FOOD AND DRUG ADMINISTRATION

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

8:30 a.m.

Wednesday, March 12, 2003

Conference Room
5630 Fishers Lane
Food and Drug Administration
Rockville, Maryland 20857

ATTENDEES

COMMITTEE MEMBERS:

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STEPHEN MOORE, PH.D.
ROBERT OSTERBERG, PH.D.
NANCY SAGER
JONATHAN WILKIN, M.D.
HELEN N. WINKLE

ALSO PRESENT:

THOMAS J. FRANZ, M.D.
Dermtech International

C O N T E N T S

P R O C E E D I N G S

(8:30 a.m.)

DR. KIBBE: I see by the clock on the wall that we are at 8:30. We have two days of wonderful presentations, but they're all packed together, which means that you must pay attention continuously for the entire time frame. No napping.

My name is Art Kibbe and I'm acting Chair. The agency always let's people act, but never gives them a permanent position. Helen has been acting Director for three years now. At my school that would allow her to go up for tenure. I don't know what that means.

The first thing we have to do is get Kathleen Reedy to read from a list of important information about conflict of interest. After that, I will ask everyone at the table to go around and introduce themselves, and please use the mike so we can be officially recorded for posterity.

MS. REEDY: Acknowledgement related to general matters waivers, Advisory Committee for Pharmaceutical Science, March 12, 2003, open session.

The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The topics of this meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All special government employees have been screened for their financial interests as they may apply to the general topics at hand. Because they have reported interests in pharmaceutical companies, the Food and Drug Administration has granted general matters waivers to the following SGEs which permits them to participate in these discussions: Dr. Joseph Bloom, Dr. Charles Cooney, Dr. Patrick DeLuca, Dr. Gary Hollenbeck, Dr. Meryl Karol, Dr. Arthur Kibbe, Dr. Michael Korczynski, Dr. Thomas Layloff, Dr. Marvin Meyer, Dr. Samuel Moye, Dr. Nair Rodriguez-Hornedo, Dr. Wolfgang Sadee, Dr. Jurgen Venitz.

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

In addition, Drs. Cynthia Selassie and Marc Swadener do not require general matters waivers because they do not have any personal or imputed financial interests in any pharmaceutical firms.

Because general topics impact so many institutions, it is not prudent to recite all potential

conflicts of interest as they apply to each member and consultant.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

With respect to FDA's invited guests, Dr. Herb Carlin reports that he does not have a financial interest in or professional relationship with any pharmaceutical company.

We would also like to disclose that Dr. Leon Shargel and Dr. Efraim Shek are participating in this meeting as acting industry representatives, acting on behalf of regulated industry.

Dr. Shargel reports he is employed full-time by Eon Laboratories, Incorporated as Vice President, Biopharmaceutics.

Dr. Shek reports holding stock in Abbott Labs and Cephalon, Incorporated, and that he is employed full-time as Divisional Vice President for Abbott Labs.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' 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 product they may wish to comment upon.

DR. KIBBE: Thank you.

And now, if we would start perhaps with Ajaz and introduce everybody. Thank you.

DR. HUSSAIN: Good morning. Ajaz Hussain, Deputy Director, Office of Pharmaceutical Science.

MS. WINKLE: Hi. Helen Winkle, acting Director, as Art has already pointed out, of the Office of Pharmaceutical Science.

DR. VENITZ: I'm Jurgen Venitz, Virginia Commonwealth University in Richmond, Virginia, and I'm here to represent the Clinical Pharmacology Subcommittee.

DR. KAROL: I'm Meryl Karol from the University of Pittsburgh, and I'm going to be the Chair of the Pharm-Tox Subcommittee.

DR. SADEE: I'm Wolfgang Sadee. I'm at the Ohio State University in pharmacology.

DR. MOYE: Good morning. Lem Moye, University of Texas School of Public Health. I'm a physician and biostatistician.

DR. RODRIGUEZ-HORNEDO: Nair Rodriguez-Hornedo from the University of Michigan, Associate Professor,

Pharmaceutical Sciences Department.

DR. SWADENER: Marc Swadener, retired from the University of Colorado, consumer representative on the committee.

DR. MEYER: I'm Marvin Meyer, Emeritus Professor, University of Tennessee.

DR. KORCZYNSKI: Michael Korczynski, consultant.

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

DR. SELASSIE: Cynthia Selassie, Chemistry Department, Pomona College.

DR. HOLLENBECK: Hi. I'm Gary Hollenbeck, Associate Dean and Professor of Pharmaceutical Sciences at the University of Maryland.

DR. DeLUCA: Pat DeLuca, University of Kentucky, College of Pharmacy.

DR. SHARGEL: I'm Leon Shargel, Vice President, Biopharmaceutics, Eon Labs, a generic manufacturer.

DR. SHEK: Efraim Shek, Abbott Laboratories, industrial representative.

DR. LAYLOFF: Tom Layloff, Management Sciences for Health, a non-for-profit health sector organization working in developing countries setting up health systems.

DR. KIBBE: Thank you.

Now, Helen, do you want to introduce us to the meeting?

MS. WINKLE: Good morning, everyone. It's really my pleasure to welcome you all here for this advisory committee meeting on behalf of the whole Office of Pharmaceutical Science.

I think all of you understand that this advisory committee really provides an important role to the Office of Pharmaceutical Science in really helping us vet the significant science that underpins our complex regulatory processes. This committee continues to provide scientific evaluation and recommendation on broad scientific issues that really help us make our day-to-day regulatory decisions in OPS, as well as in the center. And the committee's scientific input has helped us strengthen and confirm and validate many of our own internal scientific decisions and our scientific knowledge and expertise. So the committee is really valuable, and I think this is a thing I want to especially express today with so many new committee members here, the value that you all bring to us in the Office of Pharmaceutical Science.

I'm going to start off this morning just talking a little bit about what I see as really a significant juncture in the advisory committee. This committee has been in existence for a number of years, but

I think we're starting to change some in structure of the committee and the focus of the committee. I wanted to talk first about this before I talked about what we're going to do for the next two days.

The first notable change is Dr. Kibbe. Dr. Kibbe said he is acting now but he will be serving as the full Chair of this committee. Art has already been very invaluable to us as a committee member. His academic experience and his knowledge on the complicated regulatory world of FDA has helped us in clarifying and understanding a number of significant issues in the past. I think many of you know that Art goes back a long way with FDA, and that's actually how I met him, in his past life with FDA. He also brings a keen sense of what FDA needs to do in enhancing its science and technical processes for the 21st century. So we're definitely fortunate to have Art not only as a member of the committee but as its Chair.

Secondly, as I said, we have a number of new committee members. I really appreciate your being willing to serve for us here at OPS and being part of this committee. With new and important questions coming before the agency at a frenetic rate, I think it's really important that the committee members have the scientific knowledge and expertise to address the various subject matters that will come before us and provide us with the

wisdom that will help us in serving the public better. We have been really trying to balance off this committee so we can address issues in a variety of ways. We feel honored to have each of you as a member of the committee, and I personally look forward to working with each one of you.

Thirdly, I think there have been a lot of changes in the advisory committee structure. I have talked numerous times about the subcommittee structure, and I think that the structure is going to be extremely important to us in helping better understand some of the questions and some of the science that really underpins coming to the right answer to these questions.

It's difficult when we have a committee that has so many various disciplines on it to really have the knowledge and the expertise to hone in on a specific answer. So with the subcommittees being able to do some of the background for the questions, being able to discuss the questions, and come back with recommendations to the committee, I think this will help the committee better meet its obligations.

Lastly, I think we are in a time of significant changes in the agency. All we have to do is step back and look at the cGMP initiative for the 21st century and the consolidation of some of CBER with CDER, and we know that there are many changes on the horizon for FDA. And these

new and exciting initiatives will affect how we in FDA do our business now and in the future. I think that you all are an important part of helping us better understand what our obligations will be as we move to the future and help us address many of the scientific questions that will come up. So I think we're really looking at a whole new era, and you all can be a very active part of that.

I hope you all share my enthusiasm in working on these initiatives, addressing the scientific questions which will arise because of the changes in our processes and our day-to-day operations, and I hope that you will share my enthusiasm in taking on the challenges of this changing regulatory environment. It's really an exciting time.

For the next few days, we're probably going to overload you, as Art has already said, with massive amounts of information. We've got a lot packed into two days, and I sort of want to apologize. But I think the reason for this is we have a lot of what we will call awareness topics. I think with the membership of the committee changing, we need to lay the groundwork of many of the topics that we're going to be bringing up in the future. So it will be fast. Art says you need to listen carefully, but I think there will be some real good discussions.

This morning we're going to start off with a

discussion of the subcommittee structure. We've talked about this in the past. I think that structure is really pretty much finalized, and we're moving and setting up a number of subcommittee meetings. We've talked about it, as I have said, in the past. Today we're going to give you a little bit of update on the existing subcommittees and then provide you with where we're going with the future subcommittees. Most of these will be meeting in the next couple of months. So I want you all to be aware of where we are and how we're developing these particular subcommittees.

I do want to publicly, though, thank all of the people in FDA who have worked hard on getting these subcommittees up. As you see, when we start talking about it -- we have, I think, five, six subcommittees -- there's a lot of work here, a lot looking for membership, getting the people in. And we've really had to work hard on it. So I really want to thank the people on my staff and others within the agency for working on this.

After the subcommittee discussion today, we'll discuss topical dermatological drug product nomenclature. There are a number of questions which exist regarding the classification of dosage forms, including definitions of ointments, paste, lotions, creams, and gels. Dr. Yuan-Yuan Chiu will lead us in a discussion of the issues and the

internal working group's recommendations on how to address various questions.

Dr. Herb Carlin is here representing USP's Nomenclature and Labeling Expert Committee, and he will also present some of his observations and also present us with the direction USP has been going in this area.

Dr. Jonathan Wilkin, who is the Director of the Division of Dermatological and Dental Drug Products in the Office of New Drugs in CDER, will also join OPS's staff in this discussion.

After lunch, we want to continue our previous theme of just talking about topical products, and we're going to be discussing topical dermatological bioequivalence methods development. We've presented several times to the advisory committee on this topic, specifically talking about DPK, dermatopharmacokinetics, and we really want to continue that discussion. At the last meeting we sort of agreed that we needed to back off of our position on DPK to have it as the only method for doing BE for topical products. We took the committee's recommendation to withdraw the draft guidance on DPK and determined that we would take a fresh look at the whole subject of topical dermatological products and the bioequivalence for those.

So today Dale Conner, who is the Director of

the Division of Bioequivalence in our Office of Generic Drugs, will begin to reinvigorate the whole topic of BE methods for derm products and will help enhance the committee's understanding of the issues. Dr. Dena Hixon, who is our Associate Director for Medical Affairs in OGD, and Dr. Jonathan Wilkin from OND will talk about the clinical perspective on therapeutic equivalence, and then Dr. Hussain will discuss how we plan to address the topic in the future and will actually solicit the advice of the committee on developing a comprehensive research plan for doing future research in the area of topical bioequivalence.

The next agenda item and the last for the day is on also an awareness topic. Nancy Sager and Steve Moore will discuss the comparability protocol process and its specific principles. I think it will be a very interesting subject for you to hear where we're going with comparability protocols.

Tomorrow we're going to start off with an update of the cGMP initiative for the 21st century. I think all of you are familiar or have at least seen some information on this initiative. We're now starting to call it the drug product quality initiative for the 21st century. I think it's somewhat misleading to call it GMP because it's really focused on the entire quality process

from review through the GMP process.

You're probably going to think that we're a little schizophrenic or out of order talking about it tomorrow, but we didn't want to squeeze it on the agenda today because we had so much going on.

We think, though, it's really important that you have a better understanding as the advisory committee of the initiative because I think there will be a lot of things over the next few years that will relate to some of the scientific decisions that will come out of the changes in this whole, entire quality process that we'll want to bring to the committee. So Ajaz and I will talk a little bit about that tomorrow with you.

After plowing through this initiative, we're going to shift gears. We'll discuss the recommendation from the International Pharmaceutical Aerosol Consortium on Regulation and Science, IPAC-RS, on dose content uniformity. IPAC submitted this proposal to us a while back, and conceptually the agency agrees with the recommendations as presented in the proposal, but we feel that there are still a number of questions that need to be answered before we can incorporate that recommendation into our guidance. So tomorrow we'd like to make the committee aware of those questions, have some future discussions at one of the next advisory committees on the recommendation.

So basically what we'd like to do is familiarize you with the recommendations, familiarize you with some of our questions, and then go from there at a future meeting.

Bo Olsson from AstraZeneca will present the recommendation on behalf of IPAC-RS, and Dr. Walter Hauck, who has been working with FDA for a number of years and providing statistical support to us as a special government employee, will provide an assessment of the proposal. So it should be a very interesting topic. Wally Adams, who is on the OPS staff, will lead that presentation.

After the open session tomorrow and lunch, we'll present another awareness topic on bioavailability and bioequivalence of endogenous drugs. Approving such drugs continues to be a challenge here in the agency because of the different characteristics of endogenous products. Although we feel that we have made some strong scientific decisions in the past with respect to these products, we think we can continue to enhance the science and provide more complete understanding and information to help better guide the sponsors with regard to what are the correct bioavailability and bioequivalence studies to do for these products.

We have two case studies we'll present, one on levothyroxine sodium tablets and one on potassium chloride modified-release tablets and capsules. In advance I want

to thank Abbott Laboratories who has been willing to work with us and to present some of their study data on levothyroxine sodium at this meeting relating to the approaches for baseline corrections.

Dale Conner will lead the overall discussion tomorrow, and Dr. Steven Johnson and Dr. Barbara Davit will present the case studies. It will be an interesting discussion and I look forward to your input.

Lastly, we will provide an update on our research program. We're specifically going to focus on the rapid response program. Dr. Nakissa Sadrieh, who heads up the Rapid Response Team in OPS, will give you an overview of some of the projects we've been working on under rapid response. We feel that it's really important for the committee to have an understanding of the research capabilities that we have available in OPS so as different issues and questions come up before the committee, you know what we might be able to utilize internally to answer some of those questions from a research standpoint.

So as I said earlier, it's definitely a very packed meeting, but I think they will be very interesting topics. I thank you for your participation in advance, and I will turn it back over to Dr. Kibbe. Thank you.

DR. KIBBE: Thank you, Helen.

A couple of points just for everyone's

information. There is open public hearing time on both days. Individuals who wanted to make presentations had to have gotten their request in by March 3rd. So we have 1 person on today's agenda and 12 on tomorrow's. So the hour tomorrow will be jam-packed and filled with entertaining presentations.

The next speaker will be the beginning of our reports on the subcommittee updates. Tom Layloff for PAT.

DR. LAYLOFF: Good morning. It's a pleasure to be here in front of the committee again. An unusual event: this is a closing report. The committee is sunsetting. We have completed our objectives and we'll be moving on.

The interest in process analytical technology goes, I think, all the way back to the formulation. If we look at formulating a 50 milligram tablet, we can weigh out the quantities for active diluents and disintegrants of lubricants, and the only issue after the accurate weighing is achieving a uniform product. So it's relatively straightforward. You weigh this out very accurately. You throw it in a bucket, and you get to a uniform, consistent mix. Unfortunately, it's not quite that easy.

Traditionally, the manufacturers follow the active pharmaceutical ingredient as a measure of uniformity throughout the whole process. So the univariate handle is applied to a polyvariate process where you have excipients,

diluents, and other materials. And in some cases it is a poor surrogate marker for many of the components in the process.

Process analytical technology is an optimum application of process analytical chemistry tools. It's a feedback process with control strategies. It involves information management tools and/or product/process optimization strategies to manufacture pharmaceuticals. So pharmaceutical design is a critical factor as is information acquired during the process.

The 1978 preamble to the GMPs says, "There is no prohibition in the regulations against the manufacturing of drug products using better, more efficient, and innovative methods." Further, the USP in the general notices says, "Compliance may be determined also by the use of alternative methods chosen for advantages in accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction or in other special circumstances." So neither the GMPs nor the USP restrict how you make the assessments of product process streams or product assessments anywhere.

The charges to the Process Analytical Subcommittee were: What is to be gained by embracing the technology? What is the state of the art? What are the problems, hurdles, and solutions? How should the new

technologies be regulated? How should FDA be prepared to adapt to dealing with the new technologies? And what are the staff educational issues and how should these competencies be assessed?

Our subcommittee had three meetings. We did applications and benefits. At those sessions we observed that there were, in fact, assessment tools which could be adapted for monitoring the process stream on a continuing basis. Those tools could be validated or qualified, and that there were chemometric tools which could monitor the process.

We went on in our June 12-13 session. At that session I think we made a very significant contribution with a group of individuals getting together and defining the competencies that would be expected for reviewers and inspectors to deal with process analytical technologies and to define a curriculum to achieve those competencies. That was done.

Our October meeting was an add-on, and it was added on because of the perception that there would be problems with the implementation of PAT technologies with the interpretation at the time of 21 C.F.R. 11. Because the PAT is inherently computerized very heavily, the concept of validating software independent of the data acquisition units poses a very severe burden. CDER has

moved 21 C.F.R., part 11 into its compliance operations to better bring scientific knowledge of PAT to bear on those assessments.

We also dealt with rapid microbiology testing at that 23rd meeting. How should the FDA respond? Well, the FDA should develop a general guidance, a conceptual framework, and establish regulatory positions on this. The FDA has established -- I like this -- PATRIOT. Who came up with this, Ajaz? Process Analytical Technologies Review and Investigation, Office of Pharmaceutical Sciences -- you've got to say that quickly because it fits in the "O" -- Team.

(Laughter.)

DR. LAYLOFF: And it's a science and risk-based approach, integrated systems approach.

Now, that PATRIOT initiative is probably, I feel, one of the most important outcomes of the meeting because reviewers and investigators are trained and work as a team to assess compliance in the industry, and I think this is going to be a great boon because if you're not familiar with the technologies, it's going to be very difficult to review the material and very difficult to inspect it. It will be eventually stifled if it's not handled well. CDER, Office of Pharmaceutical Science has moved very quickly and properly to develop the individuals

to help deal with these issues.

There is a proposed draft, a guidance on applications with PAT.

A summary of our observations, tools. The assessment tools, data support systems, and technologies are available to improve product consistency and reduce bad production and recalls. We have had many presentations from individuals in the industry and from academia describing those tools and their ability to make those measures.

If we look at one of the problem areas that occurs, we look at the USP content uniformity test issues, the USP allows an RSD of 6 percent. If we have a normal population at 100 percent, there will be 30 tablets in a million out of 75 to 125. The USP allows only 1. So statistically no batch of a million could pass the test because there are more than 1 in 30. There are more than -- I mean, 1 in 30. We have 30 total. So the PAT initiative will have to have statistical interpretations science-based rather than these hard numbers to deal with, but that's another issue.

The agency's perspective. CDER has assumed a very strong, I think, good position. They're going to use the knowledge, experience, and guidance from other FDA components, NIST, ASTM, and ANSI and do those by reference

rather than attempting to develop guidances independently. They will reach out to those existing bodies where many people have put a lot of effort in developing guidances, such as the Design Control Guidance for Medical Device Manufacturers.

Also, they will provide a framework to manufacturers with the flexibility needed to develop design controls to comply with regulations and also appropriate for their own design and development of processes and SOPs.

Future issues. These will be left for other committees. Validation of data and retention of data. In-process endpoint detection and data acquisition and storage. Documentation and E-sig closure of decision points. Incoming material stream consistency of robustness assessments.

Regulatory incentives. The FDA has said PAT is not a requirement. It's an option for those that want to implement it. Regulatory support and flexibility during the development and implementation by meeting with FDA will eliminate the fear of delayed approval and dispute avoidance and resolution in the future. So FDA is willing to work with people, work with the industry.

It's a science and risk-based regulatory approach. Low risk categorization based on a higher level of process understanding. Continuous monitoring on stream

will assure a higher quality product. There will be a research exemption so that continuous improvement can occur without fear of being noncompliant. So you can do PAT development work in parallel with your current process stream as a research tool rather than an implementation tool and implement it when you're confident in this thing. Until the FDA has approved a new process approach, the one that is currently approved will stay in force, which is not unreasonable.

What's missing? I believe -- this is personal -- industry political will is missing. I think FDA has bent over backwards to take this initiative and have these meetings bringing people together. The ball is now in the industry's court. FDA is waiting.

How to move forward. I think the way to move forward is not to try to eat the elephant in one bite, evolution rather than revolution. Bring on stream validated or qualified PAT systems piecemeal, incoming materials ID, wherever they best fit. But piecemeal.

Acknowledgements. I'd like to acknowledge the leadership of Ajaz Hussain. He has been a greater leader in this business. And Raj Uppoor developing guidances. My former colleagues at the DPA, Division of Pharmaceutical Analysis, and Division of Product Quality Research. The colleagues on and presenters to the Process Analytical

Technology Subcommittee.

There's a compilation of reports on the FDA website, and I've given that. And comments and suggestions can be sent to: PAT@cder.fda.gov. Thank you.

DR. KIBBE: Thank you, Tom.

I think we have time for a couple of brief questions, if anyone on the full committee has any questions of Tom.

DR. HUSSAIN: Just sort of an update to all the recommendations that we have received on the PAT Subcommittee. I think this committee was amazingly efficient and effective in getting these recommendations to us. We have actually progressed quite well.

Tom mentioned the PATRIOT team. It's undergoing training and certification programs as we speak. In fact, next week they will be going to the University of Washington in Seattle for hands-on lab experience. That's the second session. And within this year, we will have completed the training program for this team.

So the training program was brought together by three schools, the School of Pharmacy at Purdue, the School of Process Analytical Chemistry from Washington in Seattle, and the School of Engineering from the University of Tennessee. So we brought the three disciplines together to do this training.

A guidance is floating around inside OPS right now, and I think we will plan to get the guidance out as soon as possible. The reason we held back the guidance is we wanted to see the evolution of the drug quality system for the 21st century, the GMP initiative, and make sure that PAT becomes a model for that. As that has evolved, the part 11 draft guidance is out, so I think we are now ready to move the general guidance forward which will actually provide not only the regulatory process for implementing PAT, but actually address many of the issues and concerns that industry has expressed to us. So it removes all perceived and real regulatory hurdles for bringing innovative technology into the manufacturing sector.

So I think what was best was, at the final meeting of the subcommittee, industry representatives at that subcommittee were very clear, saying that FDA is no longer the hurdle. The hurdle is within the companies. So I don't want to see FDA being blamed as being a hurdle anymore.

I just want to thank Tom and his leadership. In fact, if you really look at it, the proposal on PAT started in '93 with what Tom had led, but it had subsided. What I have done is brought it back and added my pharmaceutical angle to it. So the FDA initiative actually

started in 1993, and I thank Tom for that.

DR. LAYLOFF: I think I'd like to say the PAT strategy that has been implemented in OPS is basically a design strategy for a regulatory action. So it's a quality system approach on how do you regulate because it defines competencies, certification of individuals for training, and the guidance documents are all converging at once. So it's really an excellent example of a quality system approach to setting up a regulatory strategy.

DR. KIBBE: Thank you, Tom. And I'd like to add my congratulations. I think the subcommittee did excellent work. We were very fortunate to be able to bring to the table with us some knowledgeable individuals from industry who came and shared quite openly, and I think that was a good model for moving forward on things like that. You did a wonderful job.

I understand that there's training going on, and I'm sure there will be a manual or something that comes from it. And we could call that the PATRIOT missile?

(Laughter.)

DR. KIBBE: I'm sorry.

Ajaz now is going to talk about the Manufacturing Subcommittee.

DR. HUSSAIN: Well, I think the credit for naming that goes to Karen Bernard, and it was her idea to

name it that way, so I sort of accepted that.

I wanted to give you a quick update on the Manufacturing Subcommittee. On October 22nd when we met at the previous advisory committee, we had made the proposal on sunsetting the PAT Subcommittee and in its place establishing a broad, general Manufacturing Subcommittee. The progress I would like to report back to you is that now we have formed the committee. Judy Boehlert from this committee will be the chair of that. The first meeting of this committee is on the 21st of March.

Now, I would like to go back and sort of refresh your memory in terms of why we wanted this committee and what the goals and objectives are. To a large degree, we will use this subcommittee to give us advice to move forward on the drug quality system for the 21st century initiative.

The first meeting of this committee will essentially be to go back and look at the desired state of manufacturing that we have outlined in our announcement on February 20th with respect to what that is and how do we get there and essentially create a framework for the future activities of the subcommittee.

In addition to that, I think there are a number of issues which have already started, the aseptic guidance and a draft guidance that we are working on. Some of that

will be discussed here.

Also, I'll remind you this is a team effort. We are partnering with our Office of Compliance and Office of Regulatory Affairs, and we will bring the combined effort on managing the process of the subcommittee.

So I don't have much else to report on this except that now we have formed the committee and the first meeting is on the 21st of March.

DR. KIBBE: Here?

DR. HUSSAIN: Yes, the same room.

DR. KIBBE: Joe?

DR. HUSSAIN: I'm speaking for Joe and myself.

DR. KIBBE: Oh, that's good. We're gaining time. I like it.

(Laughter.)

DR. KIBBE: Thank you, Ajaz.

Jurgen.

DR. VENITZ: Good morning and thank you, Art.

I'm here to represent the Clinical Pharmacology Subcommittee. As most of the members of the committee know, this was a committee that was recommended and endorsed by the parent, the Advisory Committee for Pharmaceutical Science, about a year or so ago.

The intent of this committee is to provide feedback in three different areas, feedback to this parent

committee, in the areas of: exposure response, relationship between doses, drug levels, and effect; pediatric clinical pharmacology; and pharmacogenetics. FDA believes -- and I think this committee agreed with that -- that those are areas where the science is emerging rather quickly.

We put together the committee membership the second half of last year, and I've listed the members for you. As I said, three areas, pharmacometrics, pediatric clinical pharmacology, and pharmacogenomics. Bill Jusko was kind enough to be the acting chair at our very first inaugural meeting last year. He at that time was also a member of this current committee. You see we had two industry representatives, Michael Hale and Rich Lalonde from Pfizer and Glaxo, respectively, both of them with very extensive experience in exposure response. Myself, I was not on the committee at that time since I was on a sabbatical with the FDA. We have three experts in the area of pediatrics: Ed Capparelli, Greg Kearns, and Mary Relling. And then we have three individuals, Dave Flockhart, Howard McCleod, and Wolfgang Sadee, who is a current member of the parent committee.

We had our first meeting in October of last year, and I've listed for you the topics that we discussed as part of this meeting. Most of those are what Helen

would call awareness topics. So this was the first meeting, and we wanted to make sure that the committee members had an idea of what's going to come down the line.

