, and you can get lots of examples from our NDA files, and here is the sort of relationship. Dissolution is sensitive, it is very sensitive for product differences, but bioequivalence, there is no change.

[--- Unable To Translate Graphic ---]

However, as soon as somebody looks at this, the criticism comes up, you say, well, you don't see failed studies. That is true.

[Slide.]

Fortunately, we did have a research project at University of Maryland where we deliberately made products which would not meet the specification. Here is an example of the FDA-University of Maryland formulation which had to be slower, it was designed to be slower in terms of release, so this is a different product.

[Slide.]

Now, if you include that example here, we still are within bioequivalence standards goalpost, and here is an example of a solution. So, in a sense, what we are seeing here is a rapidly dissolving, highly permeable drug, such as metoprolol, and highly soluble drug meets the current requirements, and dissolution is a very sensitive method of assessing it.

[Slide.]

Also, there is a point which I wanted to make to address Professor Benet's point which he raised at the last meeting. We feel that conventional tablet/capsule dosage forms are likely to contain simple excipients when compared

[--- Unable To Translate Graphic ---]

to oral liquid formulations, such as syrups and elixirs. That means liquid oral formulations have a higher likelihood of affecting drug absorption due to osmotic/caloric and what I call "teasing" effect.

In fact, there is a very interesting study published in 1995, October issue of Biopharmaceutics and Drug Disposition, which used propranolol as an example. Subjects were shown the food, appetizing food, but not taken, but created an effect on bioequivalence.

Also, formulations containing ingredients designed to alter GI motility, metabolism, are not considered under Biopharm Classification System. The oleic acid example is right here, and this was a sort of entry quoted liver bypass delivery system which would not fit in.

[Slide.]

Comments that we have received, that we are addressing, are some comments regarding the basic research methods - permeability, the variability that we have in some of the experimental data that comes out of University of Michigan and Uppsala is high. That has been pointed out. Fraction F versus Peff relationship might be a soft relationship. Permeability and clearance, there is a debate going on whether we should call permeability clearance, and

[--- Unable To Translate Graphic ---]

so forth. Fick's law assumptions may not be appropriate.

The APS Workshop comments were rapid dissolution criteria is probably too conservative, and why do we need permeability in Biopharm Classification System, and there was a comment received, Professor Benet, need to consider a sub-class for drugs exhibiting high first-pass metabolism, however, there was oral, very strong support for this approach, and we plan to address all those issues as we move forward.

Thank you.

DR. DAVIDIAN: Dr. Chen.

#### **Individual Bioequivalence: Update**

[Slide.]

DR. CHEN: Good afternoon, everyone.

Some of you may know that at the last advisory committee meeting in August 1996, we talked about the topic of individual bioequivalence. Subsequent to the ACPS meeting, the Agency has convened an expert panel meeting in December last year.

At that meeting, experts from academia, drug industry met with the FDA Individual Bioequivalence Working Group to discuss and resolve some of the issues and questions raised by this committee.

[--- Unable To Translate Graphic ---]

With the input of the expert panel, the working group has now drafted a guidance recommending both individual and population bioequivalence for assessment of comparability between formulations which I will delineate in a moment.

[Slide.]

For the benefit of the new members on this committee, I will begin with brief notes as to why the Agency is interested in the concept of individual and population bioequivalence.

Basically, the average bioequivalence approach focuses only on the population averages of test and the reference product. It ignores the distribution of the metric, such as AUC or Cmax. It also ignores the possible subject-by-formulation interaction. In essence, this approach doesn't really address the question of either prescribability for a given drug or switchability between formulations.

Another concern that the Agency has for the current bioequivalence criteria is that we use 1,825 rule to all the drugs. The philosophy of "one size fits all" may not be appropriate in some of the cases, and obviously, it doesn't fit well for highly variable drugs or narrow

[--- Unable To Translate Graphic ---]

therapeutic window drugs.

More importantly, the Agency feels that we should encourage the drug sponsors to manufacture less variable formulations. With the appropriate methodology, population and individual bioequivalence will provide flexible criteria for different classes of drugs, and also provide a mechanism to reward drug sponsors for producing less variable formulations.

[Slide.]

In order to address all the issues that I just mentioned, we will use a general form of bioequivalence criteria that combines the average bioequivalence criterion plus the variance terms, which is then normalized by the reference variance.

Depending on the type of variance terms, we will have two distinct approaches. For individual bioequivalence the variance terms are subject-by-formulation interactions,  $\text{Sigma } D^2$ , and difference in within-subject variances between the test and the reference formulations.

For a population bioequivalence, the variance term will be the difference in total variances between the test and the reference formulations.

So, here the total variance is the sum of the

[--- Unable To Translate Graphic ---]

between-subject variance and within-subject variance.

One important feature of this side that we need to know is that with reference variance in the denominator, we are talking about a scaling approach where the bioequivalence limit will be adjusted based on the reference variability.

[Slide.]

Shown on this slide are the specific forms of bioequivalence criteria for the two approaches. As describe, the numerator has the average bioequivalence criterion and one or two terms of variances.

You may also note here that there is a slight difference in the denominator as what I just described for the general form of bioequivalence criteria. That is, instead of reference scaling, we have a mixed scaling approach here.  $\sigma_{w0}$  is a regulatory standard that corresponds to a limit of the within-subject variance.

Similarly,  $\sigma_{T0}$  is a regulatory standard that corresponds to a limit in the total variance.

This method is proposed to circumvent the problems that reference scaling approach may be too tight for drugs with low variability, in other words, by using mixed scaling approach, we will scale to the reference variability when

[--- Unable To Translate Graphic ---]

$\sigma_{WR}$  is greater than  $\sigma_{WO}$ , and we will scale to a constant variance if  $\sigma_{WR}$  is less than or equal to  $\sigma_{WO}$ .

[Slide.]

At the last advisory committee meeting, we talked about the possibility of assigning different values of weighting factors  $C_1$  and  $C_2$  in this equation for individual bioequivalence. However, the expert panel at a subsequent meeting seemed to be in favor of unity for both  $C_1$  and  $C_2$ .

The rationale for the choice came from the moment-based approach inherent in this equation. The equation was derived based on a notion that a measure of the distance between the two observations comprises the main difference in all sources of variance for the difference. At any time we have no way of knowing which term will contribute more than the other to the total measure of the difference, hence, to conform to the primary definition of distance, it is natural for us to fall back to the linear combination without weighting factors in the equation.

As far as the constant variance,  $\sigma_{WO}$ , the expert panel agreed to set at 0.2 as discussed in this committee meeting last summer.

[Slide.]

[--- Unable To Translate Graphic ---]

The working group has also proposed the epsilon values, that is, the variance allowance for the bioequivalence limit using both approaches. The epsilons were incorporated to compensate for the variance terms added to the criterion. The epsilon is 0.05 for individual bioequivalence and 0.02 for population bioequivalence.

In the interest of time I won't be able to get into the details, but these values were determined based on the simulation results, study power, and sample size.

[Slide.]

In addition to the regulations parameters, there were several topics discuss at the expert panel meeting on December 4th, 1996. Replicated crossover designs are necessary for assessment of individual bioequivalence, however, to assess population bioequivalence, nonreplicated crossover designs will be sufficient. In other words, the traditional two-treatment, two-period crossover studies can be used for assessment of population bioequivalence.

The expert panel agrees with this committee that subjects recruited for bioequivalence studies should come from the general population without regards to age, gender, body weight, race, or disease state.

The expert panel also recommends that for narrow

[--- Unable To Translate Graphic ---]

therapeutic window drugs, we could always scale to the reference variance. This recommendation was made because it was believed that type of drugs has low variability and by using reference scaling, we will be effectively tightened by equivalence criteria for these drugs.

[Slide.]

The question of when to apply population bioequivalence or individual bioequivalence can be linked to the question of whether prescribability or switchability should be addressed in the clinical setting, and population bioequivalence may apply to those bioequivalence studies conducted during the investigational phase of drug development where prescribability is of interest. While individual bioequivalence may apply to those bioequivalence studies conducted for generic substitution or post-approval changes, whereas, switchability or interchangeability is of concern.

Hence, we are proposing that population bioequivalence may be used for INDs and NDAs. While individual bioequivalence may be used for ANDAs and AADAs antibiotics, drug applications, as well as post-approval changes for both innovators and generic drug companies.

[Slide.]

[--- Unable To Translate Graphic ---]

I just want to say that the draft guidance is near completion at this time, and you will probably be distributed it sometime by the end of this month or next month.

[Slide.]

I would like to take this opportunity to thank my Co-Chair Rabindra Patnaik and all the members of the individual Bioequivalence Working Group in the FDA for their enduring efforts, hard work, and support over the last three years.

I would also like to express my appreciation to the expert panel for the invariable advice. Finally, my sincere thanks to our extramural consultants, Walter Hauck, Terry Hyslop, and Robert Schall. Your input and assistance are instrumental to the completion of this project.

Thank you.

DR. DAVIDIAN: Our next presentation, a slight change to the title, Locally Acting Drug Products. This will be a joint presentation by Dr. Adams and Dr. Shah.

### **Locally Acting Drug Products**

[Slide.]

DR. SHAH: Thank you very much. In the morning when Dr. Williams presented some of the groups in the

[--- Unable To Translate Graphic ---]

Biopharmaceutics areas where new guidance are being developed, he also had a block which said about the locally acting drug products, and that is the area that we will be talking now, and the locally acting drug products falls into four different categories: oral drug products, nasal and oral inhalation drug products, topical dermatological drug products, and others, such as otic and ophthalmic products, and all that.

Dr. Adams will be covering the area of the nasal and oral inhalation today, and my task is to cover the approaches that we plan to take towards the topical dermatological drug products.

[Slide.]

We had previously come to the Generic Advisory Committee meetings earlier and laid out some of the issues that needed to be discussed with respect to the topically active dermatological drug products.