So the first topic was using exposure response information to individualize dose. How can we use information from premarketing studies, from clinical pharmacology studies to optimize dosing regimens and to label new drug products accordingly? What are the data sets that we can use to make that decision in terms of how to label drugs appropriately?

Peter Lee, the Associate Director of OCPB, presented an approach that is currently used that uses kinetic information from usually a special population or drug-drug interaction studies, combines it with exposure-response relationships to predict clinical outcomes. For a given dose, what is the likelihood that we have certain outcomes? And are those outcomes acceptable? If they are not, well, that would lead to a dose adjustment.

We had feedback from the committee members. Rich Lalonde and Lew Sheiner gave an endorsement to the method in general, but discussed specific potential issues with it. In general, the committee requested to get specific case examples to get a better sense for how much this approach could be generalized.

I went on to discuss and introduce a new term

called "utility" that deals with linking clinical outcomes to risk where you look not only at outcomes but also the consequences of those outcomes and you try to incorporate that in your decision making process.

The second topic, again an awareness topic, was for the committee to be aware of what the initiatives are within FDA right now in the pediatric area. Arzu Selen presented an updated on OCPB's pediatric database where they're trying to capture on an ongoing basis PK/PD information from pediatric studies.

Rosemary Roberts discussed what is currently done in terms of the decision tree that is used to help extrapolate information from adult studies into the pediatric population.

The final topic was in the pharmacogenetics area. Here the intent again was to make the committee aware of what are some of the issues that FDA is facing right now, particularly for drugs that undergo pharmacogenetically determined either metabolism or other differences in response. Larry Lesko presented some of those issues, the labeling that is used that is currently quite inconsistent.

We then specifically discussed TPMT, an enzyme that shows polymorphic expression, and people that don't have that enzyme or that enzyme is reduced in its activity

are at a very high risk of potentially fatal side effects. So one of the questions that the committee was starting to address is, is this something that we should incorporate in the label? Should people be asked to genotype, for example? Dr. Weinshilboum was the expert that really presented on that topic.

After the meeting, pretty much within a few days after, we were informed that the committee membership is not allowed to have industry representatives. So we had to renominate two individuals, Dave D'Argenio and Marie Davidian. Both of them are experts in the pharmacometrics and statistics area.

Our next meeting is next month. You can see it's a follow-up meeting, so the topics look very similar to what I just presented to you. The first topic is again to look at risk-benefit information gleaned from exposure-response data. It's basically a follow-up to the dose adjustment approach that Peter Lee presented, and he's presumably going to show us some case examples.

We're going to follow up on the pediatric initiative, trying to develop a template that helps sponsors to collect information in a way that makes it suitable for FDA to capture it and analyze it appropriately.

We're going to follow up on the

pharmacogenomics or the pharmacogenetics topic, look perhaps at different pharmacogenomic issues as they relate to labeling.

And there's a new awareness topic that deals with drug-drug interactions as it relates to metabolism and drug transport.

That's all I have.

DR. KIBBE: Questions?

(No response.)

DR. KIBBE: No questions.

DR. VENITZ: Thank you.

DR. KIBBE: Thank you, Jurgen.

Just something I thought of that I'd like Ajaz to do. Since Jurgen was so kind to give us the names of everybody on the committee, maybe we could do that for the -- okay.

This brings us to committees that are in the "let's get started" phase, the future committees. We should start with Bob Osterberg.

DR. OSTERBERG: Good morning. I'm Bob Osterberg, the acting, as Dr. Kibbe pointed out many times, Associate Director of Pharmacology and Toxicology in the Office of New Drugs. I think our interaction here indicates that both the Office of Pharmaceutical Science and the Office of New Drugs can work together very

effectively to resolve scientific problems that perhaps individually we couldn't do.

I'd like to point out to you that the Office of New Drugs pharm-tox group does not have an advisory committee that we can go to and ask specific questions, and we don't have a research laboratory that we can ask to develop data that we can use to make regulatory decisions.

But we do have a Pharm-Tox Coordinating Committee and a Research Subcommittee of that. Interestingly, Dr. Frank Sistare, who runs the Division of Pharm-Tox in OPS at the laboratories, is my co-chair on this Research Subcommittee. Together we have been asked to develop this particular Pharm-Tox Subcommittee of the OPS.

When Mrs. Winkle told me about this particular activity that she had in mind, I saw the merit of it and I immediately said, yes, I think this is a very good idea. My predecessor in this position also said likewise, I'm told. Of course, when we briefed our Office of New Drugs Division Director, he was also very supportive of this activity.

What I'd like to do is to tell you a few things that we're doing within the subcommittee with respect to its development and this morning I'd like to mention some of the things about the committee with respect to background, its objectives, its mission, and its

membership, and a few other things.

Now, the Pharm-Tox Subcommittee is an advisory committee. We pay particular attention to the advice given because it's valuable information. The people on the subcommittee will be experts in their field. They'll be well-recognized scientists and we can rely heavily on what they suggest to us. But their advice, like all advisory committee statements, is not binding on the agency. But as you know, we mostly do agree to accept their opinions.

The subcommittee is expected to provide feedback to the Pharm-Tox Coordinating Committee and to facilitate activities down at the National Center for Toxicology Research's Non-Clinical Studies Subcommittee in meeting not only this subcommittee's research needs but Pharm-Tox's research needs because, as I mentioned, we don't have our own laboratories.

Now, the objective of this subcommittee is to provide expert advisory feedback to the Pharm-Tox Coordinating Committee and the nonclinical pharm-tox research disciplines in targeting cross-cutting areas of pharm-tox, the big problems that we see not specific to any division but across the agency, where integration of new scientific knowledge or methodology could be helpful in drug development and in helping to identify laboratory-based research priorities to address what we perceive to be

data gaps as identified by the Pharm-Tox Research Subcommittee.

We also anticipate that the committee will provide input to the National Center for Toxicology Research's NCSS -- that's the Non-Clinical Studies Subcommittee -- to address CDER's identified data gaps.

We also expect the committee to advise the Pharm-Tox Coordinating Committee in the evaluation of research data related to pharm-tox activities.

Now, meetings of the Pharm-Tox Subcommittee of OPS will occur on an as-needed basis. There's no point in having a meeting if there's nothing to discuss, but we anticipate at least that two meetings per year will occur, especially in the early phases of getting this activity together and focused on a common concern.

The agendas and topics that will be presented to this Pharm-Tox Subcommittee will come from the Research Subcommittee of the Pharm-Tox Coordinating Committee because that coordinating committee is the major Office of New Drugs pharm-tox group.

Also, activities and recommendations of this subcommittee will be given to this advisory committee and to CDER's Pharm-Tox Coordinating Committee and on an as-needed basis to NCTR's committee.

A member of this subcommittee will serve on

NCTR's Non-Clinical Studies Subcommittee and that will probably be Dr. Frank Sistare.

Now, the first topic that we think we'd like to have this subcommittee address is pharmacogenomics. It will be a trial run because, in any new committee, you want to make sure that ground rules are laid down and certain activities are ongoing without any problem. It's a shakedown cruise, if you will.

We chose pharmacogenomics because this is a very interesting and useful area, we think, that because of being able to observe a chemical or a potential drug's effect at the molecular level on human genes, we may see a pattern emerge of up and down regulation perhaps of some genes which, if we can correlate that change in the gene expressions, we might be able to see or predict what the human toxicities may be during the initial phases of drug review or drug development. So we really think this is a pretty hot topic and we're very interested in getting as many experts on this subcommittee as possible.

Now, we've already recognized that we have two members already on the committee, Dr. Meryl Karol, who is going to be our chairperson, and our consumer rep, Dr. Marc Swadener. Now, we will be selecting other people, another generalist and several specialists in this area of pharmacogenomics and genetics in general, and we hope that

they'll be able to help us in this endeavor.

We anticipate that the first meeting of the subcommittee will occur in the early portion of June, and hopefully by that time, we'll have a series of proposals to offer the subcommittee to help us.

Thank you.

DR. KIBBE: Thank you, Bob.

Are there any questions from the members? Marv?

DR. MEYER: Do you think there will be any overlap with the clinical pharmacology group, the subcommittee, in terms of their pharmacogenetic interests and activities?

DR. OSTERBERG: I would say yes to that. I can't tell you the extent because the Commissioner of FDA has asked the pharm-tox folks in the agency not only to address the nonclinical aspects of pharmacogenomics, but also the clinical aspects. So I would think at some point in time, after we get our committee ongoing and we start getting data coming in from industry -- as a matter of fact, we've had several meetings with industry in the past year where we have discussed this particular area. But we just know what to make of it. But when we think we do know what to make of it, since we're using a human genomic expression platform, we think this will bear on the

clinical aspects of it. Certainly we'll avail ourselves of the subcommittee.

DR. KIBBE: Dr. Karol, do you have anything to add?

DR. KAROL: No, other than that I'm really looking forward to working with this committee.

DR. KIBBE: Well, thank you.

Our next future subcommittee is on microbiology. Peter Cooney.

DR. COONEY: Good morning. I'm Peter Cooney. I'm the Associate Director for New Drug Microbiology in the Office of Pharmaceutical Science.

Product quality microbiology issues, including sterilization, sterility assurance, and microbial quality of nonsterile pharmaceuticals, are of critical importance in the assessment of the safety of drug products. Now, somewhere between 20 and 25 percent drug products are marketed as sterile, and the quantity and type of microorganisms associated with the majority of products which are not sterile can also be of critical importance to patient safety.

The center, therefore, believes that the formation of a subcommittee specializing in microbiology can be of great benefit in providing advice for the regulatory and scientific approaches taken in the

regulation of a great number of products that we regulate. We believe a subcommittee composed of approximately eight members with diverse backgrounds in microbiological science can help the agency in making scientific and regulatory decisions related to microbiology issues.

Now, what are some of the potential subcommittee topics that might come up in the future? These might include both regulatory and technical issues, and some of them are as follows.

Parametric release of sterile products. Should the center create a guidance and should everybody use this type of methodology?

Development of vapor phase hydrogen peroxide decontamination cycles for decontamination of isolators used in aseptic processing.

Interaction of the field and center function in microbiology relative to sterility microbial limits, endotoxins, preservatives, et cetera.

The appropriateness of microbiology review for safety and risk assessment.

The appropriateness of monitoring adverse event reports for microbiology risk assessment and determination of risks which may or may not be related to specific manufacturing processes.

The appropriate use of subject matter experts

in risk analysis following event reporting.

Decision criteria for risk management in microbiology and in manufacturing processes for sterile products.

And discussions and identification of critical processes, tests, and criteria to ensure microbiological quality.

There are many new sterilization technologies being developed. Pulse beam light, for example. Closed aseptic filling systems where the container closure system is closed and then penetrated with a needle to fill it.

Product and process compatibility issues can be discussed, and combining terminal sterilization and aseptic filling processing in the same manufacturing operation.

A critical issue that's come up now, of course, is the PAT initiative, the rapid microbial methods for detecting, counting, and identification of microorganisms associated with manufacturing processes and products. What kind of filing strategies in terms of applications for instituting rapid methods should be developed?

Experimental evaluation and/or validation of rapid methods in microbiology versus parallel testing of old versus new methods. Which approach has the most scientific validity? And is it always the same or does it depend on the specific test or process being evaluated?

And finally, what is FDA's role in harmonization of standard microbiological tests? And can future rapid methods and new technologies be harmonized?

There's a plethora of issues that we believe can be discussed in the future, and as those arise, there would be a need to have the Microbiology Subcommittee. So, therefore, we look forward to working with and receiving advice from a microbiology subcommittee.

And I'll entertain any questions anybody might have.

DR. KIBBE: Questions anybody?

(No response.)

DR. KIBBE: Thank you.

I don't want anybody lulled into a sense of false security. We're moving too quickly. This will change.

(Laughter.)

DR. KIBBE: Ajaz on biopharmaceutics.

DR. HUSSAIN: I have one observation that listening to some of the updates and presentations, I think we have a wonderful opportunity in this advisory committee to bring all aspects together and actually connect the dots. We can look at pharmacogenomics, pharm-tox, clin-pharm, the risk from clinical, from quality perspectives. So I hope you see the opportunity here to connect the dots

with all disciplines and sort of come up with more cohesive policies and procedures that not only are specific to a particular discipline but bring across the generality that sort of underpins all these activities.

The origin of the Advisory Committee for Pharmaceutical Science was in the Generic Drug Advisory Committee. That's how we started. At some point we were looking at issues and topics for discussion that went beyond generic. As a result the Generic Drug Advisory Committee became the Advisory Committee for Pharmaceutical Science.

As we grow, in terms of the complexity, in terms of the topics that we have to cover, I think biopharmaceutics becomes an important topic to keep our focus on. Especially in the next several years, we plan to have a significant research initiative in the area of the generic drug program, essentially develop methodologies for approving generic drugs based on pharmaceutical equivalence, bioequivalence. So there is a need to essentially come back and establish a biopharmaceutics committee that will focus on these aspects.

So that's the proposal that we have for you, that we would like to move forward putting this committee together and would like to develop the charter for this committee with the help of Professor Marv Meyer, who has

graciously agreed to be a chair of this committee, with the help of Art Kibbe, and develop this subcommittee to focus on certain areas.

But let me take a step back and try to outline what are the issues in biopharmaceutics. I think I'm looking at biopharmaceutics as a discipline more in terms of a critical link between quality and clinical performance. So there are many topic areas that need to be addressed in this.

If I take a step back and use the test methods that we use to assess some of these or to link quality to the clinical aspect, you're looking at drug release methodologies. How do you establish a meaningful specification for, say, dissolution tests? For the last 30 years, we have talked in terms of dissolution testing, but as we go to more complicated dosage forms and release mechanisms and so forth, what are the strategies for developing more meaningful release specifications that not only relate to quality but also provide a meaningful link to the clinical performance of these dosage forms.

For example, we are looking at several liposomal drug delivery systems that have been approved. Now, how does one establish meaningful release and quality specifications for these products or for parenterally administered microspheres, implants, and so forth that have

a very long duration in human use? How does one develop a meaningful quality control test as well as establish in vitro/in vivo correlation for some of these products?

So that's sort of the tip of the iceberg in terms of what we can start thinking about, but I think the major issues also are in methodologies for bioavailability and bioequivalence.

We have for discussion, for example, tomorrow afternoon an issue on endogenous drug substances, and that probably will become a topic for discussion in the subcommittee as we progress. What are the challenges in establishing bioavailability and bioequivalence? More so, I think what are the challenges in establishing pharmaceutical equivalence? Keep in mind I think pharmaceutical equivalence is the foundation on which we base a lot of our decisions. Bioequivalence/bioavailability comes from that in some regard. And I'll, in a minute, try to explain that process to you.

But in addition, I think the ultimate goal here is to have therapeutic equivalence for both new drugs and generic drugs in the event of post-approval changes and for approval of generic drugs.

So these are sort of the major areas or broad areas for discussion.

I think immediate needs that we have in terms of seeking help from this committee is to seek advice in terms of developing methodologies for bioavailability, bioequivalence, challenges such as endogenous drug substances.

But moving on, I think locally acting drug products would be the major focus for discussion. You also have a topic that we'll present to you this afternoon on bioavailability/bioequivalence of topical drug products. We have struggled for the last 12 years trying to develop a method for assessing bioequivalence of drugs applied to skin and we have not been successful in trying to move that decision forward in a consensus way. There are many issues and you'll get a flavor of some of those issues this afternoon. So how does one establish bioequivalence for locally acting drug products where blood levels may not be a surrogate or may not be an indicator of rate and extent of absorption at the site of action? So that would probably be the starting point for a number of discussions.

We would also like to use the committee to guide us as we develop our research programs. We have an announcement coming out soon for recruiting a director-level position for a research leader. I think as we go through and recruit that person, the biopharmaceutics research program will sort of reemerge under his leadership

or her leadership, whoever that person might be. I think that would be also a very important link to this committee and the subcommittee also.

So there are many broad topics. I think we are ready to start moving in that direction from a methodological perspective in terms of specifications and so forth, but that's not all.

I would like to bring another topic for discussion at some point. At the training some of you heard about the TIACC committee, Therapeutic Inequivalence Action Coordinating Committee. And what is that? It is essentially a quality system where we respond to complaints from consumers to physicians to citizens petitions where there is a claim that a generic was not found to be therapeutically equivalent to a brand name product. How does one respond to that? What are the mechanisms we have used?

This is a fairly established, old committee, but I think we are taking a fresh look at that committee to see how do we integrate that into a quality system perspective. What are the most appropriate procedures to investigate some of these cases, and how can this committee be more proactive? So I think that also will provide a number of very interesting situations and very interesting problems that need to be addressed. We would probably

address those in-house, but I think at some point there are general issues that come from that investigation that I think would be appropriate for discussion at the subcommittee.

But let me take a step back. I think the challenges that we see in the future in this area also deal with misinterpretation or lack of understanding of our bioequivalence, pharmaceutical equivalence, and therapeutic equivalence standards. At some point I think this committee will also be useful in articulating the right message to explain our standards because many times what we see is our standards are either misinterpreted or not even understood by the practicing community, the pharmacists or physicians. So how do we get over that hump and bring some of this discussion to explain the scientific rationale for that?

What I'm proposing here is, as we start putting the goals and objectives of this committee and the charter for this subcommittee, what we'll do is work with Professor Marv Meyer, and when we come back next, sort of develop this with his help, and then start moving towards putting the subcommittee together.

I would like to step back and share with you the general approach to approval of generic drugs per se, essentially establishing therapeutic equivalence. In sort

of a systems thinking way, I think we need to go back to the statute, go back to the 1986 bioequivalence hearing where Marv Meyer spoke and sort of reexamine where we are what we have accomplished and where we need to go in the future.

In terms of systems thinking, I go back and look at our Orange Book and how we define therapeutic equivalence. So if you go back to the Orange Book, which is available on our website, U.S. FDA System to Ensure Therapeutic Equivalence, drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under conditions specified in the labeling.

The key phrase here is "pharmaceutical equivalence." Often, especially the practicing community forgets the pharmaceutical equivalence part of our analysis. That is the foundation of approval of generic drugs. It does not get the attention or the recognition as the bioequivalence part does, and many times all the discussion is focused on bioequivalence and people have forgotten that part of that equation.

If you really look at the definition, therapeutic equivalents are pharmaceutical equivalents first and then if you put this in sort of a systems

criteria, what the subsystems for this program?

First, to be a generic drug you need to have an approved safe and effective new drug application. The generic has to be pharmaceutically equivalent to be that. They have to contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, meet compendial or other applicable standards of strength, quality, purity and identity.

Then bioequivalent with the caveat that they do not present a known or potential bioequivalence problem and they meet an acceptable in vitro standard. So in vivo bioequivalence is not an automatic need, and in many cases we don't even need that. If they do present such a known or potential problem, they're shown to meet an appropriate bioequivalence standard. So that part is often not discussed.

They have to be adequately labeled, and they have to be manufactured in compliance with the current good manufacturing practice regulations.

So you can see, as we move in a systems thinking, the link between manufacturing, the link between pharmaceutical equivalence, bioequivalence, therapeutic equivalence, everything is starting to come together. I think it will be an exciting area as we move forward. We have much more complex dosage forms coming down the pike,

and how do we deal with bioequivalence of, say, liposomal drug products where now you have a target oriented drug delivery system and there are many, many challenges.

So with that sort of a background, what I will propose is I think as we move with the Microbiology and Biopharmaceutics Subcommittee, this subcommittee would essentially link back to our established biopharmaceutics coordinating committee within the center. So the aspects are all there right away. I think what this does is it gives a much more focused discussion on this important topic.

So with that, I'll stop.

DR. KIBBE: Thank you, Ajaz. Are there any questions?

DR. HOLLENBECK: I have a question.

DR. KIBBE: Good. Thank you.

DR. HOLLENBECK: I thought I'd break the ice.

Ajaz, I have a process question. I suppose I could direct it to anybody, but you're up there right now. We begin to see subcommittees formed under the advisory committee. I guess my question is, do you have a vision of the parent committee serving more of a role as a coordinating committee and a strategic planning committee than it has in the past?

DR. HUSSAIN: I think the parent advisory

committee is an extremely multi-disciplinary committee. I think we would like to maintain that. I think that will bring the connectivity between the different disciplines, different topic areas that need to come about. But at the same time, I think you do need more in-depth discussions in certain disciplinary areas, and that's the reason for the subcommittees.

The process simply is these subcommittees report back to the main advisory committee, and in that regard, I think you have an opportunity to take all that information back because we take advice directly from you. The subcommittee reports to you. I think from that perspective you will have to be the conduit for the main advice that we seek. Whether that's a coordination function or whether that is an integration function or much beyond, I think it will be up to you and the chair of this committee to decide. So I'll throw that to Art.

DR. KIBBE: Is that okay, Gary?

DR. HOLLENBECK: Yes. I guess my question is, is the committee going to be more prospective than retrospective? My experience on this committee is we basically hear reports from these working groups, and I certainly think that's an appropriate philosophy. But my question is, how will you know when you have enough subcommittees? Do you anticipate using this committee

maybe to help you identify needs that are out there and future strategic direction?

DR. HUSSAIN: Definitely, but I think with respect to the subcommittee, for example, for the PAT, that was such a specific one, we did want to continue that because that job was done. So we sunsetted that. But now if you look at the key disciplines that we are responsible for, microbiology is a discipline, biopharmaceutics is one. CMC is a broader discipline, so we took the manufacturing part. Clinical pharmacology. So all the disciplines that are the key disciplines have been addressed, and if there is a need for a future subcommittee, it might be a transient, ad hoc, process-specific or topic-specific committee. I think you are there to advise us if there's a need for that.

DR. KIBBE: I think the workload of this committee ebbs and flows around issues and how well developed they are. Staff inside the FDA have to develop the issue to a point where advice is even worthwhile. The subcommittees are charged with looking at specific areas for that purpose. But you'll notice in our agenda even, we're going to deal with a terminology issue that would never be fruitful to send to a subcommittee. There's a limit to how many of those we want to do.

I think PAT really set the stage for me in

understanding how really effective a subcommittee can be because when you have two days focused on one topic with integrated industry input, you really get good conclusions. You bring them back here for one more think-through and then make recommendations for the agency. So it seemed to work well.

Anything else for Ajaz? Go ahead.

DR. MOYE: Ajaz, I may have gotten myself a little turned around in your conversations about bioequivalence and pharmaceutical equivalence. I thought I heard you say -- and please correct me if I'm wrong -- that bioequivalence is not necessary. Did I hear you correctly?

DR. HUSSAIN: For some products, yes.

DR. MOYE: All right. But you don't mean to suggest, do you, that bioequivalence is a second-tier consideration?

DR. HUSSAIN: No. I think it's part of the system. You have to look at that as a part of one system. For example, just to give you ana example, if you have an oral solution like elixir or syrup which is a solution, then the bioequivalence essentially has been waived for it. We don't require an in vivo assessment of bioequivalence. It is simply the pharmaceutical equivalence, and the quality attributes, the CMC review part of it, is essentially sufficient. For such a product, we would say

bioavailability is self-evident.

DR. MOYE: So essentially what you mean to do then is to re-illuminate the concept of pharmaceutical equivalence.

DR. HUSSAIN: Yes.

DR. MOYE: Thank you.

DR. KIBBE: Anybody else?

(No response.)

DR. KIBBE: Thank you, Ajaz. This gets us way ahead of the game. I can't believe that we are this far ahead. As a result, we are scurrying around to get our other presenters here, and we are at our 10:25 break at 9:45. You guys are not into it yet. I can see you need more coffee.

A couple of things I suggest we try to do first. Is there a reason for us not to go out of order with the presenters on the next topic? If Yuan-Yuan is not here, could we -- oh, she is. Okay, great.

The second thing is we'll take a small break now just to keep things in order.

(Recess.)

DR. KIBBE: I see by the clock on the wall that you should have gotten your coffee, moved back to your seat, and then prepared for the next presentation.

We will now hear presentations on the topic of

dermatological drug product nomenclature. The first presenter is Yuan-Yuan Chiu and she is ready to go.

DR. CHIU: Good morning. We're very pleased to present this topic to the committee members, and we are looking forward to listening to your comments, your advice.

The objective of this project we put together since last year is to develop a clear, concise, and science-based classification, or nomenclature system for topical dosage forms where the existing system is not adequate.

Right now, there are two existing systems. One is the USP system. Everybody is familiar from the book. And the other one is the FDA data standards. Copies of those nomenclature definitions are in your package. You could see some of the nomenclatures are very ill-defined, sort of not very concise.

So we decided that we should limit our scope to only dermatological topical administration. To make the job easier, we decided that we do not want to go into mucus administration dosage forms. We only want to discuss dosage forms which are not quite clearly defined and those are the ones including liquid emulsion, semi-solid emulsion, and semi-solid suspension. Specifically those dosage forms are lotion, cream, ointment, paste, and gel.

If one uses the current definition, either the

FDA or USP, you will see the definitions are quite broad, and it creates a gray area. So two different products with similar physical characteristics could be called the same name. And two products with similar characteristics may be called different names. So when you see a product called a lotion, actually it may be called a cream by another company. Therefore, it creates some confusion to the patients and to the physicians.

As well, it has a regulatory impact because as Ajaz said, generic drugs need to be pharmaceutically equivalent. So you have a different name. Actually it's considered a different dosage form, but they may have the same physical characteristics. They should be considered the same dosage form. So, therefore, it does have economic and regulatory impact.

We are not going to discuss solution, liquid suspension, powder, aerosol, including foams, because those definitions would be quite clear and it doesn't really need further investigation.

So we have taken all the following steps. We identified current practices in labeling and also specifications establishment at FDA and at USP. We reviewed the properties and the formulations of more than 50 approved NDA/ANDA drugs. Then we also discussed with our medical staff any efficacy significance associated with

definitions of topical dosage forms. We also reviewed the literature, textbooks, and most importantly, we also evaluated many OTC products, as well as the NDA/ANDA drugs for their physical properties in our own laboratory.

With all this in place, we came up with a proposal we're going to discuss with you today. We would like to get your input and then we will revise our proposal as needed. After that, we would like to publish our proposal for public comments. We also would like to forward our proposal to USP for their adoption.

So today's agenda is after my talk, Dr. Jonathan Wilkin -- many of you are familiar with him. He's the Director of the Dermatologic Products in CDER. He will make some remarks from a medical perspective.

Then we will have the Deputy Director of the Drug Product Analysis, Dr. Cindy Buhse, discuss the laboratory findings.