Some of the issues and the ways for determining the bioequivalency of the drug products, which is in the Federal Register identified as the pharmacokinetic ways of measuring the bioequivalency, pharmacodynamic ways, comparative clinical trials, and some of the in vitro bioequivalence, something similar to what the AIDS drugs

[--- Unable To Translate Graphic ---]

call for.

But when we go down to the topical dermatological drug products, generally, these are very difficult to do the pharmacokinetic ways of measuring the drug concentrations in the blood and all, but we thought maybe if we can measure the drug concentrations in the skin, which is the site of application of the topical drug products, it might be feasible to do the pharmacokinetic or the dermatopharmacokinetic ways of measuring the drugs, and use that principle for measuring the bioequivalency of the drug product.

So, our task is to really develop and look into some of these different methods that could be utilized for measuring the bioequivalency of the topical dermatological drug products, in addition also to look at some of the other issues, such as CMC or the chemistry, manufacturing and control issues, comparability of inactive ingredients, and the safety issues for the topical drug product especially when we may have to do the comparative systemic absorption studies primarily to see that the products are safe.

[Slide.]

The major classes of the topical dermatological drug products includes the glucocorticoids, antifungals,

[--- Unable To Translate Graphic ---]

antivirals, antiacne, and antibacterials, and there may be some other drugs also that could be added on here.

With respect to the glucocorticoids, we had the bioequivalency guidance developed based on the pharmacodynamic measurements, and that guidance was issued in June 1995.

We also had the comparative clinical studies guidance for the bioequivalency for the antifungals, which was the draft guidance, and it was issued in 1990, and there are no guidances right now for the antivirals, antiacne, or the antibacterial drug products.

[Slide.]

If we take again a look at the different aspects of the different methods that could be used for the bioequivalency, as I have shown on here, the first one is the clinicals, which generates very difficult to do for a bioequivalency determination. It is also an expensive way of doing the studies. In several instances, we find that it is insensitive method to really make the comparisons of the bioequivalency of the drug products.

The second approach, which was the pharmacodynamic approach, it is not applicable for all the types of the topical dermatological drug products. It is applicable only

[--- Unable To Translate Graphic ---]

in some cases where we could see a pharmacodynamic response after the topical application, and the example is the glucocorticoid and for which we already have the bioequivalency guidance.

Now, for the other types of the topical drug products, we feel that the dermatopharmacokinetic method, which is a pharmacokinetic way of evaluation for the bioequivalency determination, it is feasible, it is not very difficult, and it also looks like it is the logical approach.

The reason we say it is logical is the topical dermatological drug products are generally meant for the topical applications, they are not meant for the systemic activity, not meant for the systemic effects, primarily for the local area, and therefore if you measure the drug concentrations, the pharmacokinetic profile in the skin looks like it might be a logical way of measuring the bioequivalency determinations, and at least from some of the work that we have done so far, it seems like it is a universally applicable procedure.

The in vitro method, which is again for the topical dermatological drug products, also appears to be universally applicable and primarily we see its goal right

[--- Unable To Translate Graphic ---]

now as to signal the possible bioinequivalency or the possible inequivalency of the topical dermatological drug products.

[Slide.]

Trying to go back and take a look into the review aspects of what information is available in the literature that could be used for bioequivalency methods, we find that there was a review article published about 10 years ago, which was The Bioavailability of Dermatological and Other Topically Administered Drug Products, and that review article also identified that it is possible to use the dermatopharmacokinetic procedure, a method to determine the bioequivalency of topical dermatological drug products.

Last September, we had a workshop which was co-sponsored with the AAPS and the FDA on the bioequivalence of topical dermatological dosage forms, methods of evaluation of bioequivalence, September 1996. That also concluded more or less that the DPK method or the dermatopharmacokinetic method is easy to do and it should be applicable for all topical drug products.

Again, like other workshop has done, the reports come out, but then it remains to be done as to more information, more exactly how to perform the studies, and

[--- Unable To Translate Graphic ---]

all the other details about the procedures and all.

So, what we are intending to do is for the locally acting drug products under the topical dermatological drug products groups, we intend to create several different working groups which will be dealing with different aspects of all the issues, so that finally we can come up with a good guidance.

In this case, we will be also having the members of the working group coming from the different disciplines, so that we can really address all the issues that needs to be addressed in the guidance.

These groups will be specifically looking into the comparative clinical trials and the systemic absorption safety studies, the dermatopharmacokinetic studies, pharmacodynamic studies primarily to see if we need to change our existing bioequivalency guidance for the glucocorticoids, any modifications that need to be done, also to address the CMC and the in vitro release aspects and comparability of inactive ingredients.

I would like to point out here that in your handout, there is an error. It said "an active ingredients," but it should be "inactive ingredients," so please make a note of that because it makes a significant

[--- Unable To Translate Graphic ---]

difference what I am trying to say. So, it should read the "comparability of the inactive ingredient."

This is primarily because of the new rules and regulations which have come out that the topical drug products should also have qualitatively and quantitatively the same compositions and the extended compositions with respect to the brand name products. So, those issues will be covered in this category.

So, our goal is to form these subgroups and have the members coming from the different disciplines to address and prepare the guidance. This particular group has been just formed about a month ago even though we have been working on it at different times and different features, but that is our goal now, to really start working and focusing on these areas.

Thank you.

[Slide.]

DR. ADAMS: Advisory Committee members, ladies and gentlemen: Good afternoon.

I would like to talk about the Oral Inhalation and Nasal Products Technical Committee and some background information. Since 1992, the Office of Generic Drugs has been working on the issue of dose-response for metered dose

[--- Unable To Translate Graphic ---]

inhalers and specifically albuterol MDI. In fact, the Division of Bioequivalence has, since 1988, been involved in issues of bioequivalence establishment and documentation for albuterol MDI, both in vitro and in vivo.

In 1992, as I mentioned, we started on the dose-response studies with Johns Hopkins University for albuterol MDI, and after a fascinating, very interesting history, we arrived at some recommendations which were brought to this advisory committee in August of 1996 with regard to documentation or in vivo bioequivalence, and the committee found that those recommendations were acceptable.

Now, since that time, we have been ready to move on to address the issue of bioequivalence of other aerosol drug products and also to address the issue of what sort of testing should be done to characterize aerosol drug products generally.

[Slide.]

I would like to indicate first that the products that this group is considering are both oral inhalation metered dose inhalers and nasal products, and the nasal products can be both metered dose inhalers or manual metered dose pumps.

To give you an idea, if we classified these

[--- Unable To Translate Graphic ---]

products by therapeutic class, we could look at adrenergic bronchodilators, and the first drug I have listed as an example is albuterol metered dose inhaler, which is a drug that we have been spending a great deal of time on.

In addition, there are other drugs as examples in the adrenergic bronchodilator class - terbutaline, metaproterenol, and a number of others.

The anticholinergic bronchodilator, ipratropium bromide is another group, cromolyn sodium, and the corticosteroids as examples listed on the bottom of this slide. The reason for the importance of these different classes is that the testing methodologies, which may be appropriate to document bioequivalence of these drugs, may be quite different.

For instance, we do know quite a bit now about the dose-response relationships for albuterol MDI, and that is able to serve as a template for bioequivalence studies for the ipratropium bromide, but for the corticosteroids, we would expect to have a very difficult problem in terms of dose-response for this class of drugs, so that is going to impact the sort of testing necessary to document bioequivalence.

[Slide.]

[--- Unable To Translate Graphic ---]

Amongst the nasal products are corticosteroids, the anticholinergic bronchodilator Atrovent again, and cromolyn sodium.

[Slide.]

I have also classified these products based upon dosage form. What we see is for the oral inhalation products, all of the aerosol drug products are MDIs, and by that I mean these are propellant-driven systems with CFCs or alternate propellants. They may either be solutions or suspension formulations. The nasal products I have mentioned may be either metered dose inhalers or manual metered dose pumps, and these products may be suspension formulations or solution formulations.

The reason that we are making this distinction between suspensions and solutions is that we may be able to use that distinction between the dosage forms as a means of determining what sorts of testing, whether it be in vitro or in vivo, is appropriate for documentation of bioequivalence.

[Slide.]

As a result of the extensive work which the Agency has done on albuterol metered dose inhaler, we did issue a guidance in January of 1994, which was an interim guidance. There have been changes, as I have mentioned, which were

[--- Unable To Translate Graphic ---]

brought to this advisory committee in August of last year, and we are currently working on a revised version of that guidance.

In addition, we have a 1989 in vitro guidance which is currently in use, and we do feel that that needs to be updated, as well.

[Slide.]

Some of the issues which are of interest with regard to the metered dose inhaler products or aerosol drug products are inactive ingredients comparability. Dr. Shah has mentioned this. In November of 1994, the Office of Generic Drugs issued an interim inactive ingredients policy guide, and for the aerosol products specifically, our recommendations are generally that a generic product be qualitatively the same and quantitatively as close as possible in terms of its inactive ingredients, and that is formalized in that interim guidance.

Another issue which is of great concern to manufacturers, both innovators in terms of developing new products and in terms for generic products, for generic firms in terms of should resources be spent in developing a CFC product or an alternate propellant product, is a Federal Register notice with regard to essential uses for CFC

[--- Unable To Translate Graphic ---]

products which issued in March of 1997.

Other issues are chemistry manufacturing control and in vitro testing appropriate in vivo study designs for the various drugs whether we are talking beta agonist drugs or steroid drugs or others, and when might it be appropriate to look at comparative systemic absorption studies, the steroid products, for instance.

It is undesirable that these products, which are intended for local use either in the nose or in the lungs, it is undesirable that there be absorption in the systemic circulation, so there may need to be some documentation that levels of the steroids that have been absorbed systemically are low.

[Slide.]

This slide indicates that technical committees either have been established or are in the process of being established for the topical products, as Dr. Shah has indicated, and for the oral inhalation and nasal products, that technical committee is in the process of being established now.

[Slide.]

This slide is similar to one that Dr. Shah had, showing the working groups within the Oral Inhalation and

[--- Unable To Translate Graphic ---]

Nasal Technical Group. The membership of these various working groups will be comprised, where appropriate, of individuals both on the new drug side and/or the generic drug side of the Agency.