After that, Dr. Chi-wan Chen, the Director of the Division of New Drug Chemistry III, will present our proposal, the definitions, and the decision tree.

Then Dr. Herb Carlin from USP will give you an overview of USP nomenclature for topical dosage forms.

After that, I'll come back to present the questions. Then we will discuss the questions.

I'd also like to inform you this project

involved collaboration of our review chemists, our research chemists, as well as our medical staff. So it's really a true collaborative study.

Now I would like to bring Dr. Wilkin.

DR. WILKIN: Thank you, Dr. Chiu.

I would like to think about this in terms of what the issues are today and where we can be in the future.

Many know the old saw about dermatologic therapeutics. If it's dry, wet it, and if it's wet, dry it. What you may not realize is how old the old saw really is. It's lost in antiquity. There's very clear evidence in the ancient Chinese, ancient Indian, ancient Egyptian, and ancient Greek writings that already topicals were being used for their physical and sensory aspects to improve skin disease.

So originally there were no active ingredients. The therapeutic choice was based on the physical and sensory properties.

In the 1800s, there were active ingredients that began to be added to these preparations. Also in the 1800s, there became sort of a recognized list of usual terms for different types of these dosage forms. So late in the 1800s -- I collected these from a variety of medical textbooks -- colloidal baths, shake lotions, creams,

ointments were defined in the textbooks. Pastes, solutions, tinctures, varnishes, powders all had their specific place in dermatologic therapeutics.

Later in the 1900s, gels, foams, and the latest, the emollient creams have been added to the lexicon.

As Dr. Chiu pointed out, the FDA and USP dosage forms are insufficiently defined. Actually they are somewhat acceptably defined at the epicenter of what is creamness or ointmentness, but when you get out to the periphery where an ointment might become a cream if you modify it ever so slightly, it's those boundaries that are really not separated very clearly. And manufacturers produce dosage form intergrades that are very distracting to our chemistry group trying to figure out exactly whether they are, say, creams or lotions.

So what we'd like to see is a creation of mutually exclusive definitions for dosage forms and a consistent terminology. I think in addition to that, there would be the potential for relevant vehicle properties being listed in the description section of product labeling.

Why would this benefit the public health? It would allow clinicians to use the dosage form which would be a rough guide to what the vehicle properties would be in

selecting a product for their patients, and if we had some extra material in the description section on more specific vehicle properties, that could even be additive.

Examples of potential relevant vehicle properties. I have to say that this is early in my own thinking. I just looked through some papers to see what we might consider. I'm not sure yet that these would be relevant. It looks like there's a lot of overlap to me.

But viscosity may be a useful thing, maybe not actually listed out in centipoise. I'm not sure how many dermatologists would appreciate that. But maybe we could take the range of viscosity for the semi-solids and we could break it into three categories, which might even been nonlinear because there may be a psychometric appreciation of greater differences at lower viscosities and less so at higher viscosities.

Spreadability. I know the industry works with spreadability for some of their products.

Wash and rub resistance.

Skin smoothness, time curve.

Usual appearance, including color.

Odor is important to patients.

Permanence on the skin. What's the residue at 10 minutes? That can be a positive. If it's a dry skin disease, that could be a negative if it's thought to be

sticky in a moist skin disease.

Moisturization, the transepidermal water loss time curve.

Volatilization. How long does it take for the volatile components to actually leave and leave this residue?

This is from an article by Barry Salka, and I'll give that reference on one of the slides. This is not really talking about vehicles. This is talking about individual oil components of vehicles. I just would point out that he has this way of looking at it, spreading value millimeter squared in 10 minutes. That might be something that you could actually do with vehicles, and that could be helpful information for dermatologists.

This is also from his paper. The point of this slide is you have time on the x axis and smoothness on the y axis. If you have a rapidly spreading preparation, one gets skin smoothness early on, but it rapidly dissipates. If you have a slowly spreading emollient, then that skin smoothness persists over time. And different aspects could be advantageous in different skin diseases.

So Barry Salka, Choosing Emollients. It's in Cosmetics and Toiletries.

So the vehicle choice is an important factor in patient compliance. There is a huge dermatologic

literature that supports this. Often the prescribing physician today finds out about which vehicle to use simply by squirting it out on their own hand and letting their patients do this. Our thought is that we could better define the dosage forms so that they could know this up front, and we probably could capture some relevant vehicle properties to put in the description section.

Now, what will be the impact on stakeholders, especially with putting some specific pieces into the description section on relevant vehicle attributes? The innovators may find that they have just an absolutely superior proprietary manufacturing process that could reduce generic competition. I mean, that's one plausible outcome.

On the other hand, the generics have been incredibly good at reverse engineering, and if they have these specific attributes of viscosity or spreadability, they're going to have targets to achieve so that the generic product is actually going to have greater sameness with the innovator. Right now, one of the disturbing things one hears from dermatologists is you can take the innovator, squirt it in one hand, take the generic, squirt in another hand, and they may work the same in terms of reducing the psoriasis, but they have a very different feel, and patients may like the one better than the other.

Health care providers. This would be a more informed choice among products if they have really good dosage form definitions and if they have some additional attributes listed in the description section. Of course, the patients are the ultimate winners. If they end up with a product that they really like and are going to use, then they're going to have better control of their skin disease.

So looking ahead and breaking this down into the two parts, one is the dosage form part. I think USP and FDA have a really nice way of thinking about this process. Ultimately it will need industry, academia, and the professional societies to buy into this, but I think this already has a very good start.

The second part, whether we want to add something to the description section of labeling that describes relevant vehicle properties, relevant in the patient care setting, I think the innovator and possibly the generic industry already have the methods and the terminology. I think they actually develop their vehicles with this in mind. But it's something that doesn't come to FDA in the IND or NDA review process. We just simply don't see this kind of optimization of the vehicle.

So I think industry is going to have to lead this. I think that's where the storehouse of all this innovative information would be, and if industry decides

that this is desirable, to use a phrase we heard in the last section, if there's the "political will," then I think industry must be leaders in this effort.

Thank you.

DR. KIBBE: Do you want to take questions or do we want to go through all of them before questions?

DR. SHEK: Just a general question. I think we talked here about medicated topicals. What about the whole cosmetic industry? If I go and buy a wrinkle-free liposome cream formulation, will that also apply to those products?

DR. WILKIN: So the question is, would the discussion we're having today also apply to cosmetics as well as to -- you know, I think if we start out with drugs and can get the topical drug products sort of in order, the cosmetics may decide to adopt the same sort of terminology. As you know, a lot of the cosmetics is, if you will, regulated by industry. It's sort of a different philosophy. FDA becomes involved when there are problems with a product. But I think if we have a compellingly logical system, it may be something that they would want to adopt.

DR. SHEK: Just looking at the consumers being confused out there when they buy topicals, whether it's medicated or nonmedicated, if they'll start defining differently -- I don't know. Maybe the cosmetic industry

does it that way because they are so consumer oriented.

DR. CHIU: The cosmetic industry is not regulated as closely as drugs. In terms of whether they can make certain claims, if they make a drug claim, then it would be regulated as an OTC product. But if they don't make a drug claim, then they can market it as cosmetics. Like wrinkles, it's sort of borderline. Some of the wrinkle creams are actually prescription drugs and some are cosmetics.

DR. WILKIN: Well, I could add to that. I think if you look at the wrinkle products that are cosmetics, they say, "improves the appearance of." If you look at the drug products, it actually says, "to treat." That's one of the distinctions. It's subtle. I realize that.

And the other aspect in DDMAC, we have a group that looks at advertising for all of the prescription preparations, but it falls pretty much to the FTC for over-the-counter products and for cosmetics.

DR. SHEK: Just if I may as a follow-up, one concern I'm looking at here is that we will draw or distract the attention from the therapeutical optimization of the dosage form or the formulation. I know when you develop this product, you are trying to optimize their penetration through the skin or whatever the purpose is

when you design the vehicle. And now, we are going somehow maybe to distract their attention from just appearance or description and not looking at their therapeutic efficacy of the two preparations.

DR. WILKIN: I think that's an excellent point. That's something that we don't want to lose track of that piece. We know that the vehicle contributes to the success of the topical preparation in a variety of ways. One, of course, the vehicle participates in several of the main components of what controls passage across the barrier, the stratum corneum. Clearly the solubility in the vehicle provides for the actual concentration of dissolved drug, and it's only dissolved drug that acts in the concentration gradient. If you have some that's not dissolved, it's not participating in the gradient. Likewise, the vehicle plays a role in the partition coefficient. The vehicle can actually have independent effects on the stratum corneum and can modify what is the apparent diffusion coefficient.

And then in addition to that, it has some of these other aspects that may somehow be different and they may be smoothness, let's say, over time, but that might be one of the pieces that a psoriasis patient actually appreciates having that smoothness. They're more likely to use the product. They're more likely then to get the corticosteroid that's in that product into the psoriasis

lesion. So at the end of the day, it's not something that is involved in the thermodynamic aspect of getting active in, but I think it still contributes.

We have the saying in our division that the vehicle is composed of inactive ingredients, but it's not inactive and it really isn't. It contributes some very positive things. I think we haven't recognized that as much in the past.

DR. HOLLENBECK: I ask this question out of ignorance. Does a generic topical have to have exactly the same name? For instance, if I have a 2 percent hydrocortisone ointment, if I want a generic product, would it be called exactly the same thing?

DR. WILKIN: It might have a different brand name, but it would still have to have that same technical name of hydrocortisone 2 percent. Dr. Hussain actually mentioned earlier that identical labeling is a key piece. There must be identical labeling in all those relevant areas between the innovator and the generic.

DR. HOLLENBECK: And that's my question. The label would have to include, for instance in this example, ointment.

DR. WILKIN: Yes, that's correct.

DR. CHIU: Yes. We discussed this in our working group. We had OGD representatives. They told us

they have to be exactly the same. The name must be exactly the same.

DR. HOLLENBECK: And I guess my question comes from trying to get my hands around the real issue here. This is one of the real issues. You would have two products that could have the same name, yet be substantially different in their formulation.

DR. WILKIN: I wouldn't make that an innovator versus generic issue. I would submit that's plausible even in the innovator versus innovator issue. You could have one innovator with the same corticosteroid and another and they're both called lotions, and yet there would be substantial differences between the lotion qualities, if you will.

DR. KIBBE: Go right ahead.

DR. KAROL: It seems to me the objective here is to develop science-based classification and descriptions, and I'm wondering whether that can be done with such issues as smoothness and spreadability. Is there any scientific basis for describing something as smooth or less smooth and so on?

DR. WILKIN: A good question. I think there are actually two separate aspects to this. One is defining dosage forms. I think the group is taking great pains to not have such subjective pieces go into the definition of

the dosage forms. There may be some temporary things in there, but we're really sensitive to that and we'd like to make it as objective and something that one does with a physical experiment to the extent possible.

On the other hand, I think there are some subjective things that might be permissible, if they can be documented to be clinically relevant and vehicle-dependent, that could go into the description section.

So I see sort of the rough guide as getting the dosage forms defined appropriately and exclusively so that you don't have the problem we have now where some things look pretty much the same but one is called a lotion and one is called a cream.

And then the other part is thinking about -- and this is much further into the future -- can we do something with the description section that will be informative.

DR. KIBBE: Marv, go ahead.

DR. MEYER: The CDER Data Standards Manual that was in the backgrounder has some definitions. Are these the ones that are currently in use or proposed?

DR. WILKIN: We're actually going to have another speaker to that.

DR. CHIU: Those are actually for our database. So they're very rough standards. Basically we use the USP

standards, and now we are proposing different definitions for some of the dosage forms or maybe some modified definitions.

DR. MEYER: I thought it was interesting that this list really shows the difficulty inherent in this topic. For example, under salve, it says, somewhere between an ointment and a plaster, but doesn't define what a plaster is. So now you need another definition.

DR. CHIU: That's right.

DR. MEYER: Under tincture, alcoholic. It doesn't say what kind of alcohol.

DR. CHIU: But tincture actually is defined in USP.

DR. MEYER: Okay. Hydro-alcoholic is also defined?

DR. CHIU: Yes.

DR. MEYER: Not in terms of percentage, though, or does it? It is? Okay.

DR. CHIU: Those are USP definitions.

DR. KIBBE: Is there anyone else?

DR. RODRIGUEZ-HORNEDO: Briefly one comment. Is your initiative similar to what went with the process analytical technology initiative from industry where you're inviting industry leaders to come forward? Has there been an answer to that invitation?

And secondly, to what extent can some of these maybe subjective measures of the feeling of the formulations can be correlated to some chemometric measurements or something along those lines?

DR. WILKIN: Well, if you're talking about the dosage form definition part, I think this is the meeting where this is the invitation to get everyone thinking about this. And likely there will be a draft FR notice at some point. There will be some way of getting input, I would think.

DR. CHIU: Yes. When we discuss the questions, we actually are looking for other technologies or methodologies which can measure certain parameters which we have not included if you consider them essential.

DR. DeLUCA: I guess I certainly applaud the efforts to try to standardize the nomenclature here. I guess in your slides here, you certainly have gone back as long as maybe folklore for this and the time when there wasn't really any of the sophisticated analytical techniques to make measurements.

It seems that if you're going to come up with nomenclature, it has to be science-based. These different dosage forms, it seems to me, have different thermodynamic activity, different physico-chemical properties, the structure, the morphology. There are differences here, and

I think we have to look at what types of equipment and analytical techniques for characterization are available now, like atomic force measurements and that sort of thing, that have to be, I think, part of this to be able to define these dosage forms. What makes something a lotion as opposed to a cream by virtue of some physical measurement or some property that can be actually defined?

DR. WILKIN: So you're actually describing then two stages. The first is figure out what you really think are the relevant essential properties of, say, a lotion or a cream, and then figure out what the assay technology would be to document that those properties are within the certain specs for that.

DR. CHIU: We come with the proposal based on our own laboratory data which we use science criteria. Actually we did an empirical experiment. Our laboratory prepared placebo ointment and cream and then passed it around to everybody on the working group. It actually made several preparations, four or six, and asked people to identify which one would feel like an ointment, which one felt like a cream. And based on the criteria we have established, we had consensus. Everybody figured it right. So, therefore, we believe our data supports our proposal based on this empirical experiment.

DR. KIBBE: Thank you. I think we probably

could move on and come back to a whole slew of potential questions.

I would just like to comment that the creation of mutually exclusive definitions for dosage forms and consistent terminology is a wonderful goal.

DR. BUHSE: If not a difficult one, right?

Hello. I'm Cindy Buhse, and as Dr. Chiu said, I'm the Deputy Director for the Division of Pharmaceutical Analysis, and we actually do collect data in our lab. So I want to go through some of the data we collected to try to help distinguish between creams and lotions, et cetera.

I've just thrown up here some of the definitions that are included in your packet in the CDER standards manual. You can see they're fairly broad: creams, a semi-solid dosage form. A lotion is used to describe any topical solution intended for application to the skin. You can see there's really no distinguishing between any of these definitions. So we tried to use some data to see if we could figure this out.

We looked at a lot of different things for about 50 different topical dosage forms. We looked at basically what's their base composition, what are they made of. We looked at some of the physical properties that I think we've talked about here. You really can't get away from, even though you'd like to, things like appearance and

feel which tend to be very subjective.

And then we tried rely, as much as we could, on the physico-chemical properties, so those things you could actually measure with an analytical instrument, and here's a list of some of the properties that we looked at.

I just wanted to briefly go over what we did with appearance and feel, in addition to passing samples around. One of the things we obviously tried to look at in appearance is, is it clear, is it opaque. You can imagine that there are some trends. Gels tend to be clear or translucent. Creams are opaque. We also looked at does it seem viscous, does it seem liquidy. We put a drop on a microscope slide and basically looked at does it form a stiff peak, does the peak fall over, is it soft or does it spread out and form no peak. So we tried to look at some things that are still subjective but maybe could be a little bit more nailed down.

In terms of feel, there's greasy versus non-greasy, and there's a cooling sensation. As something evaporates from your skin, you get that cooling sensation. So we tried to capture that as well for all these formulations that we looked at.

We also looked at microscopy at 400 times, looking for two phases, one phase, particles suspended, not suspended, that type of thing.

I'm going to start with creams and lotions. We started with a variety of creams and lotions, and we did a multivariate analysis looking at viscosity, surface tension, specific gravity, and loss on drying. Viscosity was done using a Brookfield viscometer at 5 rpms at 25 degrees C, so we took it as a single point since most of these obviously are non-newtonian. Loss on drying was done at 105 degrees in an oven for 24 hours or to constant weight.

You can see in the upper left the scores plot. This puts the different formulations and clusters them together based on their different properties. You can see that using these variables, lotions are kind of clustered together and creams are kind of clustered together. So this analysis did separate lotions from creams, but the main separating parameter was actually viscosity. So viscosity was the most significant variable that we found that separated lotions from creams.

So we then took a broader range of lotions and creams than just this and took a look just at viscosity. Here's an example of some of our data. You can see that lotions do have a lower viscosity than creams on average, but there was some overlap between around 30,000 centipoise up to just under 100,000 centipoise.

So we went back and took a look at those

lotions and creams that seemed to overlap and tried to determine what separated them. One thing we wanted to say about lotions was that creams are semi-solids and lotions are not. We wanted lotions to be a liquid. So, therefore, we wanted a lotion to be pourable.

So we went back to these creams and lotions and determined which ones were pourable and which ones were not. We found that the ones under 30,000 centipoise were in fact still pourable even though right at 30,000 you're kind of more like ketchup. So it's very slowly pourable, but they were still pourable.

So one of the criteria we put down on lotions is that they need to be pourable, and for us that meant a viscosity of less 30,000 centipoise at the conditions I mentioned earlier.

We also then took a look at viscosity when trying to separate creams from ointments. There are still some trends here. Ointments tend to be fairly viscous. If you feel them, they seem viscous, and we see that even in viscosity. You can see for all the ointments we tested there, viscosity was greater than 500,000 centipoise.

But there is a huge overlap between creams and ointments. You can see it's about a 300,000 centipoise overlap. So we didn't want viscosity to be a determining factor between creams and ointments.

What we did find between creams and ointments was loss on drying or the volatility of the vehicle. Some of this goes back to, I think, what Dr. Wilkin was talking about. How long does it stay on your skin? What are you expecting it to do once you put it on your skin?

What we found was that, for the most part, the ointments had LODs less than 20 percent, and so they weren't losing very much weight over the time spent in the oven, and that all the lotions we looked at had greater than 50 percent LOD.

We did have one ointment, you can see there at the end, that was above the 20 percent. This is where we came down to feel and appearance. This is one of the borderline cases which we took and passed around the table and asked people to put it on. Do you think it's an ointment? Do you think it's a cream? And everyone unanimously thought it was a cream based on what they felt in putting it on their skin and just feeling it. So we stuck with the 20 percent LOD for ointments.

The other thing that obviously is very important is the chemical composition. We looked at the percent of hydrocarbon or polyethylene glycol content in the vehicle. Once again, we saw some trends. Ointments tend to have very high hydrocarbon content or polyethylene glycol content, typically above 80 percent, and lotions and

creams tend to be more water-based although not always. So we did also decide the criteria, that ointments need to have a percent hydrocarbon or polyethylene glycol of greater than 50 percent.

You can see there's one ointment on this graph that does not meet that criteria and that is the exact same sample that you saw in the previous slide that had the LOD of greater than 20 percent.

Not surprisingly, there is a trend between the chemical composition and the loss on drying. I just put this slide in to show you that as you have more hydrocarbon or polyethylene glycol content, you have less loss on drying.

So we have some scientific criteria that are separating creams from lotions and creams from ointments.

We also took a look at quite a few gels and gels are tricky. We looked at a lot of the same parameters. Gels usually go across a fairly low viscosity range; 10,000 to 70,000 centipoise is what we found in our lab. They have a very high loss on drying. They're usually water- or alcohol-based. They tend to be water soluble but not always. If you put them in a high humidity environment, they sometimes will absorb water; sometimes they won't. If you dry them, they'll sometimes dry in a thin film and sometimes they won't.

We also did thermogravimetric analysis on them, and I'll show you an example of that in a minute. We did note that gels seemed to have fewer transitions than creams or lotions.

They always contain a gelling agent. Most of the ones that are available on the market contain carbomer.

As I mentioned earlier, they tend to be clear or translucent but not always. There are quite a few gels on the market that are still opaque, and if you looked at it, you wouldn't necessarily know it was a gel versus a cream if you were just to look at it.

They tend to be non-greasy and cooling.

We also found no specific trend in microscopy. We tried to see if we could see something there, but we couldn't really.

I just wanted to show you the TGA data because it is kind of interesting and we are pursuing it further. This is an example of two different drugs that have several different formulations and manufacturers on the market. You can see drug B. There are four different creams currently on the market and two different gels for the same active drug. You can see that the gels tend to have a single transition for water. That's the light blue and the light green line. Whereas, the cream, you can kind of see some multi-transitions. If you read the literature about

that, it's often described that creams have two kinds of water in them. They have what you call free water and then you have water that's bound up in the emulsion which may have a different transition temperature. A true gel, where you have a three-dimensional structure with a solvent in it, you would expect the solvent itself maybe to just have one environment that it's in. So we kind of are seeing some of that with this TGA data, and we are pursuing this further. You see the same trend over with the drug C which comes as a lotion, a cream, and a gel.

Just to summarize a little some of the data we've done in the lab. I think, as Dr. Chiu indicated earlier, we would like your input as to further techniques we could use to distinguish between these different dosage forms.

We found that lotions were pourable with the viscosity of less than 30,000 centipoise and they had a very high loss on drying as they were mostly aqueous based.

Ointments have a very low loss on drying because of their hydrocarbon or polyethylene glycol content.

Gels. We did see that they have quite a bit of gelling agent, but we would like advice on further determining how to separate gels out, especially from creams.

And then Dr. Chen will give you more details on the definitions we came up with based on this data.

DR. KIBBE: Questions? Gary, do you want to jump in or do you want to wait?

DR. HOLLENBECK: Let me ask a couple then. Stop me when you want me to stop, Art.

First of all, your viscosity testing. Why did you decide on 5 rpms?

DR. BUHSE: We wanted a low sheer, so we chose 5 rpms. And we chose room temperature. There was a lot of discussion about whether to choose the temperature the drug is actually at, the temperature of the skin. You could make arguments every which way. What we did for this work was room temperature and the low sheer, 5 rpms. If you look at the literature, there's a variety of different --

DR. HOLLENBECK: Sure. I understand it's a challenge.

Did you shake things up before you measured it?

DR. BUHSE: What we did is we equilibrated everything. None of the formulations we used separated. I'll just say that first. They were all well emulsified or gelled. And we equilibrated them at 25 degrees for 24 hours before we measured viscosity on them.

DR. HOLLENBECK: 24 hours, okay.

I guess my other sort of analytical question

is, why didn't you measure moisture content or water content instead of doing LOD?

DR. BUHSE: We had moisture content. We had the formulation, so we knew how much water had been put in already just based on the applications to the agency.

We looked at LOD because we wanted to pick up everything that was volatile in the formulation, not just the water. There are alcohol or other agents in there that may be volatile but you wouldn't pick up in a moisture analysis.

DR. KIBBE: Does anybody else want to chime in? Do you have a question, Wolfgang?

DR. SADEE: Yes. I just have a very minor comment here on the definition of a cream. It's a semi-solid dosage form containing one or more drugs. So if it doesn't contain any drugs, it's not a cream?

DR. BUHSE: I think that's from the Data Standards Manual. I don't know if you want to address that.

DR. CHIU: Well, we're not going to use that. You will hear our proposal later.

DR. SADEE: And then viscosity is done, you say, at room temperature. Do you specify that? What temperature are you actually talking about?

DR. BUHSE: 25 degrees C was what we

considered. We wanted to make sure everything was at the exact same temperature, so that's what we chose.

DR. MEYER: In the case where you're comparing viscosity or loss on drying for the various products, these are actually marketed products? Is it possible then that where there was overlap or they weren't classified in a distinctive way, that they were just mislabeled?

DR. BUHSE: Yes, there were several. I mentioned the one product that was labeled as an ointment that we felt was more a cream. There were several lotions you saw that were above the 30,000 centipoise. So with these new definitions, we would consider those to be creams rather than lotions, yes. So we did look at over 50 different drugs, but we did not make the assumption that they were labeled correctly. We just tried to look for trends, and then some of them ended up not being labeled the way we would necessarily want to label them in the future if our definitions are adopted.

DR. DeLUCA: There's quite a bit of information in the literature on rheological behavior of these forms. I'm just wondering whether you looked at that aspect of it.

DR. BUHSE: Yes. We did a lot of literature reading and looking at the rheological behavior. All of these are non-newtonian and they're all different in terms of what kind of behavior they have.

We thought about looking closer at the rheological properties of everything. For our first cut here, we tried to keep it simple. We just picked a single point, but that would certainly be one area we could go into in the future.

DR. KIBBE: Ajaz.

DR. HUSSAIN: I think Pat makes a very good point, and I think as we go towards the complexity of the flow behavior, I think you might see certain other attributes that fall off. In fact, from a use perspective, I think the rheology, whether it's thixotropic and so forth, will also be linked to possibly how effective its use on the skin itself. So I think that's a very good point.

I had another question. I think Cindy showed on her first slide a figure where you're looking at a multivariate approach to classifying and looking at these attributes to see whether we can cluster and we can do this. She didn't mention that was a principal component analysis, the study that she has done.

DR. KIBBE: Anybody else?

(No response.)

DR. KIBBE: I think you're off the hook for a few minutes.

DR. BUHSE: You can ask later.

DR. KIBBE: Don't worry. I'll ask you why you didn't look at magmas.

(Laughter.)

DR. CHEN: Good morning. I'm Chi-wan Chen, Director for the New Drug Chemistry III Division in the Office of New Drug Chemistry in OPS.

I think Dr. Buhse has the work cut out for me for my presentation. What I would like to present is our proposal on how to better define these problematic dosage forms for topical drugs.

As Dr. Chiu mentioned in her introduction, our task is focused mainly on the topical dosage forms that are for dermatological application. That is not to say that the same kind of approach, with or without any modification to some of these dosage forms, can be applied to topical dosage forms that are not applied to skin, in other words, mucous membranes.

Also, as alluded to earlier, our focus is on five particular dosage forms for which the currently existing system or definitions in either the USP or the FDA standards manual or in the literature are less than adequate and cannot distinguish among some of the dosage forms, namely between lotion and cream, gel and cream, or gel and lotion, cream and ointment, ointment and paste. That will be our focus.

You will see that the system we are proposing to define these dosage forms consists of roughly four parts.

One is a broad classification: liquid, semi-solid emulsion, suspension. That is the first component of our system.