We will consider in detail for various drug products, various aerosol drug products, which are the appropriate tests to be conducted and what the design of these tests should be.

Thank you.

DR. DAVIDIAN: Thank you to all four presenters.

#### **Open Public Hearing**

Now, we come to the open public hearing. At this point, members of the public who wish to make a statement are welcome to do so. Please come to the mike and state your name, your affiliation, and your title if anyone is interested in doing so.

The red light has gone on. No more takers I guess.

We did have a member of the public who could not be here for this session, had a comment. His name is Al Nugent. He is a marketing representative from Midwest Research Institute in Silver Spring, Maryland. He wished to address the following question to members of the committee

[--- Unable To Translate Graphic ---]

and members of the staff.

He says, "Technical committees for the CDDI and PQRI" -- which is what we discussed before lunch -- "should be open to membership by researchers from not-for-profit research institutes. Are they and how may someone from a not-for-profit research institute join if they wish?"

Are there any response or comment to his question/comment? Roger.

DR. WILLIAMS: I guess I feel it is a little premature to answer that question just yet, but if he wanted to communicate directly with me, I would be glad to get the petition, and he could send me a letter or I could just take it from you now and try to respond to him.

DR. DAVIDIAN: Okay. He left his card.

If there are no other members of the public who wish to address the committee, I guess we will move to the committee discussion of any of this afternoon's topics.

Dr. Branch.

#### **Committee Discussion**

DR. BRANCH: I think the presentations this afternoon really nicely demonstrated a point that Roger made earlier today, that there is a high level of complexity that is required to address specific issues, and the approach of

[--- Unable To Translate Graphic ---]

getting a group together to collectively discuss the issues but also importantly to review internal information that is available seems to me a very admirable way to go about this, and the product is a guidance.

My question really is what is the availability of the information that is used to develop that guidance in the open arena. A lot of the information that comes to the FDA comes under the arena of confidential information and is used internally by staff or can be used internally by staff to develop these sort of guidances.

It would seem to me that if a company is developing a product, and that product actually lies outside the frame of reference on which the guidance is being developed, they may want to make that presentation not taking the guidance route. It seems to me fair that they should have the availability of the information on which the guidance was based, so they can argue whether that drug is inside or out of that. That is one aspect.

The other aspect is I think some of these observations are a very important repository of information, and there is a real need for some of these correlations that are being made between multiple drugs for principles like drug absorption, if you look at the individual, the

[--- Unable To Translate Graphic ---]

population and bioequivalence, for example, that database it would seem to me, and the analysis from that, would be very valuable to present in peer review press.

So, my question is what is the availability of the information and is there an intent to allow an interested person to have access to information on which the guidance was based.

DR. DAVIDIAN: Dr. Williams.

DR. WILLIAMS: Yes. I might say to Dr. Branch that some of the information that was used in support of the individual bioequivalence approach was presented publicly last August at the advisory committee meeting, so I would say generally, there is every intent on the part of the Agency to present publicly the data used in support of a guidance.

Even when we are using trade secret or confidential commercial information, there are sometimes ways we can use mean data and otherwise disguise the data, so that we can protect the commercial sponsor, but yet still we share some of the data publicly.

We did that particularly, for example, some of the committee may remember for the replicate data sets that we showed last August, that we used in support of the

[--- Unable To Translate Graphic ---]

individual bioequivalence approach.

Also, we have been requested legally and via citizens' petitions to provide the information we use in support of some of our public policy, and I think the general rule there is that we are supposed to complete the work and then it can be shared publicly. You know, it doesn't do any good to share something that is incomplete.

Of course, the University of Maryland data was all presented publicly on many occasions to support the SUPAC approach, and again there is an intent to publish that data, so that the world can see it, as well.

We have published on our own and others have published several papers on individual bioequivalence that gives some of the logic and data in back of that approach. So, we try as best we can.

Getting back more to your -- I guess an associated point -- a sponsor according to a guidance is allowed to come in with an alternate approach. I am trying to imagine some kind of situation where that approach would be justified on the basis of data available to the Agency, but maybe I am not just thinking of the right example.

DR. DAVIDIAN: Dr. Gonzalez.

DR. GONZALEZ: I do have a question and primarily

[--- Unable To Translate Graphic ---]

addressed to Dr. Chen's presentation. First of all, I applaud the efforts of the Agency to help narrow the bioequivalency issues as they pertain to drugs with narrow therapeutic index, and as many of you know, there has been a lot of public furor and emotion about drugs with narrow therapeutic indices.

There is an alliance now that goes around the country calling themselves the NTI Alliance, and the issue here, though, is while we are narrowing these standards -- and I think that is very important and very much needed -- my concern is as we learn more about the stoichiometric ratio of one enantiomer versus the other in terms of overall activity, are we going to get to the point where we are going to want to look at not just the total concentration of the drug within a set standard, but are we concerned that product A versus product B may differ ever so slightly, but yet clinically important in the ratio of one active isomer versus the other within a given formulation.