The second part of the definition has to do with chemical composition and/or physico-chemical properties.

The third one is the appearance, the feel.

And the fourth one is perhaps loosely linked to the spreadability that Dr. Wilkin mentioned earlier, the feel when applied rather than just how it looks.

So to start out, gel. We felt it was easy when we started out. It always contains a gelling agent in sufficient quantity that it will form a three-dimensional cross-linked matrix.

But then as we looked a little bit closer, we found some difficulties. How do you define "sufficient"? Now, although this is mentioned in some literature articles, we don't know whether we can actually quote those numbers. As you know, these numbers certainly will vary. The absolute amount or even the relative amount may vary from one gelling agent to another or from one preparation to another.

The next question is the three-dimensional, cross-linked matrix. Do we have to have some easy physical measurement to be part of this definition so that there is another tool that can be used to distinguish this dosage form from any other overlapping dosage form, namely cream and lotion, as I'll get into when I get to those two dosage forms?

It's usually translucent or clear and is not greasy. It provides a cooling sensation when it's applied to the skin.

A paste -- we thought we could easily tease this one out too -- as a broad category is a suspension semi-solid. In terms of composition, it contains a large proportion, i.e., 20 to 50 percent, of solids dispersed in a vehicle that's either aqueous or fatty. It's opaque. It's viscous. It's greasy to mildly greasy. In terms of application, it adheres well to the skin and forms a physical barrier, a protective layer.

A lotion is a liquid. As far as we can tell, I don't think we will find a lotion that's a suspension. I think a liquid suspension clearly belongs to a suspension. So right now we're proposing that a lotion is an emulsion liquid. It generally contains a water-based vehicle with more than 50 percent of volatiles, as measured by loss on drying.

The next feature is the viscosity. It has sufficiently low viscosity. We consider a lotion a liquid and this viscosity should be sufficiently low that it can be poured. We find that cutoff to be 30,000 centipoise, as Dr. Buhse mentioned earlier. And this sets apart a lotion from cream. We will visit that briefly again when we get to cream.

It's opaque and non-greasy, and it tends to evaporate rapidly with a cooling sensation when applied to the skin.

Ointment is an emulsion or suspension semi-solid. In terms of chemical composition, it generally contains more than 50 percent of hydrocarbons or polyethylene glycol as the vehicle and -- and this is a capital "and" -- less than 20 percent of volatiles as measured by LOD. It is translucent or opaque, and it's viscous and it's greasy. It tends not to evaporate or be absorbed when applied to the skin.

Cream as a category gave us the most difficulty and it's most challenging. As you probably can agree, we almost have to say cream is a default. When it's not an ointment, not a gel, not a lotion, it's a cream.

(Laughter.)

DR. CHEN: Basically that's what it boils down to.

Chemical composition-wise, unlike an ointment it doesn't contain more than 50 percent of hydrocarbons or PEG. It does not contain less than 20 percent volatiles. In other words, it generally contains less than 50 percent of hydrocarbons or PEG or more than 20 percent of volatiles or both. That's in terms of chemical composition what a cream would be.

It's viscous compared to lotion, as I mentioned earlier, and it's not pourable as compared to lotion.

In terms of appearance, it's generally opaque. It's viscous and it's non-greasy to mildly greasy, but not extremely greasy.

It tends to mostly evaporate or be absorbed when rubbed onto the skin.

In terms of comparison to gel, we know some creams seem to contain a gelling agent, and I think that the TGA data show that these creams, though containing a gelling agent, do have multiple transitions. So we are inclined to still keep them as creams, and perhaps the role of the gelling agents present in these creams is as a thickening agent.

On the other hand, some gels are opaque because of the presence of an emulsifier, and I don't know if we will leave them. I think we probably will leave them as a gel if we can show that it has the three-dimensional

structure by way of TGA, or maybe there's a better method than TGA.

Then lastly as far as cream, we wonder if it may be useful to separate the creams into two categories, hydrophilic versus lipophilic, for the benefit of the clinicians and patients. Perhaps it will be useful for them to know one versus the other. But that's one of the questions that we will present to you.

Next I will just present a decision tree not necessarily as part of a proposal, but as a tool to aid the thinking process when you are given a topical dosage form. This may be a good exercise or thought process to get you to where it belongs. This really is a parallel to our proposed definitions and it's based on the data from the lab on the select products and chemical composition data from NDAs and ANDA products approved in recent years.

Again, we are limiting this exercise or this decision tree to dermatological applications, and the goal of the first test is to tease out those dosage forms that we are now focusing on.

So the question we ask is, is it a liquid emulsion or a semi-solid emulsion or suspension? If it's none of the above, it has to be a solution, which is clearly defined in the standards and literature, an aerosol, a powder, or a suspension. I think both USP and

the FDA standards manual have clear definitions of suspension, which is defined as a liquid preparation containing solids dispersed in a liquid phase.

Now, if the answer to this test is yes, then you go to all the branches down in the tree.

The first test after that is whether the preparation contains a gelling agent in sufficient quantity to form a three-dimensional, cross-linked matrix. Again, we're not sure how to define sufficient and we're still exploring what the best method is to clearly demonstrate that there is a 3D matrix.

But if the answer is yes, it's a gel. It goes to the left in the green box. And if the answer is no, then you continue the exercise.

Test 3 asks the question whether the preparation contains a large proportion of solids dispersed in the vehicle. And if the answer is yes, it's a paste. We actually haven't come across very many pastes in the FDA-approved products. There is an over-the-counter zinc oxide and maybe a couple of others. But we thought this is a clear feature that can separate paste from the rest. If the answer is no, then you go to test 4.

Test 4 asks the question whether it contains more than 50 percent of volatiles as measured by LOD. You branch out from this point on. If the answer is yes, you

go to 5a underneath. If the answer is no, then you go to the right to 5b.

5a is a test that asks the question whether the preparation is a pourable liquid with viscosity less than 30,000 centipoise. If the answer is yes, it's a lotion. If the answer is no, it's a cream. You can see how we view cream as a default. It's a no, no, no. Then you end up with cream.

Test 5b, where you end up on the right-hand side after test 4, asks the question whether the formulation contains more than 50 percent of hydrocarbons or PEG as the vehicle and less than 20 percent of volatiles. If the answer is yes to both, then it's an ointment. If the answer to either is no, then you end up with a cream. Again, it's another indication that it's a default compared to ointment.

So I hope our proposal is a step in the right direction. Hopefully we have put some boundaries to better define these dosage forms and not to stifle future innovations.

DR. KIBBE: Any specific questions? Gary?

DR. HOLLENBECK: Do you want to entertain questions on the decision tree now or do you want to wait until we get to the end?

DR. CHIU: I think we could do it later at the

end when we do the discussion.

DR. SELASSIE: I have a question.

DR. KIBBE: Over here then.

DR. SELASSIE: You know the way you delineate what's a cream it's based on whether it's hydrophilic or lipophilic. That's based on the continuous phase. What happens, for example, when your continuous phase is a fatty ester, often alcohol and acid? Then doesn't that change? Does it change hydrophilicity?

DR. CHEN: I think it's the vehicle that defines whether it's lipophilic or hydrophilic.

DR. SELASSIE: Right, but I'm talking about the oil in water. Sometimes you use these fatty acids and fatty alcohols and use the esters.

DR. CHEN: And the vehicle is aqueous.

DR. SELASSIE: Right. It doesn't have a great impact on the overall hydrophilicity?

DR. CHEN: I think when we say hydrophilic, we mean it's oil in water.

DR. SELASSIE: You're strictly basing it on what the continuous phase is.

DR. CHEN: That's right, yes.

DR. SELASSIE: Okay.

DR. KIBBE: Leon?

DR. SHARGEL: I was curious about the exclusion

of suspensions as lotions. As I recall in the USP, there's a white lotion, a calamine lotion. At least there were older articles. And those are suspensions. There are several products that are suspensions that are considered by the public in its use as lotions. Is there any thought process in that?

DR. CHEN: We feel the definition of suspension as it currently exists is fairly clear, and the solids are dispersed in the liquid and it needs to be shaken before use. It separates, while lotion doesn't separate.

DR. SHARGEL: From the concept of the consumer, the consumer would think calamine lotion is a lotion, not necessarily a suspension. And how would we then distinguish if a manufacturer makes a suspension to be used as a lotion?

DR. CHEN: Hopefully this definition we're providing will clearly separate suspension from lotion.

DR. HUSSAIN: I think the point being made is, in a sense, we already call a suspension lotion, and that is well established, well recognized. Calamine lotion, for example. So that falls out from this decision. That's the point I think Leon is making.

DR. CHEN: Yes. I think the products that FDA oversees and approves may have to be revisited -- some of them -- if our proposed definition is to be adopted. But

some of the products that are truly OTC or are cosmetics, we wouldn't be able to touch them.

DR. KIBBE: I have Marv and then Pat I think had his light on.

DR. DeLUCA: Well, I wanted just to follow up.

DR. KIBBE: Why don't we get Marv and then you and then Leon goes, and Wolfgang, you've got your light on or off? Do you want to speak or not?

DR. SADEE: It's off.

DR. KIBBE: Okay. Marv.

DR. MEYER: Is there, from a regulatory point of view, a problem with a formal definition that could change terms like "generally," "tends to," "mostly" -- that appears in numerous cases -- "usually." That gets a waffle in there. Is that a problem from a regulatory point of view?

DR. CHEN: We hope it won't be a problem because we'd like to provide clear enough distinction without being too strict. So there could be borderline cases that would be exceptions. But perhaps as we refine these definitions or gather more data, we might be able to better define them. I don't know if we necessarily want to lose some of the words that are sort of vague or general. I guess our fear is there may always be an exception, and that's the reason for choosing those words, "generally,"

"usually."

DR. CHIU: May I add to this? Although we have some loose description of the appearance or the feel, however we also have other criteria in terms of composition, in terms of viscosity, and the loss on drying. So we believe in the totality of the criteria, we would be able to define a cream from a lotion and others in most of the cases. We cannot say there would be no exception, but we believe it will cover a lot of cases also.

DR. DeLUCA: I just wanted to follow up what Leon had. He gave the example of white lotion, which is a suspension. But also to come in with the process of making white lotion. So, in other words, just because you have a composition, if you don't add these in the right manner and under the right conditions, you won't get the same product. Aside from the water and the hydrocarbon, I'm wondering how much importance you put on composition.

To me property is the way because we may have a new surfactant or gelling agent or something we don't even know about right now that comes down the pike. It seems to me that it's important to be able to base these definitions on property on some physical measurement or some thermodynamic activity, not even therapeutic performance because something may have the property of being a cream or gel but maybe not be effective. So I think that I just

wanted to kind of stress that some property or measurement or thermodynamic activity, structural behavior, or morphology should be the criteria for the definition rather than composition.

DR. CHEN: And I think we can continue that discussion in our questions and answers.

DR. KIBBE: Yes. One more and then we'll go to the next speaker. Then we can come back. I think all of the speakers are still here, so we can go back to individuals.

Did you have some, Efraim?

DR. SHEK: Yes, just a comment. We have systems which are thixotropic systems and sometimes you purposely use it. They might be in the container as very viscous, and when you pour them or when you agitate the system, they become liquids. We have to find a way to handle those because what the customer feels is maybe it's a cream. When it's in the container, maybe it's close to an ointment.

DR. KIBBE: Thank you.

Herb. You have plenty of time, Herb.

DR. CARLIN: Thank you. Well, it's a pleasure to be here today and to meet some of my old friends that I haven't seen in a number of years.

The USP has not devoted much time to topical

dosage forms in the past. We are in the process of coming up with a new taxonomy and a glossary, and this is a very timely meeting because the definition of lotion is something we'll discuss in a few minutes.

I'm going to give you a little history lesson. You've had some science. You've had some other types of information today, but I'm going to give you a little history on topical dosage forms for the USP.

I went back to USP XII because before that, the titles were all in Latin. I've forgotten everything I learned in high school, and that was a long time ago. And I followed through up until the recent. We'll just do this quickly.

From I through XII was titles in Latin. Nomenclature within the USP was assigned to a Committee on Scope of the Executive Committee. Attention in naming products was paid to existing monograph titles for tradition and at that time coordination with the NF because that was owned by the American Pharmaceutical Association.

Beginning with number XII, the titles changed to English, stayed with the Committee on Scope, and synonyms were deleted from the USP. That was a significant thing, and that was part of one of the Food, Drug and Cosmetic Acts that said there could only be one name for an item. It caused a little difficulty, but we got rid of

them. Lime water became calcium hydroxide solution, a very hot, competitive item. Silver nitrate pencils disappeared and became toughened silver nitrate. Zinc gelatin boot became zinc gelatin. And it was the first time that routes of administration were added to titles. Prior to this time, an ophthalmic solution was a solution. Now it became an ophthalmic solution. The same with otic solution and suspension.

We were talking about zinc oxide, and it's funny how things pop back into your head. All I can remember is P into the Z. Or what is it?

DR. DeLUCA: [Inaudible.]

DR. CARLIN: If you did it the right way, you got white lotion. If you did it the wrong way, you got black lotion.

(Laughter.)

DR. CARLIN: It was always on the boards of pharmacy. I think the last time I did it was in 1954 making powder papers for the Board of Pharmacy in Rhode Island. Or making suppositories in August when you put the cocoa butter on the platter, it just melted by itself. You didn't have to insert it anywhere.

(Laughter.)

DR. CARLIN: In 1980, the USP purchased the NF. It should make things simpler. There still was a

Committee on Scope, and there was some revision to the topical titles trying to get these things working together. There was topical aerosols, aerosol solutions, solutions, solutions for irrigation and powders. And there was addition of two new topicals, emulsions and magmas. So, Arthur, we got your magma in there.

In 1985, finally the USP created a Drug Nomenclature Committee. It reviewed past decisions and recommended many changes to make the titles more user friendly for health care providers. It added drug topical solutions, drug gel, drug topical suspension, drug ointment, drug cream, and made the recommendation to get rid of lotions. Maybe if we had gotten rid of lotions in 1985, we wouldn't have all the scientific work that's going on today. These recommendations were passed on to the next committee.

Oh, I should give you the definitions that we had in 1985.

Drug topical solution and drug topical suspension is the general format for monograph titles of topical liquid dosage forms. This nomenclature is intended to displace lotion terminology because lotion has been criticized as difficult to define with no physical meaning. I guess since 1985 we're finally coming to the point of defining lotions.

I think they made a typographical error back then. They should have talked about topical emulsions and topical suspensions, but it's too many years ago.

Drug ointment is a preparation of one or more therapeutic agents in any of the various classes of bases described in chapter 1151 of Pharmaceutical Dosage Forms. So you've got to go read another section of the book.

Drug cream is a topical preparation that is formulated in an emulsion base. The term "cream" preferably pertains to semi-solid preparations in water-removable bases that are oil-in-water emulsions. 1985.

They had one for gel. Drug gel is a formulation in a water-soluble base and may be regarded as a greaseless ointment.

The committee from 1985 to '90 and '90 to '95 got together and sort of ratified what the previous committee had suggested and published a stimulus article, a multi-page article in Pharmacopoeia Forum, January-February 1991, entitled Nomenclature Policies and Recommendations: Review and Current Proposals and Decisions. And if you're interested in this nomenclature subject, that would be a nice one to go back to and read.

They came up with a new title, new dosage form -- and I'm confining myself now just to topicals -- of pledget. It's a vehicle carrying a topical solution.

In the '90s, we got into a lot of veterinary products and they added soluble powder, intramammary infusion, and topical gel.

There were three powder titles changed. They called them topical powders instead of just powders. And one water was changed to witch hazel. For any pharmacists present, you'll remember it was hamamelis water. It was too long for the label I guess, and they made it witch hazel. But now it's very difficult when you got into a taxonomy, where do you put witch hazel? Where do you stick paregoric? That was all part of getting rid of synonyms. The synonyms were more popular than the official titles, and maybe white lotion is going the same way.

There were two new veterinary products added in the topical area in 2000: concentrate for dip and uterine infusion.

In 2002, we formed a new committee called Nomenclature and Labeling Expert Committee. It became very obvious you can't separate the title of an item from its labeling. If you're going to get very specific in the title, then you'll have a title that's too long for the label. So you need to tie in certain labeling aspects.

And revisions to current monographs began to relate to packaging, like mineral oil enema became mineral oil rectal when suitably packaged, and light mineral oil to

topical light mineral oil when suitably packaged.

I'm going to spend a few minutes with you on the USP as it stands today. It's published every year now. So it's USP 26, 2003.

There are 310 topicals in the USP. As liquids, there are 108. One is an emulsion. Three are suspensions and 78 are solutions. And if you add those up, it doesn't come out to be 108 because there are 23 or 22 lotions, but I'll talk about that in a second because we're finally getting around to getting rid of lotions. Maybe. Semi-solids, there are 170: 3 collodions, 70 creams, 1 foam, 12 gels, 72 ointments, and 6 pastes. Most of the pastes are very old. They must be pre '38.

Solids. There's 1 gauze, 3 patches, 24 powders, 1 tape, and 3 tablets. The tablets are those that you dissolve in liquid before you add it to the skin.

You might want to know what the one emulsion is. It's called drug cleansing emulsion.

There are 23 lotions that may be changed to drug topical emulsions, drug topical solutions, or drug topical suspensions. But I doubt you'll see any drug topical solutions because it doesn't meet the criteria.

Topical solutions. There's a cleansing solution, 1; 6 irrigating, 1 liquid soap, 2 oral/topical solutions; 4 solutions; 6 tinctures, which will become

topical solutions.

I'll tell you why we did some of these things with solutions. The old-time pharmacists know that elixirs are supposed to contain alcohol until Tylenol Elixir was marketed with a big headline, "contains no alcohol." And they did such a good job with their promotion that the American public now doesn't relate elixirs to alcohol, so we decided to get rid of elixirs and call them topical solutions.

And we did the same with syrups. We found there was some syrups that had a lot of alcohol in them. We found some syrups with no sugar in them, and they've become oral solutions or oral suspensions.

There's 1 topical oil, and there are 44 topical solutions.

In suspensions, there's 1 drug and it's a shampoo, and there are 5 topical suspensions, many of which are veterinary.

For semi-solids -- well, we just did that.

Powders. There are 12 topical aerosols, 2 topical solutions, 1 dusting powder, 1 just called topical, and topical powders.

Patches. There's 1 film. There's 1 plaster, and there's 1 pledget.

And there's one gauze. You wonder if it's

worth the time.

Solids. These are tablets for topical solutions, and tapes, there's 1 drug tape.

Now that I've bored you, that's the section of the USP that we have not looked at for a long time. The Nomenclature Committee spent most of their time on things we felt more important to patient care which was injectables. If you'll recall, any of you who are manufacturers of injectables, all the title changes that went on in the last few years. Then we went to oral liquids, and that's when the syrups and elixirs were changed. And now we decided to look at topicals, and it becomes an important subject.

There are three committees at USP right now working on a taxonomy and glossary for dosage forms. So this is very timely. We have the Dosage Form Committee, which is chaired by Keith Marshal who was going to be here today but couldn't make it for other reasons. The Biopharmaceutics Committee with Tom Foster from Kentucky because we go into a third tier in the taxonomy. And the Nomenclature and Labeling Committee.

A stimulus article is in draft form and should be published in PF very soon. What I'm going to show you is some of the draft things for the taxonomy. It may change. Things change rapidly.

There are three tiers. The first tier delineates the tissues to which the active is first delivered by the dosage form. The second tier is the criterion for this group is based on the general type of dosage form involved. And the third tier is the individual dosage form grouping depends on the release pattern from the active.

Here's an example of the first tier. You can see gastrointestinal, tissues of body fluids by injection, mucous membrane, skin surface, and lung. What we're talking about here today is the topicals. You see skin surface breaks down into topical and transdermal.

You go to the second tier, and you see we break it down: skin surface, topical, liquid, semi-solids, solids. Liquids are broken down into emulsions, water in oil, oil in water, suspensions and solutions. The semi-solids are collodions, foams, ointments, pastes, creams, gels. And the solids are powders, which include aerosols, patches, plasters, films, gauze, tapes, and this slide was official last week. It's already changed. The sticks have been changed to tablets because we don't have any sticks. They went out with silver nitrate.

And the third level, which is still working very hard at the USP, breaks it down into conventional release or modified release. And modified release breaks

down into a variety of ways: extended release, which are very common; delayed release, which used to be enteric coated; targeted release, which we don't have any in the USP yet; pulsatile release; orally disintegrating we don't have any but that's where it will fit; and orally dispersing. I'm not too sure what that is. The first time I saw it was when this slide was given to me the other day.

So you see we're having a taxonomy, and then there will be a glossary. And that's changing day by day but will be part of the stimulus article that will be published in the Pharmacopoeia Forum.

So you can see over the years, USP has converted official titles of dosage forms -- converted from those that indicated a formulation or a method of manufacture to describing the finished product in terms believed to be most useful to the prescriber, dispenser, and patient, also by adding the route of administration to the title -- example, ophthalmic, otic, nasal, vaginal, rectal, topical. It should be noted that the type of packaging and labeling may become more significant players in designing dosage form titles.

Now, to the one thing that's of interest to this committee. In 1985 it was decided to get rid of the term "lotion." We're now getting it to be on the top of the plate. So we made a decision a year ago to delete

lotions and convert them to topical suspensions or topical emulsions. We then had a meeting with FDA and realized that FDA was now beginning to look at this situation. So at our next meeting, we tabled the motion, waiting to see what will come out of your activity and the USP activity. So really what's going on in this committee is very important to us because we were just ready to kill "lotion," part of it because there are lotions that are suspensions and there are lotions that are emulsions. And it is vague. And thixotropic is another problem that comes in here.

So, we're very pleased to be here with you today to listen to the deliberations, and I thank you for your patience of listening to this history of non-activity. Thank you.

(Laughter.)

DR. KIBBE: Thank you, Herb. Stick around. There might be questions. Don't go wandering off.

Does anybody have questions directly for Dr. Carlin?

(No response.)

DR. KIBBE: I guess not.

DR. CHIU: I would like to present our questions. We also welcome comments outside the scope defined by the questions. When you look at the question,

please also refer to this table in your package.

The first question is the appearance and the feel of the topical dosage form is part of the proposed definitions. In conversations with practitioners and evaluation of the literature, words such as "greasy," "non-greasy," and "cooling" are often used when describing these dosage forms. Is there any value in including these attributes in the definitions?

DR. SHARGEL: I just have sort of a question. In terms of if you label a product a cream or an ointment, and the manufacturer then in its labeling says this is non-greasy, it's smooth, it's whatever attributes, how does that work together in terms of the labeling saying this is nice, smooth thing, whereas you may title it in USP as an official name?

DR. CHIU: The labeling has two parts. One is the name of the product, the established name, and the other part is the description section. So certain properties may be included in the description section. However, it must meet all the definitions for that name. So that's how it works.

DR. SHARGEL: Just to follow it up, if the manufacturer then gives an attribute in its labeling, how would that be in terms of quantifying that attribute, or is there any need to do that if it's already quantified as a

suspension?

DR. CHIU: Could you elaborate?

DR. SHARGEL: If a manufacturer said it has a nice, smooth feel or non-sticky or something, that's sort of a sell point.

DR. CHIU: That would not be sufficient to say this is a cream or this is a suspension because there are other properties they have to meet in the definition. So if this preparation is a liquid suspension, which we would not consider as a lotion or a cream or anything, we would just say you have a liquid suspension even though it feels not greasy or greasy.

DR. SHARGEL: The reason why I asked is because the consumer may want to know that or a physician may want to know something about the attributes.

DR. CHIU: Right. Those attributes then will be described in the description section of the package insert.

DR. HOLLENBECK: Yes. I guess I would follow up on that. You're not proposing that we label a product really smooth hydrocortisone ointment.

(Laughter.)

DR. CHIU: No, no, no. We would just say hydrocortisone ointment. But in the description section, the firm may want to say this is not greasy or greasy or

something like that.

DR. HOLLENBECK: Yes. I think this could be useful in the description section, but it isn't really part of your criteria to identify what is a gel, what is a lotion, what is a suspension. Right?

DR. CHIU: It is not a sufficient criteria. It may be just part of it because usually a lotion is not greasy and an ointment is greasy.

DR. KAROL: In looking at the definitions and the four broad categories you gave us in the beginning, you said that the first thing we would look at would be the broad definition. Then would be physico-chemical characteristics, and then the appearance and feel, and the fourth one would be spreadability. It seems that the definitions are clear based on the first two, the broad category and the physico-chemical characteristics, and there really is no need to include the appearance and feel or the spreadability in any of the definitions. Your decision tree distinguishes all of these various forms based upon physico-chemical characteristics and chemical emulsions and so on. So I don't think including greasy or non-greasy and spreadability in the definition is necessary.

DR. CHIU: Okay.

Jonathan, would you like to address that?

DR. WILKIN: Well, I would agree with that sentiment. I think there are two places where we think about the attributes of a vehicle. One is in the decision tree to define what particular dosage form it would be, say, an ointment or a cream, and then the other is where we might list some other relevant properties in the description section. I would hope that in the end all of the attributes of the vehicle that help determine its lotionness or ointmentness could ultimately be physical, tested properties, recognizing that there are some pieces that when one is looking at viscosity, for example, it's technique dependent. So I think it's more than just simply saying we need viscosity. We would need to define the technique where one is actually looking at viscosity. But I think in the end, the dosage forms ideally should be rooted in very specific physical measurements often defining the assay technique.

On the other hand, getting into the description section of the labeling, I think there would be an advantage if we could take these psychometric sorts of senses of really greasy, not very greasy, and sort of the intermediate things, and if we could somehow find a device that would help us with that, that would make it more predictable so we're not relying on 20 or 40 human subjects to tell us about the greasiness feel, I think that would be

better even also for the description section. So I think in the end, the more we rely physics, really the better we're going to have consistency from one description section, one dosage form definition to the next.

DR. KAROL: I think we also run into trouble with these subjective measurements because we're really interested in the patient's description of whether this is greasy or spreadable and so on. Are these materials going to be tried on patients to get their reaction as to how greasy they are, you know, patients with eczema and so on, or is this a control panel that's going to decide on these descriptions?

DR. CHIU: I don't think we had planned to do that. But, Jonathan, in your clinical trials, do you include an element to have patients to report back?

DR. WILKIN: I think there may be patients or human subjects for some of these. For example, we may find that moisturization is best defined as sort of the time curve for transepidermal water loss. There are nice devices that one can put on the skin after applying some topical product and look over time at the amount -- I mean, all of us right now are losing a lot of water through our skin. And topical products can shut that off. In diseased skin, it's even higher. So that might be something where you actually need live human beings who have skin that one

is going to look at.

But once again, I think to the extent that these things can be made into physical assays, we're going to have much better consistency from one label to the next in what they mean.

DR. RODRIGUEZ-HORNEDO: Along the same lines, it appears that in your definitions perhaps there could be inconsistency with the feel or this greasy or non-greasy or cooling effects. You might have ointments that do not feel greasy or gels that do not have a cooling effect. So what are you going to do under conditions such as those? It concerns me that then it may create some level of ambiguity that may be unnecessary even if you had the physical measures. So I'd like to know how would you address that.

DR. CHIU: If you look at a formulation with the definition together, you will see based on the composition you could determine ointment is more lipophilic. So lipophilic usually is more greasy. So we just don't have technology or methodology to measure the greasiness, but it's sort of coupled with the composition.

And the same thing with the cooling effect. It is coupled with the volatiles present in the formulation.

That being said, is it important to put the sort of subjective language in the definition? That's the question.

DR. KIBBE: Ajaz?

DR. HUSSAIN: I don't remember. Going back to the report that Cindy presented, we did look at some surface tension, interfacial tension, and so forth. Does that have any link here with the issue of something that happens on interface and something that is related to interfacial tension and possibly other attributes?

DR. BUHSE: We looked at surface tension and we didn't find that it correlated to anything really. We could certainly look at it deeper.

DR. HUSSAIN: You didn't look at it from a greasiness perspective, the correlation from that perspective?

DR. BUHSE: No, we did not. In fact, we did most of our surface tensions on creams and lotions and not, in fact, on ointments.

DR. KIBBE: Gary, and then I think I'm going to take the privilege of the chair and say something myself.

DR. HOLLENBECK: It seems that there's agreement that the decision for calling it a lotion or a cream or an ointment should be based on objective physical testing as much as possible.

But Jonathan's comments earlier about a prescriber wanting to know the general characteristics of these systems I think adds a reason for us to have within

the description, this usually has a cooling effect, this is water washable, this is normally a greasy kind of product. I think that kind of general information helps you make a choice in terms of which one of these forms you might want to use for a particular application.

DR. KIBBE: I teach pharmaceutics and pharmaceutical dosage forms. We teach heterogeneous systems. A lot of the definitions that you put out here, if my students wrote them down, I'd take off full or half credit. They'd get it wrong.

(Laughter.)

DR. KIBBE: We have criteria for establishing what these things are based on the composition of them, and then we assume that the physical characteristics will be a result of the composition. We define them based on the base or the vehicle and not on the active ingredient.

For us, gels are clear. They're either molecular or colloidal dispersions in water. If they happen to become opaque, it's because we've added an active ingredient to it. But if you make a semi-solid which is clear, whether it's colored or not, it's a gel.

Ointments. We have four categories of ointments depending on what we use as an ointment base. It's clear what they are. They are in gradations greasy, starting with hydrocarbon bases going to absorption bases,

which are usually compared, if you will to lanolin, which can absorb water and it's a byproduct of the wool industry. I always like to tell my students that lanolin is on wool on sheep so that when they get caught in the rain, they don't shrink.

(Laughter.)

DR. KIBBE: But it's that greasy material that covers it.

We go from absorption bases to water-washable bases and then to water-soluble bases. So if you have ointment on the label, if you say that it is a hydrocarbon base, absorption base, water-washable base, or water-soluble base, then I know exactly how it's going to feel or behave on the surface of the skin.

A paste is an ointment with lots of solids. We know what happens when we add solids to any heterogeneous system. It makes it more viscous and it makes it more occlusive.

Ointments and suspensions can be lotions. Lotions is a terrible term, but we use it all the time.

I would throw out there that a magma is a suspension whose viscosity is such that it acts as a semi-solid rather than a liquid.

There is another term that we throw around a lot called insufflation. Those of you who are interested

in insufflation, that's a powder that's blown into a body orifice.

Liniments, which haven't been mentioned, are liquid solutions intended for external use with certain kinds of characteristics.

I wonder if our level of scientific sophistication is getting us away from the basic understanding of some of the classic definitions and how they help us understand things. If we could establish these classic definitions and then say, if people are so interested, how does the active ingredient change the characteristic of that base and how does that base affect the characteristic of the active ingredient, we might not need to do a lot more defining.

I read all of this stuff and I wonder what we're gaining and what we're losing. I think I'm reluctant to -- clearly question 3 says loss on drying and that's because creams are emulsions and there are only two kinds. And if we said that this was a cream and it was an oil in water, it would have certain characteristics. If it was water in oil, it would have another. Cold creams and vanishing creams are different because of exactly how they're made. And those are the classic bases from which everything else is relatively derived.

I think we might be overdoing it here.

DR. HOLLENBECK: Well, I'll jump in and respond to that first. I sort of felt the same way as I read my backgrounder. I was trying to figure out what is the problem we're actually trying to solve. And yet, as I've listened to presentations, a few things really have resonated with me.

Art described a system that isn't working. The confusion that you currently have I think is evidence that the system isn't working. Maybe that's our fault as teachers of pharmaceutics.

The idea that some clear guidance to prescribers might help them make better choices in terms of pharmaceutical care I found to be a strong reason for maybe clarifying these categories.

The generic drug product issue I find as maybe a reason for greater clarity too, that you would like to approve a generic product if it's a paste that is really a paste according to your definition.

So I think I've come to the feeling that there is benefit to provide some clarity in a system like this.

Having said that, I feel that you're quite a ways away from it. You've got a series of laboratory tests and some primary criteria which might help you do that. But I have a lot of problems with the decision tree. Like Art, I can't even get to gel because I don't see the word

colloid on your decision tree anywhere. So I think there's a lot of work to do there.

But I would speak in favor of perhaps five or six categories here that might provide some clarity.

DR. KIBBE: I'm not saying that we couldn't improve the system, and I think one of the problems we have is that only a small percentage of the people who deal with these things actually know the classic definition well enough and know the reasons for it to make sense out of it. Clearly that doesn't include the physicians unless they happen to be dermatologists who were once pharmacists and then became dermatologists. I think that's part of what we have to address.

DR. CHIU: This is exactly the kind of comments we would like to hear. If we are not on the right track or if we are overdoing it or undergoing it, we'd like to know, and we would welcome specifics. Gary, you're talking about there may be other attributes or other things, like gel should include colloidal, and we agree. We are here to listen. So we really would like to hear a lot more specific recommendations so we can move forward.

DR. MEYER: I think Gary asked an interesting question. What problem are we solving here? Is it a bioequivalence Orange Book problem in that you don't want to approve a cream as an ointment and vice versa? Or is it

directions or a description in the labeling that you want to be expanded and appropriate ways to test that? Just what are we solving here by the decision tree or definitions or what have you?

DR. CHIU: The problems are multiple. For example, one company has made a lotion and then they want a line extension. They made some minor modification of the formulation, but it hasn't changed the characteristics. And they said, now, I have a cream. So then you have two products because the definition is not clear enough. Then if the generics need to copy it, then they have to copy the lotion from cream, actually lotion, cream, that could be a product called the same name.

Then when you have products of a different characteristic, one company calls this hydrocortisone lotion, the other company calls it hydrocortisone cream. Actually they have the same physical characteristics.

So, therefore, it is important to clearly define the different terms so we know what dosage forms we are talking about.

DR. HUSSAIN: I think there are two ways of thinking about this problem. One is I think there's a need for reexamining the naming system itself, and I think there is a lot of confusion. So I think one of the aspects is I think we want to float the proposal of identifying the

problem that needs to be addressed and what is the solution to that, I think you're looking at that as the start to a proposal. So consider that as you discuss this because FDA alone cannot handle this. Industry has to be part of this discussion. Academia has to be part of the discussion.

Clearly I think this is just the tip of the iceberg. This problem is not unique to topicals. It is inherent in every dosage form. I'm struggling with one dosage form right now. What is an orally disintegrating tablet. So I think it's time to rethink and provide a much firmer foundation to this issue.

DR. KIBBE: One of the problems that seemed to be coming out is that we want a product that's called a cream to be exactly the same every time it's called a cream, which means that we need to maybe subset some creams, or there are creams which are oil-in-water emulsions and creams which are water-in-oil emulsions. So that's two subsets. And if you want the industry to follow along, you almost have to have the equivalent of a USAN Committee for naming products when you're dealing with heterogeneous systems.

It would be reasonably easy for me to say, okay, you are claiming an ointment. Which one of these four categories of ointments have you made? Tell me what the components of your base is and I'll tell you which one

you fit. And you can say you're a hydrocarbon ointment. You can say you're absorption. You can say a wash and so on.

If you want to continue to keep lotion, you can say that this is a suspension or an emulsion lotion. The problem comes when you have both in the same combination and those things.

But do you want an acceptable nomenclature committee at FDA for topicals that when the companies come forward and they want to call it X, you say, well, your base doesn't allow you to call it X? Your base is really this kind of a base. You have to call it Y.

Go ahead.

DR. WILKIN: Well, I was going to respond in part to the query about what are we trying to fix. I think we had definitions in the past for these different dosage forms at a time when there weren't many other examples within a class.

If you look at the literature on taxonomy or systematics, just sort of the general way one approaches trying to divide things up and making order out of chaos, some sense, some structure, one of the ways of thinking about definitions is called a typology, and it's saying in general this would be lotionness. And then you'd list some categories. So what you've done is you have a definition

of a lotion that's pretty good at the epicenter of lotionness, but we know that there are intergrades between lotions and creams. So as one marches out towards the border, then we at FDA have these difficulties when products come in deciding whether we're going to call it a lotion or a cream. So I would say that's one issue.

The second issue is the part about the intergrade. We had an example. And I don't think I'm divulging any proprietary information here. It was a topical that was a cream, and the sponsor wanted to have a line extension. So they were going to keep the active ingredient at the same concentration. They were going to keep the inactive ingredients in the same ratio to each other, but they were going to add a substantial amount of water. If you just think of the problem between what is a lotion and a cream, technically at some point there's going to be a drop of water added to this that's going to then convert it from a cream to a lotion.

Now, I don't know that we have to precise the boundaries quite to that extreme, but the boundaries are so soft right now that we have things that I think have more lotion-type properties that we call creams and other things with more cream-like properties called lotions. I think that's part of the confusion. I'm not going to say this is a horrendous public health issue. I just think it could be

made better. It could be made more relevant.

Then the second part is it seems like we're focusing an awful lot on the composition. It's absolutely true that the properties of the vehicle are critically dependent upon the list of ingredients and also the quantitative aspect, how much each one is there. But I would say that the manufacturing process adds a lot of emergent properties that you can take the same, literally, mix and manufacture it in different ways, and you can end up with different viscosities. So I think there does need to be something beyond just simply basing this on what is the dominant ingredient. I think we may need some more physical measurements to add to it.

DR. KIBBE: I agree about the difficulty of putting a line between lotions and creams. I think your work using 30,000 -- oh, and by the way, generally accepted, we are now using millipascals instead of centipoise. It's the same unit value; 1 centipoise is equal to 1 millipascal. But internationally if you're publishing, you want to publish in millipascals.

That being said, I think making a decision as an agency on where the delineation is is, of course, difficult and worth doing. But you can still define the lotion as either an emulsion-based lotion or a suspension-based lotion with viscosity less than 30,000 millipascals.

I don't think you have to do an as extensive a redefinition as it sounded like we were going down.

DR. CHIU: We can easily do that. During our discussion, we thought a liquid suspension is clearly defined. Maybe we don't need to say that some of them could be a lotion. But we can relook at that element and then include this.

With respect to the subclasses, which is hydrophilic cream, hydrophobic cream, we have a question there later. Our thinking is the subclass information could be put in the description section of the package insert rather than use them to define the name. So, therefore, the name would be a cream and then a cream is a cream that either is hydrophilic or hydrophobic. But that the information would be important.

But we have that question later. We want to ask you whether that's the right approach.

Could we go on to the next question?

DR. KIBBE: Anybody else?

(No response.)

DR. CHIU: The next question is about viscosity. Laboratory work found viscosity to be the most discriminating property that separated lotions from creams. In addition, most literature sources describe lotion as liquids and creams as semi-solids. In the proposed

definitions, lotion is distinguished from cream based on pourability which we found in the lab to be a viscosity less than 30,000 millipascals.

(Laughter.)

DR. CHIU: I got it.

(Laughter.)

DR. CHIU: Using the Brookfield viscometer at 25 degrees and 5 rpm. Is this reasonable?

DR. HOLLENBECK: Well, I would like to congratulate us on harmonizing the units for viscosity today.

I'd say fine as a screening tool, but we all know that rheological characterization is a very complex process. Somewhat arbitrarily choosing 5 rpms and 25 maybe is as good as any other choice.

I'd make a couple of comments there. I do think you ought to sheer the system first. Usually if you're trying to assess pourability, you're pouring it out of something. Normally we shake these things. So I would sheer the system and then measure its viscosity.

The second thing I would say is this is perhaps one of the most powerful tools that you have to somehow identify this three-dimensional abstract network for gels. You can look at time-dependent, sheer-dependent behavior here, and maybe that's a tool that you can use to help

discriminate gels from other systems.

DR. CHIU: Any other comments?

(No response.)

DR. CHIU: Number 3. Laboratory work found loss on drying to be a discriminating property that separated ointments from creams. In addition, a review of the current submissions to the agency found that ointments had a large percentage of hydrocarbons or PEGs in their bases. In the proposed definitions, ointment is distinguished from cream based on the proportions of volatiles, less than 20 percent LOD, and composition, hydrocarbons or PEGs greater than 50 percent. Is this reasonable?

DR. KIBBE: That fits directly with the common definitions that we give all the time. The four classes of ointment bases all contain none or low amounts of water, the water-soluble one being PEG, and then creams are always emulsions and in most cases greater than 20 percent water.

DR. SHEK: Well, if that's the case, why not just talk about water and say ointments don't contain water, and if it contains water, now it's a cream?

DR. KIBBE: Some ointments have some water. Absorption ointments can contain small amounts of water. If you take an active ingredient that's water-soluble and you want to incorporate it in an emollient, which creams

are not as good at, you can take it up in a water-absorption base. It still would be an ointment because it's below a certain amount of water. But you're right.

DR. SHEK: I'm just saying you can change the definition and just decide anything which is water it's not an ointment, it's a cream, the way it feels.

DR. CHIU: We will look into that.

Other comments?

(No response.)

DR. CHIU: Question number 4. The distinction between hydrophilic and lipophilic creams is made based on the composition of the continuous phase. Is there any value in including these two types of creams in the definitions?

As I mentioned earlier, our original thought is to put this kind of information in the description section of the package insert, not use it to define creams. So both hydrophilic and lipophilic creams will have the same name. Drug cream, like that. So we can add this into the discussion as well.

DR. KIBBE: I'm so used to using the emulsion type rather than saying hydrophilic and lipophilic. It's either an oil-in-water emulsion type or a water in oil, and it carries the general characteristics of the external phase when it's applied. So you can use that.

When we start talking about hydrophilic-lipophilic, my mind immediately goes to hydrophilic-lipophilic balance, the HLB nature of the surfactants, which surfactants are in there.

DR. SHEK: I'll support and agree because I think the oil in water, water in oil is very, very important fact in the way you design the dosage form, the way it really acts. So I think this part is important. I agree with you that a definition of whether it's lipophilic or hydrophilic might be confusing.

DR. CHIU: The next question has three parts about gel. Gel is distinguished from cream based on the presence of sufficient quantities of a gelling agent to form a three-dimensional, cross-linked matrix. Is this reasonable? Should "sufficient quantities" be defined? Which literature sources should be used as references?

DR. HOLLENBECK: I don't know what to do with this one. I don't know how to analytically discover the three-dimensional, cross-linked matrix on a regular basis.

DR. CHIU: When you make a gelatin or gel, actually the entire container contains a long cross-link to one molecule. So this is how we got the idea it should be a three-dimensional, cross-linked. However, we do not really know how to actually do this. What is the minimum gelling factor that should be there so therefore you always

get a three-dimensional, cross-linked matrix?

DR. HOLLENBECK: I know we're mixing physical tests with composition all through this system. But this is one that I would resolve based on composition. I think you know the things that form gels, hydrophilic colloids, celluloses, carbapols. If those things are in there, you have a gel. You may end up with a paste later on because you added a lot of solid or an emulsion if you put something else in there. But it seems to me the first kind of screening criteria for a gel might be based on composition more effectively than this more difficult thing.

DR. CHIU: The question is how much is the minimum amount to be present because if you add a little bit, it could be an emulsion factor rather than a gelling factor.

DR. HOLLENBECK: Yes. Again, depending on which hydrophilic colloid you use, very small concentrations can give you large viscosities and large concentrations can give you small viscosities. I think in a screening sense, if those materials are in there, you have a gel. Then you can look at your other criteria later to maybe separate it into subsequent categories.

DR. KIBBE: I have a small concern with that, and that is that there are things that are gelling agents

when you use them to make a gel, which are emulsifying agents when you use them to make an emulsion, which are thickening agents to stabilize suspensions when you're making a suspension. And to say that you have to have X of an ingredient isn't defining the result. The result is that gels are semi-solid systems with dispersion of small or large molecules and predominantly aqueous, and when the base is made, the base is clear.

DR. HUSSAIN: Just to go back to that, I think the 3D structure -- the point you had made earlier. You get to the rheology, and I think the rheology will provide that information because it's the yield point there, and that's where it comes from. That probably would be a better approach to that.

DR. HOLLENBECK: But we know that you can have that kind of behavior for creams as well. So I would argue that you can't have a gel without the hydrophilic colloid.

DR. KIBBE: That's the definition of a gel.

DR. HOLLENBECK: Yes. So that would help you in terms of your screening characteristics to get to a gel.

DR. KIBBE: But I wouldn't worry about sufficient quantities.

DR. HOLLENBECK: That's right. I agree with that.

DR. CHIU: So you don't think we need to worry

about whether it contains sufficient quantities. Just the presence of gelling agents and then look at the physical characteristics.

DR. HOLLENBECK: Yes.

DR. CHIU: 5b. Some currently marketed gels contain an emulsifier that gives the dosage form an opaque appearance. Should the presence of an emulsifier in a formulation preclude a dosage form from being classified as a gel? Should it then be considered a cream instead of gel?

DR. KIBBE: You're going to leave me with this one. Right, Gary?

DR. HOLLENBECK: Yes.

DR. KIBBE: This is so good.

(Laughter.)

DR. KIBBE: This is why have scientists working years and years to come up with esoteric definitions that take 40,000 words.

If the base is a gel, then it's a gel. If the active ingredient, in order to be able to be uniformly incorporated into a gel base must be emulsified because it's oleaginous in nature and you need an emulsifying agent, then I think you're really on the horns of making a call. Do you have a micro-emulsion, which is a colloidal dispersion and therefore makes the gel cloudier than it

would normally be? Do you have an oil-in-water emulsion where the external phase has been gelled to make it a semi-solid? Or have you solubilized the active ingredient in a gel?

Enjoy yourselves.

DR. BLOOM: Do you have any TGA data that will provide any information to make this distinction?

DR. CHIU: Cindy?

DR. BUHSE: We have some data which I showed you. We're collecting more now. So we don't have a complete conclusion yet on TGA, but based on our initial data, we have collected additional samples of gels and creams that contain gelling agents whether they're used as gelling agents or emulsifiers. We went out and specifically looked for some of those materials and we have those in the lab currently.

DR. BLOOM: Maybe that will be useful too maybe in the "sufficient quantities" part of the last question that we were looking at.

DR. SHEK: Yes. It's interesting whether we start with a cream and made it a gel or we start with a gel and made it a cream because if you start with a gel, my question is, if you have an emulsifier, what are we emulsifying there? There has to be now another phase, I would assume, there which is now lipid and we add water.

Otherwise what are the emulsifiers doing there? Right? So that's why I'm asking the question, what did we start with.

DR. BUHSE: I think one of the things we've really seen with our committee is that the formulations that manufacturers are coming up with are very complex. They have not been to Art's class and learned what they should be doing.

(Laughter.)

DR. BUHSE: And they have everything in there that you could possibly imagine.

DR. HOLLENBECK: I guess I think an emulsion trumps a gel.

(Laughter.)

DR. HOLLENBECK: So if you've got oil, if you've got surfactants, if you're creating this multiple-phase system, then your gel actually becomes a thickening agent, a term that Art used earlier. I believe as you move from the more sort of homogeneous colloidal system, the gel, to the heterogeneous emulsion system, I'd rather call that a cream because then I want to know what the external phase is, and the properties of that system really depend more intrinsically on its emulsion characteristics than the gel characteristics.

DR. KIBBE: I think we have the same problem, though, here as we had with differentiating cream and

lotion and using 30,000 millipascals is useful in that case. In this case if the oil phase, quote/unquote, that we put into our gel represents 1 or 2 percent of the weight and it's only the active, have I really gone all the way to making a cream? That's why I was throwing out the possibility that we might have added enough surfactant to actually solubilize. Or have we made a micro-emulsion which is really distinctly different than a standard emulsion that you make? Or have we really gone to an emulsion? I think the agency is going to have to try to think through when does it cross that line.

I agree with you that suspensions trump solutions every time. Emulsions trump -- and we go from there because as soon as you have an emulsion, you can define it, oil in water, water in oil. You know a lot of the characteristics. Along with the viscosity, you've defined your system. You either have an emulsion that's a liquid and pourable or you have an emulsion that's a semi-solid and unpourable. The characteristics of the feel of that emulsion on you is directly related to whether it's oil in water or water in oil. One cools, the other doesn't.

So I agree with you. Emulsions trump. But when have you gotten there?

DR. CHIU: 5c. What is the most appropriate

analytical technique that can be used to identify the three-dimensional structure of a gel?

DR. KIBBE: Nair, this one is yours.

DR. RODRIGUEZ-HORNEDO: I deal with solids, not semi-solids.

(Laughter.)

DR. RODRIGUEZ-HORNEDO: I can't answer this one.

DR. HOLLENBECK: Just to repeat, I think rheological characterization is the only way I know to do it. To look at the extent of hysteresis in a full-blown rheological study might help guide you in that direction.

DR. CHIU: The last question. Is the overall approach taken in the proposed definitions appropriate? I think we have some comments, and if there are further comments, we'd like to know.

DR. SADEE: I just have a general question. I didn't take Art's classes.

(Laughter.)

DR. SADEE: So I do not know about these things.

What are the implications if we design very firm guidelines that distinguish one from the other? And also, what is the implication if certain definitions or certain terms are left out? Are those no longer usable?

For instance, salves and liniments and concoctions or milks or however you might label a product.

DR. KIBBE: Yes. Don't forget collodions.

DR. SADEE: That's right. So are these then no longer usable if it were to be a drug because it doesn't fit into the definition?

DR. CHIU: If this becomes a formal policy at the FDA, it will only apply to future products, not retroactive. Once this becomes a USP policy and published, then USP usually lets companies phase in existing marketed products to change their names. So sometimes it could be 10 years to phase it in. But for the agency, we do not retroactively ask companies to change their current labeling.

DR. SADEE: But proactively then it would mean that those are the only terms that should be used in the future.

DR. CHIU: If today's proposal, say, is accepted by everybody, then for liquid emulsion, semi-solid emulsion, and semi-solid suspension dosage forms will then use these five terminologies for topicals for skin use.

DR. SADEE: I'm just wondering also about some international issues whether products imported or exported, for that matter, would fall under these definitions.

DR. CHIU: Products marketed in the United

States will need to follow the new definitions, but the products exported to other countries will have to follow the definitions the other countries adopt.

DR. DeLUCA: What are some of the legal implications here with regards to these definitions and intellectual property and patent infringement cases and stuff like that? Has anybody thought about that? When you starting putting definitions, is this going to be a factor also?

DR. CHIU: In the agency if we propose and then finally adopt a new policy, it will go through our Office of Chief Counsel. So the legal aspect will be reviewed by them. If the approach is not considered legal under the FD&C Act, then it won't be finalized.

DR. KIBBE: Marv?

DR. MEYER: Specific to your question, I think the overall approach seems appropriate. I really like the decision tree because it causes you to focus in on your decisions along the way, and it's also helpful in coming up with a classification.

What would be the down side of just eliminating gel from your nomenclature? Because that seemed to be the one with the iffiest definition and no perfect physico-chemical test. In other words, it looks like gel would fold into either ointment, cream, or lotion. And that

couldn't be, according to Art.

Part of the problem is that we're dealing with an historical thing, and we're trying to make it fit contemporary attributes. Why couldn't you?

DR. KIBBE: A gel is a solution that has become a semi-solid. A suspension, which is a heterogeneous system as opposed to a homogeneous system of a gel, when it becomes a semi-solid, becomes a paste or an ointment. An emulsion becomes a cream. Okay? And that's where the difference is. While you might think it's subtle, those of us who have been involved with this stuff don't necessarily think it's that subtle a difference.

Gary?

DR. HOLLENBECK: I like the decision tree idea too, but I know this is not the place to go into great detail. But this is really going to be a challenge. As I look at your decision tree, the first thing I notice over on the right is an aerosol. Well, an aerosol is inherently an emulsion. So I can't get to that box by going through your --

DR. KIBBE: Some of them are solutions.

DR. HOLLENBECK: Some of them are solutions. Well, okay, proving my point.

(Laughter.)

DR. CHIU: We removed aerosol because of the

way it is administered.

DR. HOLLENBECK: I understand.

DR. CHIU: It needs to be under pressure. So it's quite different from other semi-solids.

DR. HOLLENBECK: Yes, I understand that, but you'd need a yes to get over to that box for many aerosol products.

As I told you before, I can't get to a gel with your current decision tree because it's not a suspension or an emulsion.

And one other thing. If you mixed calamine with propylene glycol or glycerine or something like that, I'd call that a lotion, and my sense is that you're not going to see much loss on drying if you study that. So you really do have a challenge I think facing you in terms of making the decision tree work.

DR. KAROL: I guess my only comment about the decision tree -- I think it's very good and very effective -- is the definition of a cream. It's a negative definition, and it's like saying if something is not black or white, then it's red, but of course, it could also be green or blue or something else. So I think eventually you're going to run into problems with the definition of cream.

DR. KIBBE: Have we run out of things? Are we

all hungry enough for lunch? Are there any closing remarks?

DR. CHIU: I would like to thank everybody for very constructive input.

DR. KIBBE: I enjoyed it. It was fun.

DR. HOLLENBECK: I think you and I did, Art. I'm not sure about everybody else.