DR. WILLIAMS: Well, there were really two separate questions there, and both of them were certainly good. The narrow therapeutic index issue is an important one, and you are absolutely right, there has been some issue raised recently with state boards of pharmacy.

[--- Unable To Translate Graphic ---]

I think individual bioequivalence does work to resolve some of those concerns, and I think the committee knows now this concept of continuous scaling based on the reference variability allows the possibility if the reference product has low intrasubject variability, you might go from, say, 80 to 125 to, say, 90 to 111, and we could imagine that for certain drugs like perhaps phenytoin, which we believe has low intrasubject variability, and perhaps warfarin, as well.

There is a slight caveat to this observation, though, which is if you have a narrow therapeutic range drug where the reference has high variability, you may end up broadening the goalposts, and we are not sure, but we think an example drug like that is cyclosporin. You have to be careful with the dose, you have to titrate and watch for toxicity, but yet we think the intrasubject variability of cyclosporin is high.

Now, if we always scale, you may see -- and I have no data in-house -- but you may see cyclosporin multi-source products that are approved on the basis of a wider set of goalposts. I don't know how we will deal with that publicly, but this is as good a place as any to bring it up.

DR. DAVIDIAN: Dr. Vestal.

[--- Unable To Translate Graphic ---]

DR. VESTAL: My question and I guess comment also relates to that issue of individual bioequivalence. I guess the comment is, first of all, I think that the analysis that has been performed, the conceptual analysis at least over the last several years by the group working on this problem is quite elegant, but as I remember our discussions last August -- and maybe some of the others can correct me if I am wrong -- there was some question in our minds as to whether this was a real problem. It seemed like we didn't see a lot of data to indicate that this was something that needed to be -- a problem that needed to be fixed.

I think I recall that the sponsors who addressed this felt somewhat the same way and were concerned that the new approach might require more subjects or at least more time and cost as I remember.

So, maybe we could have a response to that. It looks like we are moving ahead, but maybe not without more data, and a corollary question would be, well, did the expert panel that you brought in look at the same data that we saw and feel the same way, or feel that there was, in fact, a problem that needed to be fixed.

DR. DAVIDIAN: Does Dr. Williams or someone want to address that, and then Dr. Brazeau and Dr. Goldberg after

[--- Unable To Translate Graphic ---]

that.

DR. WILLIAMS: I always get these tough questions. There are many things we can say about individual bioequivalence, and I think in one way or another we have said them all at one point or another.

The equation does several things, and we have to remember that it has value aside from the fact of the subject-by-formulation interaction. For example, it allows us to scale, and we both think for highly variable drugs and narrow therapeutic range drugs it has a value.

It also has the value that it rewards within certain boundaries the concept of a less variable formulation, so as opposed to the current situation where a highly variable formulation sometimes in and of itself serves as a block to multi-source substitution, this equation works to resolve that particular problem.

Now, the reality, of course, and where the rubber meets the road is this issue are there significant subject-by-formulation iterations out there. Of course, we showed the data set of 10 or so data sets last August where sometimes it appeared there were.

However, that is a biased data set. You know the reason for performing a replicate design is kind of a driver

[--- Unable To Translate Graphic ---]

for why we got that data in the first place. I am going to try to make my answer brief, because we could talk about this a long time.

In the final analysis, I think our experts did endorse the general approach. The committee will recall that it also endorsed the use of replicate designs to get the information, and I think our feeling is we are going to put the guidance out for public comment, it will be a Level 1 comment based on Good Guidance Practices, so we are not about to rush into this in the next several months.

Certainly, we can bring it back before the committee and discuss it next November if they would like. Maybe we will have the comments from the public by then. I think in the final analysis, perhaps the question comes down to certain key issues.

One is the question of burden, are we really adding to the burden. Now, our current feeling is maybe for many drugs -- right now they do about 30 subjects in a two-period crossover, that is 60 total administrations. You might find when we do some of the power calculations, that they have to do 15 people in a four-administration study.

So, the total number of administrations isn't much different perhaps for at least some and perhaps many of the

[--- Unable To Translate Graphic ---]

drug products we are talking about. Of course, we understand there is a burden with a four-administration study as opposed to two-administration in terms of dropouts and some of your clinical study costs, but I think you could argue that it is not a substantially greater cost. We would certainly be interested in estimates as to what the additional costs might be.

The other question comes up -- again, we can debate this in many ways -- is what impels you to do something different. You know, I have always said maybe the better debate is to say given two choices confronting us now, which one would you choose, because you really have two choices confronting you now.

Even if you choose to stay with the old system, you have to say what is your argument for staying with the old system. It is a very hard regulatory question, and I'm not sure I have real clear answers.

DR. DAVIDIAN: Dr. Brazeau.

DR. BRAZEAU: I wanted to just kind of agree with Dr. Vestal that, you know, one of the issues that was discussed, I remember, at the last meeting was show us the problem, you know, is there a problem, what is wrong with bioequivalence as we know it.

[--- Unable To Translate Graphic ---]

We had asked for, you know, we had seen the limited number of data sets. Now, my question is have you been able to get additional data sets to actually show us that there is a problem.