DR. KIBBE: Well, I've got an exam being given tomorrow by a colleague in my class that covers this issue, and if I lost all of these definitions, I'd have to go back and give them all 100s because none of the definitions that I ask them for would be right.

We are now officially adjourned for lunch. We will return for the open public hearing at 1:30. The individual who is speaking, Thomas Franz, is he here? Good.

(Whereupon, at 12:30 p.m., the committee was recessed, to reconvene at 1:30 p.m., this same day.)

AFTERNOON SESSION

(1:27 p.m.)

DR. KIBBE: Well, folks, I hope you have enjoyed your lunch and camaraderie with your colleagues and you are prepared to work diligently through the afternoon.

We are lucky today that we will probably end on time. Remember, that if we get out of here early today, we will make up for it by getting out of here late tomorrow.

Good news and bad news about tomorrow. We have one hour for an open public hearing. We started out with 17 people. We're down to 12. So we have a chance of actually getting through the one in two, instead of three. So, we're getting better.

After lunch, we start with our open public hearing. We have an individual, Dr. Thomas Franz, from Dermtech. Is Dr. Franz ready to go? He looks ready.

DR. FRANZ: I'm Dr. Franz. I'm the Chief Medical Officer for Dermtech International, which is a contract research organization in San Diego.

I have no vested interest in the material I'm going to present because as a contract research organization, we do work for all the pharmaceutical and cosmetic companies, and whatever method the agency chooses to promulgate for proof of bioequivalence, we will do. So we make money no matter which direction the agency goes.

What I'm going to talk about today for consideration is the use of the cadaver skin model as an in vitro way to assess the bioequivalence of topical drugs. This model has been around for a long time, widely used in the pharmaceutical industry, the new drug part of it, in terms of developing topical formulations. I'm really not aware of any pharmaceutical company in developing a new topical drug that doesn't use this particular model system to optimize formulations and thereby maximize bioavailability. So there is a great deal of use of this particular model.

Through this model, which uses cadaver skin in an in vitro chamber type setup, one can very easily measure the rate and extent of absorption of any topical drug through the skin. So it's measuring parameters that are by definition those that we use to define bioequivalence.

As I mentioned, there's long experience with this. It's not only widely used now, but if one goes back to the literature of 30 to 40 years ago, one will find lots of articles on this particular model as it was evolving in its infancy. And particularly 30 years ago, classic work by Katz and Paulsen and others at Syntex pretty much developed the procedures that are now used by most pharmaceutical companies when Syntex developed the first of the high potency topical steroids, Lidex. So there's a

long history of use.

Even today what we're finding is many generic companies have found it necessary to resort to this model as a means of screening their formulations prior to going to some expensive clinical tests because sometimes reverse engineering gets them in the ball park but doesn't necessarily define the innovator formulation precisely. And more critically, given the variation in innovator lots from lot to lot, it's even become popular to screen innovators and choose that innovator lot which best fits your generic lot. So there's tremendous background in the use of this model.

There's also good in vitro/in vivo correlation, and I'm not here talking about clinical in vitro/in vivo correlation, but just if you take the data that one gets in this in vitro model and then do a similar test of bioavailability in living man, usually using radioisotopes, but not necessarily always using radioisotopes, there's very good in vitro/in vivo correlation. In our hands -- and I've been working at this over 30 years now -- I've never found a situation where the in vitro and in vivo did not correlate.

Well, what I'm proposing is use of this model to screen topical generic drugs for proof of bioequivalence. For those of you who have followed the

tape stripping procedure that was proposed a number of years ago, loosely characterized as DPK, it's clear that the agency would like to see two sets of data presented in order to validate any model.

One would be to take a situation where one has a generic and an innovator drug that have been shown to be bioequivalent by clinical testing and then show that whatever model system you use can come to the same conclusion.

Then, of course, the reverse would also be nice to have. Take a generic and innovator that were shown to be not bioequivalent by clinical testing and show them not to be bioequivalent through use of the model.

Unfortunately, it's hard to come across that type of data because generally if that type of data is available, it's not presented to the agency. So nobody really has it. So the first one is relatively easy to find, but the second one is a little more difficult.

What I'm going to present today is some data using the first example of two formulations that have been shown to be bioequivalent by clinical testing.

Within the last year or two, Spear Pharmaceuticals has had a .01 percent and a .025 percent Retin-A gel, tretinoin gel, shown by clinical testing in acne to be bioequivalent to the innovator products which

are known as Retin-A. So the question that I am posing and have data to answer is, will the cadaver skin model reach the same conclusion?

Now, if one focuses on the finite dose part of this, the cadaver skin model basically is one which uses a finite dose approach, a finite dose referring here to a situation where we're going to be dosing the skin with amounts that are clinically relevant. We use approximately 5 milligrams per square centimeter, just a little bit more than what most patients would use. Most patients are probably going to be in the range of 2 to 3 milligrams per square centimeter, but 5 turns out to be a little bit easier to use in vitro. So that's the dose we use.

Basically the model system involves taking a piece of cadaver skin. We're usually obtaining frozen, cryopreserved skin from skin banks. From a single donor, one obtains multiple sections, and these multiple sections are mounted over a chamber in which the under side of the skin, the dermal side, is bathed by warm isotonic saline, and the top of the chamber is exposed to ambient conditions, just like exist in this room that most of us will be applying drugs under those similar situations.

So the key to the model system is that it basically mimics two critical parameters that determine the rate of absorption. One is that there is a temperature

gradient across the skin going from 37 degrees Centigrade on the inside to room temperature on the outside which results in a skin surface temperature of about 32 degrees C. That's what exists in vivo and that's what we mimic in the chamber. And likewise, there's a water activity gradient across the skin so that it's close to 100 percent humidity inside and then whatever room humidity is on the outside. These two physical parameters are key to getting results in vitro that agree with what happens in vivo.

The receptor solution is stirred, and then of course through the sampling port, we're able to remove at various points in time the receptor solution and take an aliquot for analysis and then replace with fresh solution so that there's always an infinite sink existing in the dermal bathing solution.

So this is basically the cadaver skin model. As I mentioned from a single donor, we get multiple sections. They are all screened using tritiated water to probe for defects in the skin and certain criteria by which that skin is either acceptable as being intact or rejected as not being intact.

Generally, enough sections are obtained from any donor so that the generic product will be applied to four replicate chambers and the innovator will be applied to four replicate chambers. The data from those four

replicates will be averaged to give a single value for that donor, and then in the data I'm going to present, we had a target number of eight donors in the particular test.

So this is showing the results, the rate of absorption profile over a 48-hour period for the two tretinoin products at the .025 percent concentration. The y axis is showing the flux or the rate of absorption in terms of nanograms per square centimeter per hour, and then the x axis is time. And we're plotting the samples at the mid-time of that sampling period. So, for example, if the first sample were taken at 2 hours, that data point would be plotted at 1 hour. As you can see, there's relatively good agreement between generic and innovator product with standard error bars being given.

The next slide shows similar results for the .01 percent gel. Unfortunately, bigger error bars in this particular case. There were a couple of donors for which there was larger variation than usual, but this is presenting the data without any of the data being excluded. This is simply showing everything as it was obtained, but still in my estimation not bad agreement between these two products.

Using log-transformed data, we see here the results on top for the .01 percent tretinoin first. AUC is basically total absorption from 0 to 48 hours. Fmax stands

for the maximum rate of absorption. And ratio is the ratio of the generic to innovator product, very close to 1. And then the 90 percent confidence intervals, showing that for the .01 percent product, they easily feel within the 80-125 percent range, and therefore the .01 percent tretinoin did seem to be bioequivalent by this particular test.

On the bottom is shown the same results for the .025 percent tretinoin products. Again, the ratio for the AUC is very good, very close to 1, and the confidence interval being met there. Maximum rate of absorption, because of the greater variability in a couple of the skins, did not quite make 80-125 but was, indeed, very close.

I will point out here that we are throwing out no data. For those of you who may not be familiar with the vasoconstrictor test, currently as we've looked at final reports, the data from greater than 50 percent of subjects are thrown out. I think the value is closer to 70 percent so that basically only 1 out of 3 subjects who go through a vasoconstrictor test end up to be acceptable in that particular test. Here this is our first cut at the cadaver skin model, and so we're throwing nothing out. But there are easily some constraints that could be put to throw out data in terms of particular donor skins where the variability is very large. So we'll just point that out,

that right now we're throwing out nothing.

So based on the data shown here, we think it clearly shows the cadaver skin model could be used to determine the bioequivalence of certainly most topical products, most if not all topical products.

The second part of the criteria that have been raised by the agency of taking two products which clinically are shown not to be bioequivalent and then showing them not to be bioequivalent in your model -- it's hard to get data to answer that particular one. But I will, from this test, just present the data we obtained in another form.

That is, we had two concentrations here. We had a .01 percent and a .025 percent. Now, as far as I know, there's no data from an acne clinical study to show that those are or are not bioequivalent, but we certainly know clinically, from the standpoint of irritation, that they are not the same, and it's very easy to generate that kind of data.

So what I've done here is actually take both the Spear data, .01 versus .025, as well as the Retin-A data, .01 versus .025, and showed that by this test they are clearly not equivalent, as can be seen here. Since we know that clinically they're not equivalent in terms of irritation, I think this does go at least part way to

meeting the second criteria by which the agency will judge the use of some test as a surrogate for clinical testing.

So in this presentation I just hoped to show you that this is a model, probably a one-size-fits-all model as the tape stripping was hoped to be, that should be considered by the agency. Obviously, the data we have at this point is not sufficient, but I think it's sufficient to show that it is a model well worth looking at, and particularly with the recent demise of tape stripping, it should be looked at.

I'll also point out that about 10 to 15 years ago the agency briefly did consider this method and several symposia were jointly sponsored with AAPS to look at it. Then all of a sudden, it disappeared off the radar screen. It was buried without the last rites. I've never heard why, but I think it's time for it to be resurrected.

Thank you.

DR. KIBBE: Thank you. Would you stay a second and respond to questions? Marvin?

DR. MEYER: Tom, would it be helpful in a test like this if the company wishing to have approval of their product could actually formulate one that was 20 percent lower in concentration, all things being equal, and include that as part of, say, a three-way test so then you could have kind of your control that it is able to detect a 20

percent difference or whatever percent?

DR. FRANZ: Yes, it would be very easy to do. Yes, very definitely. The problem is there's no incentive for any company to do that right now because when they get that data, they still have the clinical data that they've paid for and now they've got this extra clinical data that gets them nowhere. So they do it out of the goodness of their heart, and I haven't been able to find a company that's willing to do that. But that is an easy answer to the problem.

DR. MEYER: What would you expect you would see if you did Retin-A versus Retin-A or Spear versus Spear in a study? Would the confidence limits fall outside of 80 to 125?

DR. FRANZ: I think so if you're talking about testing them clinically.

DR. MEYER: No, no. With this system.

DR. FRANZ: Oh. That's what I'm showing in this last --

DR. MEYER: Those are two different strengths, though.

DR. FRANZ: Yes. I'm not showing the --

DR. MEYER: I'm saying if you just repeat it. Instead of doing product A and product B at the same strength, you did product A twice. What's the variability?

You had standard errors, as I understand it, which hide some variability.

DR. FRANZ: Yes. I didn't bring data to show that. What we've found, for example, is we've taken three different lots of Retin-A and run them side by side on this test and they basically overlie each other. There are still big error bars, as is true for any test that involves human tissue, a lot of variation. But when you do enough reps and enough donors, you do get means and you do get confidence intervals which you can meet.

DR. KIBBE: Jonathan.

DR. WILKIN: Actually I think I'll hold off because I'm going to give a presentation later, and I can mention decision criteria, what arms to have in the study.

DR. KIBBE: Okay.

Pat?

DR. DeLUCA: In your slide here, is that a Franz cell that you're using?

DR. FRANZ: Yes.

(Laughter.)

DR. DeLUCA: Is that your cell or what?

DR. FRANZ: Yes. It's not patented. I get nothing out of it.

DR. DeLUCA: Okay, no. You're very modest.

DR. KIBBE: In this last slide, is there a 2.5

to 1 ratio?

DR. FRANZ: It's a little less than that, yes. It's not 2.5 to 1. I think it's like 2 to 1, something like that.

DR. KIBBE: Okay. So if you normalize for dose, they wouldn't be equivalent?

DR. FRANZ: There's not a linear relationship between concentration and flux, if that's what you're getting at.

DR. HOLLENBECK: Is it worthwhile investigating synthetic membranes in your model?

DR. FRANZ: No. We've tried that and we sometimes get flip-flopping of data. People have always said, well, maybe it doesn't match quantitatively but it will quantitatively. But we've tried that and sometimes we find that formulation A is greater than B in human skin and then B is greater than A in some synthetic membrane. So we've not ever found that useful, but people continue to look at that. That's for sure.

DR. MOYE: I couldn't help but be drawn to the comment you made about the missing data. If I understood right, you said that all the data that you had were included in this analysis.

DR. FRANZ: Yes.

DR. MOYE: And I guess I was willing to assume

that, but you pointed that out.

Then you also said, if I understood you right, that up to 70 percent of patients are excluded or data are excluded from -- are there other evaluations, competing evaluations of bioequivalence?

DR. FRANZ: Yes. The vasoconstrictor assay is a pharmacodynamic assay for the class of topical drugs known as corticosteroids. In the agency guidance, there's a criteria that each subject must respond in a greater way to a higher dose than a lower dose, and if the ratio between the high dose and the low dose, what they call D2 and D1, is not greater than 1.25, that patient is excluded. But we've seen a lot reports from a lot of CROs where the data from 70 percent of patients are excluded because they don't meet that D2/D1 ratio.

So I think we can look at this test in terms of absolutes, but I think the other way to look at it is in terms of what we've got now. It's not that great. Whether you look at clinical testing or the vasoconstrictor assay, they leave a lot to be desired. So let's not hold this to some enormously high standard. Let's hold it to the same standard as we're holding these other tests to.

DR. KIBBE: Efraim.

DR. SHEK: I have a question. I don't know too much about intrinsic diffusivity because usually you would

expect to see a lag time. And here it looks like it goes very quickly through the skin, and my question would be if you have other drugs which don't diffuse as well, whether you'll see differences in the lag time and then differences in the AUCs.

DR. FRANZ: Well, yes. This is an unusual drug in that it does seem to permeate very fast with very little lag time. We've done this drug many times in vivo too because it's a teratogen, so there's a lot of interest in systemic toxicity. So this is an unusual drug. With most topicals there is a pretty significant lag time which could become another parameter for comparison.

DR. KIBBE: Ajaz. Oh, I'm sorry. Jon.

DR. WILKIN: In terms of not looking at the data from 70 subjects in the topical corticosteroid assay, my understanding of how the Office of Generic Drugs actually asked this study to be done is they're looking for the 30 percent or 50 percent of human subjects who are actually very sensitive to the effects of the topical corticosteroids over a wider range of concentrations so that in essence, they are better detectors. They're better subjects for picking up subtle differences from one preparation to another. The subjects who are no longer used, which may be 70, but it may be a lot smaller percent, turn out to not vasoconstrict quite as readily or else they

are relatively vasoconstricted from the beginning. I think that's the major piece. It's the idea of selecting subjects who are sensitive and good responders for the assay.

DR. KIBBE: Okay. Seeing no one else, thank you very much. I appreciate it.

Now we're going to get with our FDA presentations, and Ajaz has one.

DR. HUSSAIN: Well, again, good afternoon.

As I mentioned this morning, topical products pose significant challenges for us in terms of approving therapeutically equivalent generic products. I think one of the reasons is that when we measure blood levels or if you're able to measure blood levels, that is not a level that is reflecting the site of action. Even in Dr. Franz's presentation, he's looking at flux, which is a receptor phase, concentration in the receptor phase, but the site of action is the skin. So you have to infer what was the concentration at the site of action. So I think that's one of the challenges that we face in trying to arrive at methodologies for approving generic drugs or even, I think, approving innovator drugs in the post-approval change scenario when there are significant manufacturing changes.

For the last 10 to 12 years, we have been working on this, and I do want to acknowledge Dr. Vinod

Shah and others who have worked extensively on this and have actually created quite a body of scientific literature and knowledge on this that had led to a draft guidance on dermatopharmacokinetics, skin stripping, where we were unable to establish consensus between the clinical community and the pharmaceutical community.

As a result, I think we took that guidance, withdrew the draft guidance, and said, but that doesn't mean that that methodology is off the table. In fact, as we come through this discussion and when we come through a proposal for moving forward, I think we would like to bring that back as a focal point for discussion in sort of a different light. So I don't want to get the message out that DPK is not a method on the table. It is a method on the table, but I think we're going to reposition that.

For today the goal of this discussion is to take a step back, go back and reexamine the challenges, reexamine different perspectives, and propose a path forward in terms of a research program. After you listen to the presentations, then what I would like to do is come back and propose a path forward in terms of a research program which we will bring for an extensive discussion at a subsequent meeting. Whether that is the entire advisory committee or the Subcommittee of Biopharmaceutics, we haven't decided. But that's the plan.

So this is an awareness topic for all of you to go back and reflect on the challenges we face. And the three presentations we have on the challenges are Dale Conner, Dena Hixon, and Jonathan Wilkin. The sequence of the presentations is somewhat different than what we have on the screen. So I'll ask Dale to start the presentations, followed by Dena, and then Jonathan Wilkin. Then I'll come back with a path forward.

DR. KIBBE: Does anybody want to ask Ajaz a quick question? He's not escaping, so we'll get him later.

Go ahead, Dale.

DR. CONNER: As usual, my task is usually to go over the basics of bioequivalence while others give the more meaty and perhaps even more interesting topics. Obviously, I go first because you need to understand the basics before you understand the more important or high level concepts.

Actually topical drugs fall into what we largely refer to as locally acting products. Those of us who are involved in doing bioequivalence every day have found these an extremely challenging set of issues to do bioequivalence. If you're used to being a pharmacokineticist and doing systemic drugs, by comparison those seem very straightforward and easy even though not always.

First, we have to clearly say what we're talking about here because for those who don't deal with dermatologic products or deal with the skin all the time, there is sometimes confusion. What we're dealing with in this discussion is products applied locally to the skin to treat diseases or conditions of the skin. So, for example, what's been discussed earlier before lunch, creams, ointments, gels, however you define all those, solutions, suspensions, and other things that are used for the above, to treat diseases of the skin.

We want to make very clear we are not talking about transdermals, nor are we talking about certain types of products that might exist as an ointment but whose endpoint is to administer drug into the systemic circulation to treat a systemic disease. So those particular products, transdermals especially, are using simply the skin as a route of entry into the body rather than the actual site of activity or the site of the clinical condition. So it's very important because that is, strangely enough, a point of confusion for some.

First, I'd like to go over a very brief single slide about the evolution of scientific thinking. Perhaps you could say that dermatologists have a history of not trusting generic drugs or generic drug products. Early, way back in the ancient era, decades ago, the early

regulatory approaches to generic topicals were simply to treat them -- if they were pharmaceutical equivalents, it was an ointment versus another ointment, it had the same amount of drug in it -- pretty much the assumption was, well, there's going to be no problem with inequivalence or these are not going to be non-therapeutically equivalent. By today's understanding, it was kind of naive view that the skin is very simple and these products are very simple and I don't really have to worry too much about the clinical effectiveness of these products as long as they have some fairly superficial similarities. So back then, waivers of in vivo studies were granted for most, if not all, of these products.

The result of this, by today's understanding this is not a simple situation and the skin is not a simple organ nor are these products simple, uncomplicated products. And therefore we ended up with clinical observations at first by dermatologists that some of these products that were supposed to be equivalent and switchable were not in any way therapeutically equivalent in their hands. They were seeing very large and noticeable clinical differences in the community in the patients they were trying to treat between these products which were supposed to be equivalent.

So we come to a point in time where the

corticosteroids, which at least at the time made up a large percentage of the dermatologic products, most of the observations were in the corticosteroid area.

McKenzie and Stoughton developed a bioassay that was related to the ability of topical corticosteroids to cause a blanching effect of the skin. This is a pharmacodynamic effect probably caused by a steroid effect of vasoconstriction in the superficial vessels of the skin. So if you apply a strong steroid to the skin, you'll see, within perhaps a few minutes to an hour, the skin becomes light. After the removal of the drug, it's a temporary effect. It might last 24 hours or perhaps a little bit more, depending on the drug.

But these investigators attempted to quantitate that with, at first, the potency of different steroid agents, and eventually Dr. Stoughton actually applied this technology to try and discern if there were any differences in equivalent products containing the exact same drug. His work, which was published in one or two different articles, showed that many of the steroid products on the market that were allegedly bioequivalent were, indeed, not bioequivalent or therapeutically equivalent by his assay.

So this and other advancing knowledge in this area led to a change in the way these products were regulated, in that it changed to, for a great many of them,

certainly the new products being tested through in vivo bioequivalence testing rather than just simply granting waivers for all of them.

One of the successful developments that developed from McKenzie and Stoughton's original work was the current Guidance on Topical Dermatologic Corticosteroids, which uses that same blanching effect and attempts to have a quantitative measure of this blanching effect and relate it to potency and certainly bioequivalence of pharmaceutically equivalent products.

So first off, a definition of bioequivalence. This is definitely with a generic drug's flavor, in that we term them as pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions.

The pharmaceutical equivalence part has some importance to the topic that we discussed earlier before lunch because those definitions that you debated and discussed really are one of the defining characteristics of whether two products are pharmaceutically equivalent. By pharmaceutical equivalence, we mean it's the same dosage form. It contains the same amount of drug and is used for the same conditions with presumably the same labeling and indications. So the definition of the same dosage form, a

cream versus an ointment, a gel versus a cream or a lotion, that has a great deal of importance when you're determining pharmaceutical equivalence. Therefore, if a drug is an ointment and somebody else develops another formulation that doesn't happen to meet your definition of an ointment, it cannot be matched up as a generic drug against that first reference-listed drug. So the definition of dosage form has a great of importance when you're determining pharmaceutical equivalence.

So just a few thoughts on bioequivalence. What we're trying to achieve here through bioequivalence is therapeutic equivalence. We want the products that are switched for each other to be equivalent when used in patients, and that's equivalent both on the efficacy side and to have equivalent safety profiles as well. So that's really the endpoint that we're all looking for. If one is, for example, either a new formulation of a currently approved product or a generic drug product that can be substituted for a reference-listed drug, in the end when those substitutions or changes are made, through objective measures the patients and their physicians should not be able to tell the difference based on therapeutic evaluation between those two products. That's the ideal and what we're striving for.

Bioequivalent products, therefore, can be

substituted for each other without any adjustment in dose or additional therapeutic monitoring over and above what's normally done for that type of patient and the most efficient method of assuring that TE is to assure that the pharmaceutically equivalent formulations perform in an equivalent manner.

So one of the important messages that I always try to get across, because sometimes people get confused, is that bioequivalence testing is all about the formulation. It's a test or comparison of the formulations as opposed to bioavailability where there are many other issues that are studied, including drug substance characteristics and how the absorption characteristics of the drug substance, regardless of which formulation it's in, also play a factor in what you would really like to know. With bioequivalence and formulation comparisons, it's all about how that formulation performs in making its drug available to the body.

The regs in 21 C.F.R. 320.24 lay out a number of different ways to approach the demonstration of bioequivalence. As you see, for this topic, for these topical products, choice number one -- and these are thought to be in order of preference for most products, especially systemic products -- may not be suitable for this particular set of products. Usually we are faced with

doing topical dermatologic products with number two or number three, either a pharmacodynamic comparison or a clinical comparison, to try and determine equivalence and therapeutic equivalence.

I show this. This is one of my favorite slides. I show it even when I'm not talking about bioequivalence sometimes because I like it so much. But it really displays to me what this whole process is. I drew it out for myself so that I can understand and explain what is the object in bioequivalence.

We have a series of processes. The first slide I'll show you is the oral product, and then I'll change this a little bit to show you two versions or two ways of thinking about the topical products.

So the oral one is something that we, I think, all know something about. It starts out with a dosage form that's manufactured or designed by formulation scientists to have certain characteristics. Usually in this particular case, the drug is in solid form, and it makes a transition during this process into a solution which is then absorbed through the GI tract. It ends up going through the gut wall, ending up in the blood. Eventually the blood carries it to the site of activity and you have a therapeutic effect, whether it's a desirable or undesirable one. So this is a schematic. It's not a kinetic

description. It's simply the simplistic set of events that happen.

And where do we want to intervene and take measurements to determine what actually happens with the dosage form? Because that's really what we're trying to do. Most of the things that I put in green and blue are characteristics that are determined by the patient or the study subject.

The thing that we have control of and are trying to test as formulation scientists are how this dosage form performs when you give it to patients or to study subjects. Unfortunately, we're not able to look directly at those events and measure them, so we have to measure them at some downstream event, normally in the blood or in some cases at a pharmacodynamic or therapeutic effect.

The important points to make from this is normally blood is best for systemic purposes because it has some very nice properties. It's not extremely variable. It's not too many steps in my little scheme away from the event we're really trying to get some insight about. It either has a linear -- I drew a little plot down here to show you. The response is on the y axis that we're actually measuring, which are the plasma concentrations, and the dose is on the x axis. So it usually either has a

very nice linear relationship of response to dose, or at worst, it has some kind of nonlinear relationship, which actually kind of goes up in the air on this plot, which in effect makes the test even more sensitive than it normally would if it were linear. So based on those properties, it's a very nice way to actually determine equivalence and bioavailability.

On the other hand, if we move towards further down the stream to perhaps what we're all really interested in, which is the therapeutic effect, when we do clinical or pharmacodynamic effects, they don't quite have as nice or well-behaved properties. They generally have a sigmoidal dose-response curve. So if you have a clinical response or a pharmacodynamic response that you're measuring and you want to relate it to dose or, in the case of bioequivalence, slightly different doses from different formulations, you're faced with this relationship which, in effect, has three sections. The section on other side, here at the bottom and here at the top, are plateaus.

So if you're testing your two formulations in this dosage range, you get very little, if any, sensitivity between those doses. So if I were up here on the plateau, giving much more drug than I really need to get my maximal effect, I could have perhaps a 100 times different dose and I wouldn't be able to tell the difference. The same thing

with the bottom plateau where I'm just not giving enough to get an effect. To get a good bioequivalence comparison you really need to be at this middle section, the steep part of the dose-response curve. This is my representation. They don't all look like this. I drew it especially steep for illustration purposes.

So if you were going to do this type of bioequivalence test, it is really important that you pick your dose to do the test at the proper part of this curve so you can get sensitivity to tell the difference between the two doses from your two different dosage forms. So that goes in a straight line from beginning to end. No problem.

However, that's not exactly the set of sequences that we're dealing with with the skin. We have now a locally acting product. Now, I have two versions of this slide. The first one is what I would call a simplistic or naive model because people come all the time and say, well, for skin products why don't you simple measure the blood and do bioequivalence that way?

On my scheme the dosage form partitions drug into the skin. Then it diffuses to the site of activity. You get a local therapeutic effect, and then eventually it diffuses through the skin. It's picked up by the superficial blood supply, and it goes into the systemic

circulation. Most people look and think of it this way and say, well, you know, you could just measure the blood and infer back. Even though in our previous scheme the blood acts as an intermediary between what we really want to know and the event we're trying to measure, the blood is later. But perhaps we could still infer back and it would still be okay.

This is, in a way, a naive view that there's only one way through the skin, that any drug that comes into the skin goes to the site of activity. It goes past the site of activity, is picked up by the blood. And we have the same types of characteristics of the data and the same problems I just discussed.

If you talk to dermatologists, though, or people who are experts in the skin, one of the critiques of that first scheme is, well, perhaps there not just one way through the skin. The previous slide looked at the skin as a homogeneous slab with a homogeneous set of layers with only one pathway through each one. However, if you look at the skin, there are holes in the stratum corneum, there are other routes through the skin.

So it might be more accurate from the dermatologist's view to say, well, I have my path 1 which passes to the site of activity, creates a therapeutic effect and goes to the blood, but I might have another path

which bypasses that site of activity and eventually ends up in the blood without ever being reflected at the site of activity. Or it might contribute some variable amount to that site of activity in an indirect way.

Now, this all of a sudden says that if I measure blood, I have some confounding sources of drug which may not relate back to drug bioavailability to the site of activity.

So what we're left with with this type of scheme is that we really need to measure a PD or a clinical response to determine what's really happening, how that drug from that product is available to the site of activity within the skin.

Of course, I mentioned the particular problems of doing pharmacodynamic or clinical response is that we don't have a nice, well-behaved straight line of response versus dose. We now have some technical issues to work out to make sure that that's a sensitive test.

I have two examples of things that have been tried in this area. The first I think has been talked about. Dr. Franz talked about it a little, and I mentioned it before. I guess the success story, or the current success story, is the adaption of the blanching effect for a biotest to do topical corticosteroids, to do equivalence of topical corticosteroids. That procedure has come a long

way in the last 30 years that it has been developed. Now I'd like to think Dr. Stoughton, who is no longer with us, would be very happy at how his method has developed because he certainly had a significant part in it and tested some of the early developments.

But it involves assessment of the blanching effect. It used to be a human observer would simply come in and say, that's a 1 or that's a 2. And now we have an instrument that actually reads the color change in the skin. We have some very, very sophisticated pharmacodynamic modeling methodology that really does do a great job in trying to quantitate this effect.

As far as the subject washout that we've been talking about, we've really not seen much more than 30 or 35 percent. Part of the procedure is a subject enrichment type of approach where you're really looking for responders. If you included all comers, all of us respond to this blanching effect differently. Some people barely respond at all. Some blanche at even the slightest amount of corticosteroid. But what you want are people who have a reasonable response rate over the dosage range that you're actually looking for so that they can tell you, based on their own response, whether there's a difference between the products or not.

So you tend to want to select out those people

who don't have any sensitivity, who either over-respond or perhaps have little, if any, response. And we all differ. Everyone this room probably has a slightly different blanching response. So it's very important to make sure that you have the right responders in the study, and often that means that 30 or 40 percent of the people you evaluate don't make the cut as far as being a responder.

One of the problems with dermatologics that, again, most people don't realize is, with an oral drug, if you want to increase the dose you give to somebody, you just take two tablets or three tablets or four tablets for most products, and you get four times the dose. With a topical product, on a given area of skin, you simply don't have much control over the dose. You can stack up thicker and thicker amounts, but that really isn't giving a higher dose per unit time for that area. So your ability to control the dose and to get yourself into that ideal area of that curve is very limited.

With this topical corticosteroids method, they did it in a very clever way in that they controlled that dose by simply putting the product on the skin for varying lengths of time. So they put it on and they get it right off again, and that's the way they control the exposure to the skin. It's a little bit of an artificial way of controlling things, but it works very nicely as far as

getting this blanching response over time and over dose.

Part of it is also to establish through testing what the dose-effect relationship is and that we are indeed studying it on the sensitive part of the curve. That's part of the procedure and part of the subject evaluation as well. So all of the problems that I mentioned in doing this type of study and this type of approach -- there's an attempt to actually do those properly in type of test.

The other one, which has also been mentioned, is termed dermatopharmacokinetics. So far it's been less of a success than of the other one. We've spent a lot of time and a lot of good research on this. In that case, the product is placed on the skin and removed at several time points. The stratum corneum, the upper layer of skin, that was exposed to the drug is removed by skin stripping with tape, and then that tape is analyzed to look at how the drug diffuses through the layers of stratum corneum. So more or less a kinetic approach is used for the uptake into the stratum corneum which is the outer barrier layer of the skin.

The problems or the critiques, I guess, of this technique were that, to go back to my multiple pathways, that this really just studied only one pathway, the stratum corneum itself. It did not really give much insight into other ways of getting into the skin or into the site of

activity like hair follicles or sweat glands.

There was limited, if any, relation to drug availability at the site of activity. So we didn't really have a great correlation to the actual drug appearance at the site of activity.

And last but not least, there were sometimes different results from different labs. If you were in previous advisory committees, Dr. Franz was one of the labs that studied this. He's a well-known expert in this area. We had some trouble with different labs coming up with very different results.

So for those reasons, which obviously if different labs, all done by well-renowned experts, come up with different results, it really does shake your confidence quite a bit in any method. So as Ajaz said, although this method is not completely dead, there are still a lot of things that would have to be worked out before this would become a successful method.

So to recap, the special considerations for BE of topical products.

The semi-solid topical products are complex dosage forms in contrast to what they used to think many, many years ago.

The skin is not a homogenous slab of tissue, and there are several pathways that the drug can get into

the site of activity and into the body, some of which are stratum corneum, sweat glands, and hair follicles.

Plasma concentrations, at least in our current way of understanding, are not suitable for looking at drug availability at the site of activity. Now, if we really developed this idea and got a lot more data, our ideas may change in this area, but at our current level of understanding, it just doesn't really look like a good approach.

Surrogate measures, like some of the ones we've discussed, may not always adequately reflect the availability at the site of activity, and one of the burdens of validating a surrogate measure is you really have to show that it does provide information that is clinically relevant as far as equivalence.

And the clinical PD measures that we currently use, for the most part, successfully tend to have some problems of their own. There's a high degree of variability, which means that you have to study quite a few patients. They may, depending on how you do them and the dose issues that I've referred to, lack sensitivity unless they're done correctly. With all these products, you have a limited ability to control dose.

DR. KIBBE: Does anybody have any questions? Leon.

DR. SHARGEL: Well, Dale, you've heard me before about the use of plasma concentrations.

DR. CONNER: Yes. Leon is one of the people who always comes in with the plasma concentration idea.

DR. SHARGEL: But I didn't quite finish.

DR. CONNER: Okay.

DR. SHARGEL: We go at this periodically for those who are not aware.

When you're doing plasma concentrations, even for so-called systemically absorbed drugs, it's really a surrogate marker for the site of action in most cases. So if the drug is working in the brain or in tissues or such, we're assuming that the blood somehow is related to the site of action as well as safety, and it's also a measurement of exposure.

It seems to me that there's a paucity of data in most cases in doing locally acting products. There's a discouragement of looking at blood levels, and the general thing is, well, it may not mean anything.

Is there data available -- and I'm beginning to see a little bit here and there by hearsay, not too much published yet -- that would say if I did topical or locally acting products, would I see equivalent blood levels? And the next question, of course, you could say, well, even if you see equivalent blood levels, it doesn't mean anything

because it's not the site of action.

DR. CONNER: Well, I don't think scientifically you can ever dismiss anything, especially when you have no data that supports its dismissal. What I'm saying is at our current level of understanding and assuming that the concepts and the conceptual framework that I've laid out is correct or accurate, it doesn't look good with our current level of data and understanding.

That does not mean that data wouldn't be welcomed to support that. Any method that we've talked about or any that we have yet to talk about needs to be explored. Even if they don't always look good from our own current conceptual understanding, that doesn't mean that data wouldn't convince us that our conceptual understanding is in correct. So I think that all of these things that we conceive of, including things that we've studied in the past and perhaps dismissed, still more data can change our minds. Good scientific work is always welcome in any of these areas. I specifically want to say that I'm not discouraging any work in any of the areas of any ideas that have been brought up.

DR. KIBBE: Marvin?

DR. MEYER: Dale, are there good examples of where you have a secondary pathway for absorption and that is able to bypass the site of local activity? Or is that a

hypothetical?

DR. CONNER: Well, I'm trying to think of -- usually they've been in in vitro testing like diffusion cells and things where you can actually show stain going down into hair follicles. In some of the cases, the actual site of activity for some products is the hair follicle. So you're actually trying to get drug down in there. Drug that might go through the stratum corneum and perhaps bypass that is drug that's lost in the therapeutic effect. So a lot of it is theoretical, but I'm not currently aware of any that actually says that, although that doesn't mean it does not exist.

DR. KIBBE: Ajaz?

DR. HUSSAIN: Just to sort of add to what Dale suggested, I think when you have a solution dosage form where it's homogeneous, I think those are not a concern. But as soon as you have a suspension type of a product, then the particle size ranges, if there are differences, then I think that brings up a concern in the sense localization of particles in certain appendages may result in either an adverse effect at that site or it could be used as a targeting to that site. Dale is right. These are at least to a large degree in theory, but there is some evidence that the particle size differences might be linked to certain differences in therapeutic or safety concerns.

DR. WILKIN: I can just add that I think it was Hans Schaeffer's group demonstrated for one of the topical synthetic retinoids that particle size in a certain range would increase delivery into the follicle, not necessarily the hair follicle, but the sebaceous follicle. So it was a good target for acne. That's where acne develops.

DR. CONNER: I think Hans has also done some animal work where he used rats and through giving them light burns and allowing them to recover, the hair follicles are eliminated and the skin comes back with its normal properties except now there are none of the holes there that were caused by the hair and did some work on showing the differences in permeation between having hair follicles and yet the same skin on the same animal not having those hair follicles and looking at permeation. So he's done some work on that as well simply trying to look for how much of an effect, having these holes in has on permeation through the skin, of various drugs with various properties.

DR. KIBBE: Shall we go on? If you think of something else interesting that you want to ask Dale, he'll be around at least for an hour or so.

Continuing our inverse order, we now have Dr. Hixon.

DR. HIXON: Hi. I'm Dena Hixon. I'm the

Associate Director of Medical Affairs for the Office of Generic Drugs, and I want to talk about the clinical endpoint bioequivalence studies that we currently do for these locally acting drug products. I also want to just briefly discuss the difference between establishing bioequivalence for these products and the systemic drugs and then some of the specific challenges that we get into with dermatology drug products.

As Dale has mentioned, systemic drugs are delivered to the blood stream specifically for distribution to sites of action in the body. Bioequivalence of these systemic drug products can be determined with PK studies. The PK studies are relatively short studies. They show relatively little variability in their results, and they require relatively small numbers of subjects. Those are also less expensive studies than the clinical endpoint studies.

Locally acting drugs are those that are not intended to be absorbed into the bloodstream and instead are delivered directly to the sites of action in the body. Of course, with derm products which we're talking about, this involves sites of action in the skin, but we also have locally acting drug products with sites of action in the mouth, eyes, ears, nose, vagina, urinary tract, or gastrointestinal tract.

This list of locally acting drugs is certainly not intended to be an exclusive list, but the types of products that we deal with include topical acne creams, lotions, or gels; topical or vaginal antifungal creams or suppositories; oral lozenges for oral candidiasis; ophthalmic drops for conjunctivitis or other eye conditions; otic drops for external otitis; oral vancomycin for pseudomembranous colitis; nasal sprays for rhinitis; and orally inhaled products for asthma.

Now, certainly for these locally acting drugs, as has previously been stated, the pharmacokinetic studies are not adequate to establish bioequivalence, and for some products, such as the topical steroids, we have pharmacodynamic studies, the skin blanching studies that were discussed. But most of our locally acting drugs require clinical endpoint studies to demonstrate bioequivalence. And combination products such as a cream that's a combination of a steroid and an antifungal, for instance, would require both a clinical endpoint study and a pharmacodynamic study.

Our typical clinical endpoint study is a three-arm comparative trial of the generic versus the reference-listed drug versus placebo. These studies involve treatment of an approved indication for the reference-listed drug in a patient population and according to the

approved labeled dosing. The trial design and endpoints are very similar to those in the NDA.

I would point out here that the purpose of clinical endpoint studies is certainly not to establish safety and efficacy de novo, but to show that the effectiveness of the generic product is equivalent to the effectiveness of the listed drug.

Both the generic and the reference-listed drug must be statistically superior to placebo with a p value less than .05 in order to assure that that study is sensitive enough to show the difference between products if there, in fact, is a difference. Basically the bioequivalence requirements are the same as those established for other types of BE studies, the PK studies specifically.

We have a number of challenges that we face with these clinical endpoint studies.

First of all, the clinical endpoints are significantly more variable than pharmacokinetic endpoints but still must meet the same established bioequivalence limits. This may require several hundred patients in a bioequivalence study with clinical endpoints.

The study duration may be up to several weeks depending upon the approved labeling of the reference product, and these studies, of course, are very expensive

to conduct because of the number of patients involved and the duration of the study.

They also may present more safety concerns than PK studies partly because they involve a patient population and partly just because of the duration of exposure.

Some of our challenges are the unknown inter-subject variability within the reference population. We don't know if the difference from one group of subjects to another in patients just using the reference population might actually be more different than the bioequivalence requirements that we have established to show that the generic drug is bioequivalent to the reference drug.

There also is some difficulty in achieving consistency between studies. We don't have any one required study design that sponsors need to follow. In fact, we encourage sponsors to come to us with their proposed protocols for these clinical endpoint studies, but there's no requirement that they all be exactly the same. So, there are some challenges in looking at study designs to make sure that the population that is being studied is appropriate and that the endpoints that are chosen are appropriate. Those are probably the most significant components of the study design that need to be evaluated and need to be acceptable.

Of course, some products require multiple

studies. Those combination products that have both a topical steroid and a topical antifungal are one example. Another example outside of the dermatology field is the nasal sprays because they require pharmacokinetic studies in addition to the clinical endpoint studies and some very stringent in vitro studies.

As far as some of our challenges that are specific to dermatology drug products, we have, of course, the antifungals and other anti-infectives. We found a significant number of patients in these trials needing to be excluded from the evaluable population because their baseline cultures were negative. This, of course, has nothing to do with the performance of either the reference or the test drug product, but simply because of the sensitivity of the cultures. In some cases, with antifungals, it's almost half of the study population that has had to be excluded because of the baseline cultures being negative.

Also, the possibly of false negative cultures has led to some difficulties in interpreting the outcome of these studies because with the difficulties in growing fungi and other agents in culture media, it is quite possible to get a significant number of false negative culture results. That makes for more difficulties and more expensive studies.

With acne products, we have to deal with multiple endpoints in that acne involves treatment of not only inflammatory lesions, but also non-inflammatory lesions. So we end up with lesion counts that are inflammatory lesion counts, non-inflammatory lesion counts, and total lesion counts, and there are often some disagreements between FDA and sponsors in terms of what's important: the percent reduction from baseline, the actual reduction in lesion counts from baseline, or the actual lesion counts at baseline and at end of study.

In addition, there are some differences of opinion regarding the duration of studies for these acne products.

We find that sponsors are well aware of the fact that they need a large number of patients to show bioequivalence, and it appears as though sometimes the patients who are included are not severely enough affected to show a considerable effect size, and that really seems to result in some decrease in the ability to demonstrate bioequivalence with these products.

Also with topical acyclovir, which is indicated for treatment of recurrent genital herpes or limited life-threatening mucocutaneous herpes in an immunocompromised population, we've had a lot of difficulty in going back and forth with sponsors and our discussions with the primary

new drug review division about what is the appropriate study population and the appropriate endpoint for studying these products because herpes can be a very different disease when you're talking about genital herpes versus orofacial herpes and when you're talking about recurrent versus primary disease. It's important that we use a population for which the reference drug is effective in order to establish bioequivalence between the two formulations.

That basically is the end of my presentation. Does anybody have any specific questions on clinical endpoint studies?

DR. KIBBE: Does anybody have questions? Marvin?

DR. MEYER: Are there any ethical issues associated with a study population that's known to respond to, let's say, the innovator product, and then you're going to ask that patient to either take a product that may be as good -- hopefully is but may not be -- or a placebo which you know isn't going to work? So two-thirds of your patients are being switched to something that may not work as well.

DR. HIXON: Thanks for bringing that up. I did mean to add that in cases where a placebo treatment is not considered safe or ethical, that a placebo is not required.

But in a case where a placebo is not being used, it is very important that we have some justification for why that study is sensitive enough to show a difference between populations. In some cases, that's very straightforward. If it's a case where the placebo effect is very little, there's very little chance of spontaneous resolution, and the treatment effect is extensive, say, 70, 80, 90 percent, then we can feel more secure that we are, in fact, looking at a study that can show the difference between treatment products.

I haven't seen a situation where we've had ethical concerns about doing the trials without placebo, just comparing a test to a reference product. In cases where it's a life-threatening indication or a serious illness, we certainly have escape clauses where a patient who doesn't respond within a reasonable amount of time is excluded as a treatment failure and assigned to treatment with a known effective drug product.

I guess that goes back to what some of our endpoint problems are too because we find that the easiest endpoints to evaluate are those where we can have a clear-cut success or failure and look at the percentage of success or failure in the two different populations. But it can get a little more complicated when we're dealing with continuous variables as endpoints, and of course,

sometimes we have to do that.

DR. KIBBE: Lem?

DR. MOYE: If I understood you right, it sounds like there are fundamental problems with guidelines for the clinical studies here. Not only has consensus been reached on endpoints -- and you tell me if I'm wrong, but if I understood you right, there's been no consensus on effect size, confidence interval width, sample size, duration of follow-up. Is that correct?

DR. HIXON: I need to clarify here that we're not determining efficacy of the products so much as we're looking at bioequivalence of products. So these are comparative trials and we're looking at the difference in outcome between the test and the reference. The actual effectiveness of the product has already been demonstrated in the NDA for the approved product. So we have the same bioequivalence limits for clinical endpoint studies that we have for pharmacokinetic studies in that studies with dichotomous endpoints need to fall within plus or minus 20 percent as far as the difference between test and reference, and studies with variable endpoints fall between 80 percent and 125 percent.

Now, as far as our difference in study designs, certainly it's probably not appropriate for us to come up with one design and say that every generic company that

comes in has to follow that design to the T because what they really need to do is study that product for the approved indication and show that their drug is as effective as the reference product.

So, for instance, going back to the acyclovir situation, acyclovir could be studied either in immunocompromised patients with primary genital herpes or in the orofacial herpes in immunocompromised patients. As long as the effectiveness of one of those indications is the same between test and reference, we can assume that the effectiveness for the other indication would be the same. And there's no reason for us to require one of those study designs over the other.

DR. MOYE: Well, I'm glad to hear that because I wasn't suggesting that.

The tenor of your talk to me was that you were having problems with guidelines. In fact, even though -- and I would agree with you -- there should not be one and only one clinical trial design that's appropriate, there certainly is a family of designs that are appropriate and other designs that are inappropriate.

Let me ask you specifically. Are you comfortable with the family of designs that are appropriate?

DR. HIXON: Yes. In fact, for any given

product, we look back at what has been done in the NDA trials and also what has previously been accepted for ANDAs.

I guess I'm not making myself clear in discussing that these are challenges. The challenges are when the very first generic drug comes in. It takes a tremendous amount of time and effort to go back over all of the information that has been provided to the agency about the NDA, what kinds of studies were done in the NDA, what is the labeling for the approved product, and what is the sponsor proposing to do. We generally consult with the new drug review divisions and come to a joint decision about whether the proposed study design is appropriate or not.

On the other hand, many sponsors come in and say what kind of a study do we have to do. They don't even go to the effort of proposing a specific study. Of course, it takes a tremendous amount of time and effort to come up with proposals for what they need to do.

DR. MOYE: Well, that to me doesn't sound like a problem that is specific and unique to your group. That to me sounds like a problem that's endemic across the FDA regardless of which class of drugs we're looking at. You have sponsors who come in who have a design that they think is appropriate and the FDA may disagree and have some discussion there, and a half hour later, here comes a

sponsor who has an open heart and is willing to do whatever the FDA says they want done.

DR. HIXON: The issue here is that we're talking about generic formulations and the requirement for generic formulations is not to establish safety and efficacy de novo. The requirement is to establish bioequivalence, and it puts a tremendous burden on sponsors, as well as the FDA, to design and conduct bioequivalence trials with clinical endpoints that may require hundreds of patients and may require weeks of treatment of those patients in order to get their answer as to whether their drug is bioequivalent to the comparator. I think our whole purpose is to talk about what other options are there to try to get around such complicated study designs and such a complicated way to show bioequivalence.

DR. MOYE: But still keep rigorous methodology and be able to draw conclusions that are confirmatory.

DR. HIXON: Right.

DR. MOYE: Thank you.

DR. KIBBE: Ajaz?

DR. HUSSAIN: Just to sort of build on what Dena was discussing and the sort of challenges I see with respect to the clinical approach to bioequivalence is essentially one is the goal post she talked about. We are

applying a goal post of 80 to 125 that was essentially derived from the PK based comparative evaluation. Now, as we look at a clinical endpoint based comparison, I think one logical question is, is that an appropriate goal post that we need to consider?

At the same time, should that goal post be one-sided or two-sided? Because in cases where you have a product which shows just marginally higher efficacy in the confidence interval criteria, is there really a difference between the two products?

I think we run into a number of these questions on a daily basis because now you're comparing the equivalence of the two products, and what should the goal post be would be one way of looking at some the challenges that we face.

DR. KIBBE: Anybody else? Leon?

DR. SHARGEL: Actually, Ajaz, you raised the point that I was going to ask. Admittedly a clinical bioequivalence study -- in a sense you are looking at a clinical endpoint, though, on these. And because the variation is a lot greater than PK, and you're still sticking currently to the 90 percent confidence intervals of 80 to 125 percent, should that be reexamined in lieu of the variance?

And also an ethical issue. You're exposing a

lot more subjects in order to try to meet that 80 to 125 as you're trying to do that. And is that appropriate to do that?

DR. HIXON: We certainly are open to the idea that that may not necessarily be the most appropriate goal posts for bioequivalence, but we need data on innovator products and just what the degree of variability is in the innovator product in order to think about changing those goal posts.

DR. SHARGEL: Do you generally have a dose response on the innovator products that you can refer back to and give you some idea of that?

DR. HIXON: I'm not sure that dose response is what we need. I think we need more of the type of data that takes groups of patients who are randomized groups, both taking either the same lot or different lots or different batches of the RLD to see just what the variation is between those patients and whether we're actually requiring a tighter bioequivalence limit between the test and reference than what you would see within groups of patients taking only the reference product.

DR. SHARGEL: The reason why I ask in the Emax model you're at the dose which you can't see differences in the bioequivalence. This has been brought up to the agency before. It's nice to know whether we would be able to

predict differences in products.

DR. HIXON: An interesting point. I don't know that I have a comment to that.

DR. KIBBE: Anyone else, if we have a comment to that? Wolfgang.

DR. SADEE: If you have a bioequivalence confidence interval and you set that, well, it depends on the product. On some products it's important. If the method is such that you cannot measure it, because there's too much variability, then I would suggest that delivery through the skin is inappropriate. So there may be components that just absolutely have to be dosed exactly, and if you can't do it accurately, then it's inappropriate. On the other hand, there are others were it doesn't matter that much and then you can relax the criteria. But it should really be the drug and the conditions treated that should predicate as to what you determine there, and it should be flexible.

DR. KIBBE: An FDA comment?

DR. WILKIN: I was responding to the query on whether we have dose ranging information for innovator topicals, and I can tell you that we always encourage it. We think it is an important piece of drug development to find a dose -- I mean, it's both efficacy and safety we think of in the dose ranging. It turns out that that's

often one of the more anemic portions of the NDA when it's submitted.

If you look at the ICH document -- I think it's E4 -- on dose ranging, there's a major portion of that document that's devoted to phase IV dose ranging. So that tells you even on systemic products we're not always getting dose ranging information in the NDA.

So I'm not sure if OGD came over and went to our document room and started looking for this whether you would find it very often, especially on the older products.

I think that was one of the pieces that Dr. Hixon was talking about with Dr. Moye. One of our difficulties is the endpoints change over time. For a product to become a generic, that means it's off patent. So it may have been 10 years ago and it may have been the thinking of the FDA and the industry at that time what were the appropriate endpoints. Those endpoints may be different for the same indication or the indication may have been divided into two indications today. Things happen.

And so I think part of this extra work that she's describing her group does is to try to make a fair linkage with what was actually done for the innovator in the past and still bring it up to the things that you're talking about, making sure that it's a good quality trial

design that can be defended in 2003.

DR. KIBBE: Jurgen, we'll let you be last. How is that? And then we'll get on to the next speaker.

DR. VENITZ: It sounds good to me.

One question, one comment. The question is in your clinical bioequivalence studies, are they a parallel group design or crossover studies?

DR. HIXON: They're parallel designs.

DR. VENITZ: So you're using basically the 80 to 125 which is based on crossover PK studies as your target, your goal post, for parallel group designs. That's the reason why you end up with those large numbers.

So my general comment then -- and I anticipated that you were going to say it's a parallel group design -- just like Wolfgang said, I don't think there's any magic between the 80 and 125 even in the PK sense. I've been involved in those things for close to 20 years. I still haven't figured out who came up with 80 to 125.

(Laughter.)

DR. VENITZ: Now we're applying it in a level above the PK. Now we are applying it in the clinical endpoint studies. So I don't see any rationale why you shouldn't be able to flexibility use criteria that are more appropriate based on the endpoint that you have and what's considered to be clinical significance.

In addition, we have the argument that the 80 to 125 is definitely inappropriate because it really assumes that you have a crossover design. So you're looking at the variability within each subject not between two parallel tracks. So I think you've got a lot of good reasons to say that 80 to 125 percent is way too strict.

DR. KIBBE: You'll still be around and we'll be able to get additional questions, if we need to.

We need to get our last speaker up here. I'm determined to get done on time or else I'll be late. Go, Jon.

(Laughter.)