DR. WILLIAMS: No, I think the way we kind of structured the recommendation of the committee was move towards the approach which would be based on replicate designs and that in and of itself would generate the necessary information.

DR. VESTAL: Just a quick follow up. I had the impression that there were sponsors out there that may have actually had more data, and I think the point is well taken. I wonder whether they offered to share them or there was any effort to get them just out of curiosity.

DR. BRAZEAU: I remember us talking about data, you know, that there should be data available from HMOs and all this in the discussion last fall or August.

DR. WILLIAMS: We have not seen any influx of information. I mean when we put the guidance out, that is certainly something we could do, you know, when we ask for public comment, we can say is there available information from replicate study designs that would argue for a need to look at subject-by-formulation interaction or not.

[--- Unable To Translate Graphic ---]

I might point out that our system is designed sort of not to get the information if you think about it. First of all, we do all these studies generally in healthy males, so if you are going to see a subject-by-formulation interaction, your chances of seeing it there might be diminished.

Second of all, your information from the public, you know, again, I interpret it in terms of a signal-to-noise problem. You know, your signal-to-noise from the marketplace is so difficult.

I think the question is how much would you rely on information from the marketplace or the absence of information from the marketplace.

DR. DAVIDIAN: Dr. Goldberg.

DR. GOLDBERG: We talk about signal-to-noise ration, we talk about narrow index drugs, we talk about patient variability, and yet in the proposal, what I see here is choosing individual variability versus population based upon time.

Is it in the pre-development stage or the post-development stage? It has nothing to do with the drug itself. What I am wondering about, can the concept or the use of individual bioequivalence be tied to something like

[--- Unable To Translate Graphic ---]

the BDCS.

DR. WILLIAMS: I think there is a logical connection there. One of our hopes is that whatever the hopefully modest increases in burden that would arise from applying individual bioequivalence would be offset by not requiring many bioequivalence studies at all in vivo. I think that is the intent behind the Biopharmaceutical Classification System.

There was another aspect to your question. Oh, the argument for using the population approach in the IND phase is based on the fact that we don't think switching occurs, it is not a switchability issue. So, you can basically use nonreplicate designs with scaling using population equivalence as opposed to individual equivalence.

DR. GOLDBERG: It has been my experience that there is very often switching, and it's switching manufacturing procedures, it is switching equipment, it is switching from capsule to a tablet, and so it goes back to SUPAC-IR, whether they really would require these changes, because there are changes from beginning to end of development.

DR. WILLIAMS: I didn't mean switching -- yes, we certainly acknowledge that, you know, the change in

[--- Unable To Translate Graphic ---]

manufacturing during the IND process can be quite extensive, you know, you are scaling up to-be-marketed image.

I think I was talking switching patients from one formulation to another. You know, that is the underlying thesis of individual bioequivalence, that the right question is the switchability question.

DR. DAVIDIAN: Other comments? Dr. Vestal.

DR. VESTAL: I just want to make sure, Dr. Williams, that you understand that conceptually I like the idea of individual bioequivalence. I just think it would be nice to see more data.

DR. WILLIAMS: I think we agree and our hope is that we will start seeing data if we put it out as a guidance.

DR. DAVIDIAN: I just have one comment of my own to add, and that is the statistician once again. I also support the general principle of individual bioequivalence. I remember my concern about it -- and I don't want to get technical here -- was just the issue of unusual outlying observations, which we all know occur, and their impact on the properties of the statistical procedures used to establish individual bioequivalence or not.

I was wondering if the working group has looked

[--- Unable To Translate Graphic ---]

into that at all since the August meeting. My concern is that the measure relies both on estimates of mean and variability, and estimates of variability are much less well behaved in the presence of outlying observations.

Dr. Chen.

DR. CHEN: That is a very good question. As a matter of fact, the working group has been considering this question for a long time, and right now we haven't really come out, you know, a good methodology for outlier analysis or identifications, but with time, I mean when we publish or when we distribute this direct guidance for public comments, we will welcome all the recommendations or input from all the statisticians who are interested in this area, and we will take it into consideration in finalizing the guidance in the future.

DR. DAVIDIAN: Any other comments from committee members on this issue? Any comments on any of the other issues raised by the presentations? Dr. Brazeau.

DR. BRAZEAU: I have a question I would like to address to Dr. Shah about the locally acting drug products. Of these various subgroups that you talked to us about, what do you think would be the ones that you would focus on first?

[--- Unable To Translate Graphic ---]

My impression would be that perhaps one of the best ones to look at would be the comparability of inactive ingredients and the different topical dosage forms, because I think we have got such a confusion in what is in these products and how they can potentially impact on the absorption of some of these drugs.

DR. SHAH: Right. Actually, we will be starting to look at -- all the groups will be working together, but when issues come up, will be discussing with separate groups, so that we can move forward with the response to it.

Eventually, all the groups will be working, you can say concurrently. Maybe one group may meet today, the other group may meet tomorrow, and so on, and so forth, but all the groups will be working together, and will be trying to meet more frequently as the combined group to see where we are in the process of developing the guidance.

DR. BRAZEAU: Would you anticipate this would be one guidance or would this turn out to be multiple guidances?

DR. SHAH: As I said earlier, that we have just formed a group and this is conceptually what we are thinking. We have not yet figured out whether we should make one guidance or multiple guidances, but eventually,

[--- Unable To Translate Graphic ---]

maybe we can put everything into one major guidance. That is the goal.

DR. BRAZEAU: I think with the topicals, you are going to be able to do something similar to what you did with the orals, classify them as different types, because it is going to be a function of the drug and the vehicle, and I think that may be something useful when you try to evaluate these is to think along the same lines like you did with oral absorption.

DR. SHAH: Thanks.

DR. DAVIDIAN: Dr. Williams, did you have a comment?

DR. WILLIAMS: A follow-up comment. Someday I would like to come back before this committee and talk about in vitro methods, because I think in vitro methods -- and maybe this was your point, Dr. Brazeau -- offer some real opportunity to reduce burden, regulatory burden.

In my mind, the harder the challenges, how do you set the goalposts for an in vitro test, particularly when you are trying to correlate to a clinical observation that can be incredibly noisy and imprecise, where you can hardly detect a difference of 100 percent sometime in the amount of drug in the formulation, and yet we know in vitro methods

[--- Unable To Translate Graphic ---]

can be much more precise in terms of distinguishing what is there and what is delivered.

I had always thought that somehow individual bioequivalence might offer an opportunity there in terms of you might start from a certain set of goalposts and then scale based on the variability of the reference in vitro, but I think that may be a very naive thought that needs a lot more nurturing before we can bring it to the committee.

In any case, I think you are on to something there, Gayle, where it could be a good discussion before this committee.

The other thing I wanted to say is we actually skipped past a question of Dr. Gonzalez, which was the chiral question. I might remind the committee that at one point in time we were very concerned -- and I think it is still quite a valid question -- about the ratio of different enantiomers and the possibility of that ratio being susceptible to differences in rate.

Some of you may recall that this was an issue when we approved multi-source versions of verapamil. Now, based on that, it was very nice that the Agency was able to sponsor some public research -- and can somebody help me, was that done at Hopkins or Georgetown? Georgetown. Are we

[--- Unable To Translate Graphic ---]

prepared to discuss that before the committee someday?

DR. SHAH: Yes, but not today.

DR. WILLIAMS: Not today. But I think what we tried to do there was to create an experimental setting and subjects that controlled rate of administration into the GI tract and to look actually at the ratio of the enantiomers in the blood to see if it was susceptible to differences in rate. Again, it will make a nice discussion perhaps at our next meeting.

I might also say that this analytical methodology I think has become fairly routine in terms of measuring enantiomers, so maybe analytical methodology has caught up with the question, so that we don't even have to ask it anymore, but it is a great issue for product quality, and I think we want to keep addressing it.

DR. DAVIDIAN: Surely, someone else has a comment, question.

DR. BRAZEAU: This is related more to the analytical aspects. I wondered what the Agency has done with respect to as we go to getting more LS/MS/MS and how are the going to go about looking at some of these very sophisticated techniques of analyzing drugs with multiple MS tandem MS and how they will go about validating those type

[--- Unable To Translate Graphic ---]

of assays. Have they thought about that or will be thinking because that I think is where we are headed with some of the newer techniques.

DR. HUSSAIN: Yes, I think that several groups are just becoming active in that, especially one in DPQR, which will address some of that.

DR. DAVIDIAN: Dr. Goldberg.

DR. GOLDBERG: I would love to see less acronyms or some of the acronyms explained.

DR. BRAZEAU: I guess I am thinking about the tandem mass spectrometry where you have two mass specs connected link to link to a liquid system, and those are being very sensitive. We have got aspects like capillary electrophoresis that is being used for all different types of analysis of drugs and peptides and proteins, and I think those are the kind of things that the industry is going to start -- or is utilizing those techniques, will probably be utilizing more in the future, and that is going to impact on how things get interpreted as far as equivalence and what you are going to be able to do, and I think that the Agency needs to be proactive and be aware of these techniques. I am sure they are, but how are they going to impact on some of the guidances they are developing.

[--- Unable To Translate Graphic ---]

DR. DAVIDIAN: Roger.

DR. WILLIAMS: I might mention just as a followup to that comment, you know, I think PQRI has a component to it that is flexible enough to take on topics like that, either in terms of analytical methodology or bioanalytical methodology.

Also, under the leadership of Tom Layloff, who unfortunately is not here today, we do have this Division of Testing and Applied Analytical Development in St. Louis and Laurel, and I know they are many times on the cutting edge of some of this analytical methodology and can help us a lot.

DR. DAVIDIAN: Any other comments, questions?

[No response.]

DR. DAVIDIAN: If there are no other comments from the committee, we will adjourn the meeting.

[Announcements.]

DR. DAVIDIAN: The meeting is adjourned.

[Whereupon, at 4:30 p.m., the meeting was recessed to be resumed at 8:00 a.m., Thursday, May 8, 1997.]