DR. WILKIN: I'll build on some of the topics that Dr. Conner and Dr. Hixon presented and describe this from a dermatologist's point of view.

As you know -- and many of you may actually have family members or people that you know who have chronic skin diseases like atopic dermatitis and psoriasis, and you know that dermatologic disease can be chronic, costly, and it's very common. So there's a huge market out there. Topical products are the mainstay for most of these dermatoses, and getting good quality generic topical products would lower the costs and increase the availability to patients. So I think everyone can agree that facilitating good quality generics to the market is

what everyone would really like to see.

Dr. Conner and Dr. Hixon have described some of the historical difficulties. 320.24(b)(4) says that for most topicals, we look at clinical endpoints.

They mentioned the clinical reports of lesser effectiveness. One of the additional things that comes out in the derm literature and you hear at the meetings is that a dermatologist can squirt the innovator in one hand and the generic in another hand, and they have a very different feel.

And then there's just ill will, bad press. I think there are a few examples that are probably valid examples, but then you see all these ads out there. They show a Starbuck's coffee and they say, would you drink generic coffee? Well, then why use generic topicals? And there's not much substance to them, but it's out there and I think it does affect how clinicians think of generic products.

Now, traditionally the focus has been limited to what everyone calls Q1 and Q2. Qualitative sameness. It's the same list of ingredients. Quantitative sameness, those ingredients are there in the same amounts as found in the innovator. But a noticeable difference in vehicle properties can also come from Q3, if you will, structural or the phasic differences. It depends on how one actually

manufactures a product that leads to the structural attributes.

And I'll give you sort of a very homespun example. I call it the law of Duncan Hines and Wilkin.

(Laughter.)

DR. WILKIN: If you ever go to the grocery store, you'll see, competing with Betty Crocker, these boxes of cake mix, chocolate cake mix. My wife is a cGMP cook. I'm not. So I had to learn that when it says you preheat the oven, that means you turn it on and you leave it on but you don't put the cake in until that red light goes out because that means it's actually heated up. So I have solved all of the wrong ways that you actually do this, although now I think I can do it right.

The point is that over time I have managed, using identical ingredients, using Q1 and Q2, identical starting properties, to end up with incredibly different structural creations.

(Laughter.)

DR. WILKIN: But one positive thing I can add is that even when it's really thin and really hard, if you soak it in milk for 30 minutes --

(Laughter.)

DR. WILKIN: So the point is that there are important vehicle attributes that also come from the

physical structure of these topical dermatologic products and just simply knowing Q1 and Q2 really does not predict all of those important properties.

And there's another complication. 314.94(a)(9)(v) in the Code of Federal Regulations tells us that even Q1 and Q2 are not essential for topical products. It's got those nice adverbs that Dr. Meyer pointed out earlier that FDA uses all the time. It says, generally they're the same. But it allows for the setting where they're not as long as the sponsor can demonstrate there's no change in safety.

So the manufacturing process is blinded to the generic manufacturer. That's proprietary information.

Even when Q1 and Q2 are identical, the product can still have different physical properties, depending on how it's been cooked. One example that Gordon Flynn gave years ago, when speaking to the FDA group, was using the same recipe, in the evening someone turned the cooling coil system off so that what was in the vat cooled to room temperature very slowly, and they got a very different type of product than when they used the cooling coils to chill it down rapidly. One was fairly viscous and the other was non-viscous. Just one simple step in manufacturing can make a substantial difference.

So thinking of all these different degrees of

freedom, it's helpful to think about those when we're thinking how do we actually facilitate the approval of generic topical dermatologic products. The question is, what do we need to know? What is the simplest information structure that has everything in there that's necessary but also sufficient and nothing in excess that would get us to generic approval? I call that regulatory elegance, that process of thinking through that.

I use the term "elegance" in the sense of the organic chemists who talk about the synthesis of an organic chemical in the fewest steps with the highest yield. That same term "elegance" is celebrated by the mathematicians if you have a mathematical proof that starts out with the fewest assumptions and it takes the fewest steps, and you can end up proving the thesis.

And I think we should embrace that at FDA, but I think it's the larger regulatory community. It's industry and it's academics and the professional societies. We need to look for regulatory elegance. It's the identification of the simplest information structure required for a regulatory decision. It wouldn't be the absence of regulatory creep that we're always accused of, adding new things that we want to know. And in truth, we're all information junkies, everyone. I mean, we'd like to know more about things, but we have to focus on what do

we really need to know because information costs money. So it's the opposite of regulatory creep. It's trying to find ways to thin out the parts that are not needed.

So demands focus on what I call the 3 R's of regulatory elegance. The first would be reduction. It's the number or extensiveness of required tests. Refinement would be the optimization of test design for max information at minimum cost. And replacement, which I think, if we're going to go for honors in approving these generic topicals, is where we really need to go. We need to replace. We need substitution of a simpler, cheaper, more informative test.

So how I see this in the paradigm of getting to the new generic topical dermatologic drugs, in the short term it's reduction and refinement. And Dr. Hixon described the acne studies and how difficult they are. I submit that you can actually look at a smaller number of subjects, bring them in at 9 weeks, 10 weeks, 11 weeks, 12 weeks, average their inflammatory lesion counts, average their non-inflammatory lesion counts over those different visits, and what you'll do is you'll take out intra-subject variability, and by doing so, you can dramatically increase the power. So I think there are ways that you can maximize information from a small number of subjects that can be more economical, and we've offered to participate with OGD

and think of ways for the more common products.

The long term is replacement, and it's development of alternative methods. I intended an "s" on the word "methods" because I don't think in the end there's going to be one method for all of the topical dermatologic classes. Antifungals. We may find at the end of the day that there is a role even for DPK, although I know it's been through the committee in the past and gotten a negative response. On the other hand, there are some other dermatologic conditions that clearly I think would need something other than DPK. So I think it's multiple methods that we need to think about, and we need to develop ways of guaranteeing the Q3 sameness, at least to the extent that the innovators have that consistent from batch to batch, from lot to lot.

Thinking about alternative methods, I'll not spend a lot of time on this because I recognize this group knows about the FDA and USP performance parameters for new methods. I think they're very nicely discussed in the USP chapter, but I did want to have them in my slides.

Next, in addition to the performance parameters of a new methodology, is the concept of validation of utility. I think the very first step is intra-laboratory reproducibility. Can the same investigator on different days run the same experiment and get the same result?

And then the second stage is can someone else in another lab take the written instructions for conducting this method and get the same kind of result.

And then the third step, which is really the highest hurdle, is demonstration of replaceability. That's replacing what we're currently doing.

Now, I would define as the controlled artifact stage that point in the development of an alternative method where there has been substantiation of those performance parameters that are outlined in the USP chapter that reproducibility has been found intra-laboratory and also between laboratories, and it's awaiting that final essential step of can it really truly replace what we're currently using which is the clinical trial or the corticosteroid multi-point, Stoughton-McKenzie blanching. That would be another one that could be considered.

So there is a group of folks that will be coming in over the next, I suppose, three or four years, and they'll be presenting their models. And I call them the Guild of Alternative Method Enthusiasts and Researchers. Incidentally, that contracts into GAMERs, if you want to look at the acronym.

(Laughter.)

DR. WILKIN: When they come in, they're often sold on the method at the controlled artifact stage.

Although Dr. Franz mentioned he's going to make money regardless of which method is chosen, many of them are going to make more money if their method is chosen. I think that's been somewhat offputting in the past, maybe a little bit more to the Dermatologic Advisory Committee than this committee.

But let me just encourage some tolerance here. This is the group that is actually going to do the brainstorming, the hard work in the lab, take some risks. If we're ever going to have an alternative method, we're going to learn it from this particular group. So the GAMERs ultimately are our friends.

But when they bring it to that controlled artifact stage, we still need the evidence of replaceability, and that's where this committee and others need to play a role in what I think of as the peer review process.

So the final step of validation is peer reviewed demonstration of replaceability. There are a lot more things that I could have put under here, but I have limited it to just two.

The first one is does this new alternative method actually make biological sense. I think one of the things that we had a good discussion with back for DPK is it was going to be used for skin diseases where there was

no healthy stratum corneum. In fact, many of the diseases had no remnants of stratum corneum, and yet the method relied on looking at healthy stratum corneum. So I think those are the kinds of things that you have to think about the first principles. Do they actually fit?

And then the second part is can the method reproducibly demonstrate equivalence between the innovator, the reference-listed drug, and a clinically demonstrated bioequivalent product so that we have the clinical data comparing the two.

Superiority or inferiority to a clinically demonstrated superior or inferior bioinequivalent product in an adequate, well-controlled, blinded comparative study with at least three arms. And I think it would be nice to know that it is sensitive enough to pick up differences, but it's also specific. It would be a horrible method if we accepted something that would actually pick up differences from one lot to the next for the innovator. I mean, we want to have something that doesn't narrow the goal posts too much but finds it to be just right. So, very helpful for the future.

I'll stop at that point.

DR. KIBBE: Who wants the first crack?

DR. MOYE: I have a question.

DR. KIBBE: Yes, please.

DR. MOYE: The GAMERs' laboratory is a wet lab or a dry lab? Are they actually doing experiments on physical entities, composite entities?

The reason I ask that is because there is new emphasis on the use of computing as a tool to carry out these kinds of research experiments to the point that there is a new institute at NIH which is involved in doing essentially simulation at the basic science level. Now, we might have thought that that was foolhardy 15 years ago, and it still may be. It's yet to be proven, but there have been important advances in computing technology that suggest that, to some degree, we can move from a 100 percent reliance on bench biology to a reliance on a hybrid system that has some real biology components and some mathematical components.

In the era where clinical trials now can cost hundreds of millions of dollars and there is now a trial being carried out that cost a quarter of a billion dollars, we are rapidly going to run out of resources to carry these things out. And in looking at alternatives, computing as a hybrid is turning into a very admissible approach.

I was wondering what your comments were on that.

DR. WILKIN: Well, I completely agree with you. I think we have to be very open to computer-based systems,

incredibly information-rich ways of looking at things.

But I can describe, I think, what most laboratories are doing today.

And it just occurred to me I'm probably going to regret the GAMER thing. We'll have to think of another name for them.

(Laughter.)

DR. WILKIN: But those folks who are the creative minds that get it to the controlled artifact stage.

Generally what they look at is they look at different concentrations in the same vehicle. We have to remember that ultimately the alternative methodology that we're thinking about, the ultimate utility is to let us know that you have two products with the same active at the same concentration and different vehicles. So it's really to tell us that the vehicles are the same, but most of the work that's done at that very early stage is looking at different concentrations in the same vehicle, which I think you would want to know anyway. You'd want to know that it's linear, it has a range that it's going to be able to detect, those sorts of things.

So it's, I would say, 99 percent wet in that context, but it's not so much looking at an innovator and a generic. It's really looking often at homemade material

that is of different concentrations. I think it's a good first step, though, really.

DR. MOYE: If I could follow up. I would encourage you, if you could contact your compatriots over at NIH, because they're grappling with this same issue, and they apparently have some very good mathematical formulations for underlying biologic processes, components of which may be useful for your group.

DR. WILKIN: Well, maybe they also have some money that can help fund some of these studies too.

(Laughter.)

DR. WILKIN: I see Ajaz writing all this down.

DR. KIBBE: Anyone else?

(No response.)

DR. KIBBE: Just a couple of chairman comments. I think Vince Lombardi would be happy to embrace the GAMERs. He believed that those who got into the fight, whether they won or lost, were better than those who stood on the sidelines and applauded. I appreciate the innovators and the entrepreneurs who try to come up with solutions. I recognize us and the agency need to take a careful look at those proposed solutions to see which ones really are useful for the public good. But I certainly do appreciate them coming to the plate.

I want to thank everybody for their

presentations. We will have a short break. During the short break, there is a --

DR. HUSSAIN: I was going to wrap up.

DR. KIBBE: Good.

DR. HUSSAIN: Well, actually I had dinner with Art last night, and his advice was, don't make any slides. And I'm following his advice. No slides. Right?

DR. KIBBE: This is an auspicious occasion where Ajaz has rigorously followed my advice.

(Laughter.)

DR. HUSSAIN: I think what we wanted to do was to present to you the challenges we face and then what are the next steps. In terms of the next steps, what we would like to do is to come back to this committee or the Biopharmaceutics Subcommittee to present a research plan and a research plan for moving forward with respect to methods for topical bioequivalence. The approach that we have in our mind right now is a tool box approach. One size or one method does not fit all situations.

So to take an example of the dermatopharmacokinetic, the skin stripping, studies, I think we have an opportunity for improving the protocol and applying it to a class of products where I think it would be very appropriate, for example, antifungals where the site of action is itself the stratum corneum. So I think

what we would like to do is bring a classification system forward where I think we can use a body of evidence of different methods and different techniques to address a number of issues. Not all the products would be addressed this way, but I think it would be a starting point.

In addition, I think we'd like to open the discussion on the goal posts. How should we approach the goal posts with respect to topical products? And I think I totally agree with Dr. Sadee that I think it has to be based on the underlying risks, underlying mechanisms, and so forth. So how do we approach, how do we come up with a decision tree to say how do we decide what is an appropriate goal post for this? Should it be a one-sided, noninferiority sort of thing? Or what should it be? So that would be another aspect.

Dr. Wilkin essentially has added Q3. Let me go back and explain that concept. For example, if we have a gel -- and now, I'm defining a gel as a solution with a 3D structure because of the hydrocolloids. A generic has to be Q1 and Q2. What does that mean? It has to have the same ingredients, water, the same hydrocolloids, and Q2, quantitatively it has to be the same, that is, within plus/minus 5 percent of the excipient.

Now, with that, if you're really looking at it, in my mind from a pharmaceutics perspective, bioequivalence

is self-evident. You really have to go back and think of that. But that's not defendable right now, and I think we have to defend that position. What is the driving force there? It's the thermodynamic activity. And if you start arguing from there, I think the Q3 perspective Dr. Wilkin has brought on the table is the physics of that dosage form, and I think that has been missing. He created a wonderful opportunity for PAT in this area.

But I think with respect to understanding the rheological behavior and the physico-chemical attributes of the dosage form, I think we can provide a high degree of evidence to say that bioequivalence will be self-evident. And we would like to start proposing a research program to address, in a step-by-step manner, how do we get there.

We are fortunate. I think we do have funding available for this research program now, and I think we will not only think about different clinical studies but at the same time manufacture products ourselves. And I think we did not have that opportunity before. I think we will have that opportunity.

So I would like to stop here. I'll let you know that when we come back this is the research plan that we'll outline for you and seek your input in discussions on how do we take the next steps.

DR. KIBBE: We stand adjourned for 15 minutes

until 3:30.

(Recess.)

DR. KIBBE: Our break is over.

We're down to our last two presenters for the day. I want to congratulate everyone on their energy and their involvement. I am really looking forward to these last two presenters getting us started on another pathway for the agency. My colleague Marv is dragging along behind, but we won't wait for him.

Nancy Sager.

MS. SAGER: Good afternoon. I know it's been a long day, so I hope this will keep your interest until dinnertime or close to it.

I'm presenting the introduction to comparability protocols, and I will be followed by Dr. Stephen Moore who will give you some more details on the protocols. I'm going to cover what is a comparability protocol, why has FDA issued a guidance on comparability protocols, what are the benefits of using a comparability protocol, and what is the purpose in making the advisory committee aware of this guidance. Then I'm going to turn it over to Dr. Moore who will follow with some more details on comparability protocols.

A comparability protocol is specified in our guidance as a well-defined, detailed, written plan for

assessing the effect of specific postapproval chemistry, manufacturing, and controls changes on the identity, strength, quality, purity, and potency of a specific drug product. This plan is supposed to be designed for future anticipated chemistry changes. And the protocol would be able to be submitted as part of the original NDA or ANDA application or it could be submitted as a postapproval supplement in a prior approval supplement and request approval at that time.

Why did we develop a guidance? The concept for comparability protocols was first introduced for biotechnology products in 1997 as part of the regulation writing process. It was a way of introducing a procedure for companies to come in and provide plan for these changes in complex materials. We had gotten a lot of requests from industry to extend this concept to all drugs, the synthesized chemicals and other things other than biotech products, and we had gotten requests for additional guidance, what should be in a comparability protocol. So we in the Center for Drugs just published a guidance that details what we would expect in a comparability protocol, the basic elements, and Steve is going to talk about that in more detail.

Why did we develop it? As I said, we wanted to provide recommendations to applicants on developing a

protocol to assess the effect and give more specific details.

Again, this is one part of a bigger plan in developing risk-based approaches to the CMC process at FDA. A well-planned protocol can provide FDA with sufficient information for FDA to determine whether the potential for an adverse effect on the product can be adequately evaluated and whether that risk is lowered so an applicant could report their change in a lower reporting category, which I'm going to talk about in a little bit more detail in a couple of slides.

One of the questions that we often get is why do we have to wait for FDA approval. We've done the studies. The studies turned out good. Why can't we just implement the change without FDA approval? One of the reasons we ask for FDA approval on the most complex chemistry changes is that we need to assure that the right studies were done and that the study results were interpreted in a way that we would draw the same conclusion from the same results.

Another aspect of the comparability protocol is it augments the Scale-Up and Post-Approval Changes, the SUPAC guidance and the Changes to an Approved NDA and ANDA Guidance. For those who aren't familiar with these two guidances, Changes to an Approved NDA and ANDA Guidance is

a general guidance that specifies reporting categories for certain postapproval chemistry changes. The SUPAC guidances are dosage form-specific. We have a SUPAC Immediate Release Solid Oral Dosage Form, Modified Release Solid Oral Dosage Form, and a Nonsterile Semi-solids SUPAC Guidance. These actually are very detailed guidances recommending for specific changes what data should be provided in the reporting categories. By specifying these up front, it allows for -- a lower reporting category to FDA means they can implement the change faster than if they didn't follow this guidance. If a change wasn't done under one of these guidances.

It's also consistent with and complementary to FDA initiatives on pharmaceutical cGMPs for the 21st century, which I think you're going to hear about more tomorrow. I think it's on tomorrow's agenda. This will help promote continual process and product improvement and innovation by facilitating CMC changes.

As I said, I was going to talk a little bit more about the reporting categories or reporting mechanisms for postapproval chemistry changes. One of the benefits of using a comparability protocol approach is that if an up-front protocol is agreed upon, the applicant can propose a lower reporting category than FDA would recommend if there was not a protocol that had been reviewed by FDA, if they

just came in on their own without consulting with the agency ahead of time.

The statute specifies four different reporting categories: prior approval supplement, which means you can't implement and sell your product using this chemistry change, whether it's a manufacturing, chemistry, or control change, until FDA approves the supplement.

Changes being effected in 30 days and changes being effected supplement still require FDA approval, but these both allow a company to distribute product at their own risk prior to FDA approval. If it's a CBE-30 supplement, it requires the applicant to wait 30 days after they submit the supplement to FDA before they can distribute the product. The changes being effected supplement means as soon as it's submitted to the FDA, they can start distributing the product.

An annual report is our lowest reporting category, and these changes that are annual reportable can be implemented immediately, and they're reported once a year in a cumulative report to us.

So, first of all, a company can get a reduced reporting category with an approved comparability protocol.

The second important benefit is that an FDA request for additional information to support a change is less likely when the change is covered under an approved

protocol. We've reviewed the protocol. We've reviewed the tests and procedures you're going to be using. There should not be a need for additional information requests unless there's some change in the science or technology that maybe warrants additional questions.

The third benefit is that it could allow an applicant to implement CMC changes and place product in distribution sooner than without the use of a comparability protocol. If the reporting category is lowered, then they may not have to wait for FDA approval before they can start distributing their drug.

It also allows companies to design their own SUPAC based on their knowledge of and experience with a product. We have three SUPAC guidances that we mentioned before. It's unlikely that we're going to write many more SUPAC guidances dosage form-specific because there are so many kinds of dosage forms, and they take a lot of resources to write. There are only a handful of products maybe in a certain dosage form class. The immediate release and modified release solid oral dosage forms probably covers about 50 percent of our applications in the FDA, but for things like liposomes and these more unusual dosage forms, it's unlikely that we'll ever write a SUPAC to cover a very narrow class of dosage forms. So this allows a company to kind of design their own SUPAC based on

their development information, their knowledge and experience with the product.

It also allows again the reduced reporting category for a product that isn't covered by a SUPAC guidance or another type of guidance.

So what's the advisory committee's role? At this time, CDER has little experience with comparability protocols. We've accepted protocols in the past typically for packaging changes, changing resins and things like that. As Steve will explain, these comparability protocols are almost wide open for use as far as what kind of changes might be covered under them. There are a few limitations that Steve will describe, but they're really expanding into areas that we have not reviewed protocols in in the past. So we may at some point ask the advisory committee to comment on issues raised by the public comments on the guidance or perhaps even specific proposals for a comparability protocol, asking for their scientific opinions on the aspects of a protocol.

Just to wrap up my part of the presentation, as I said, the guidance published on February 25th and it's open for public comment until June 25th. I've included the web address for those who are interested in getting a copy.

Now I'll turn it over to Dr. Moore.

DR. MOORE: Thank you. Nancy has given a very

nice overview of the comparability protocols.

I want to speak now on more of the specifics associated with actually using the comparability protocol and the content of some of the guidance that's out there as a draft on the web.

Some of the specifics I want to cover: When might a comparability protocol be useful for a CMC change, what are the various product-specific and process-specific considerations one might have I think to do a comparability protocol? When might a comparability protocol be inappropriate? And what are the basic elements of a comparability protocol, and what are some of the specific issues to be considered for comparability protocols for various types of CMC changes?

First of all, to address when might a comparability protocol be useful for a CMC change. As Nancy mentioned, comparability protocols are applicable to a wide variety of CMC changes. There are some exceptions as she also mentioned. I'll go into that just a little bit later. The comparability protocols can apply to many of the kinds of changes that are described in our SUPAC and BACPAC and changes to approved NDA and ANDA guidances, as Nancy was mentioning.

For example, comparability protocols are not meant to supersede those guidances, but really to add on to

those guidances. One example is that you could take a SUPAC level 2 change for an immediate release tablet such as scale-up, and that would be a CBE type of change, or the category for reporting that change will be CBE. One could use a comparability protocol and provide the specifics for that particular drug and that particular process and be able to get a reduction of that particular change down to an annual report.

Comparability protocols could also cover many types of changes that are not described in any of our guidances. For example, the BACPAC guidance specifically excludes changes to products that are derived from natural sources or products that are derived from biotechnology, and the guidance we're talking about here would, in fact, cover changes you could make to products that are derived from biological sources, for example, conjugated estrogens; for example, synthetic peptides. One might think that this might even be the most usefulness of the comparability protocol to fill in all those areas where we really don't have any guidance.

Continuing some more with some ideas about when a protocol might be useful. They're useful for single or it could be multiple changes. Hopefully those changes would be related changes, the same kind of changes that one might submit in an ordinary CMC supplement, and each of

these changes being discrete and specific. This is not a deviation from the way we are reviewing supplements in general now.

Changes of a repetitive nature might be particularly useful because one would have a single document where you have the comparability protocol described, and then maybe multiple supplements could come from that in actually implementing changes of a like nature.

But the bottom line is you really have to specify up front what are going to be the tests and the studies and the analytical procedures, and most importantly, the acceptance criteria for demonstrating that the CMC changes will not adversely affect the product, that is, with respect to its identity, its strength, its quality, purity, and potency, as these factors may relate to the safety and efficacy.

Turning to some of the product-specific and process-specific considerations one might go through in determining whether a comparability protocol would be useful or would be applicable, consider first the complexity of the product structure. That is associated with really the ability that we would have with the analytical techniques that we have to characterize the chemical, physical, microbiological, and biological

properties of the product. For example, routine testing in the simplest case and inclusion of stability studies. But in other cases where the change becomes more complex and there may be a propensity of the change to actually change the structure of the drug itself, then one would need to go in to do characterization studies too.

Also a consideration to the degree to which the differences in the product structure and the physical properties can be detected by these analytical techniques.

And the degree of product heterogeneity, if present. This doesn't apply that much to purified, synthetic chemicals, but it would apply in many cases to products that are derived or purified from biological sources.

And what is the effect on safety of changes in the impurities? Changing the process may generate different impurities or the purification process change may exclude impurities or cause other impurities to flow through into the final product. So that's a consideration one has to make on safety.

Some more product and process considerations are the robustness of the product, the ability of the product to remain unaffected by the changes, and the rigorousness of the manufacturing process. That means the ability of the process controls to ensure that the product

remains unaffected by changes.

Of course, one is expected to meet the approved drug substance and/or drug product specifications after a change. This is not much different than the way we view supplemental changes without a comparability protocol being involved.

And of course, one has to have in place appropriate and sensitive analytical procedures. These have to be established and validated or qualified in the case of characterization type analytical procedures in order to detect the effect of the change on the product.

I now turn to when a comparability protocol might be inappropriate or not useful. Comparability protocols have to be specific and discrete, so protocols that are very broad and for nonspecific plans are not going to be very useful.

A change whose adverse effect on the product that cannot be definitively evaluated by the prespecified tests, studies, analytical procedures, and acceptance criteria also would not be very appropriate.

One has to think about this with respect to the particular product and the process that you're dealing with. Will the analytical procedures be able to detect changes? The question comes into play if the product is very complex. Like some of the natural products that we

have are extremely complex. One then questions whether even the high-powered analytical techniques that we have that are state-of-the-art would be able to detect the changes.

Any change that warrants a submission of a new IND or a new original application also. I might also mention changes that a comparability protocol would try to substitute for information that's required to be in an NDA for our review and approval would not be appropriate.

A change that requires efficacy, safety, that being either clinical or nonclinical data, or PK/PD data to evaluate the effect of the change. For example, certain formulation changes, clinical or nonclinical studies to qualify new impurities. What we're talking about in this last bullet is changes that go beyond just a CMC-only type of change. They start to become multi-disciplinary changes where medical staff, pharm-tox staff are involved, for example.

Other examples that may be difficult to justify. Changes in the drug substance or drug product specifications. There are exceptions here such as adding a test or changing the specification to accommodate a change in the analytical method itself without actually causing a decrease in the product quality.

A change in the qualitative or quantitative

formulation of the drug product, and there are exceptions here. If you have the data and are able to have a sufficient knowledge and understanding of the product, you may be able to make changes in the excipients which may be under a level 3 change in SUPAC, et cetera, and be able to reduce that to a lower reporting category.

A change in the type of delivery system, of course, is going to be difficult because it's so complex, the interplay between the device and delivery of the drug.

Also, changes from plant, animal, or multicellular source to a different source are the kinds of things that are very complex changes likely to ensue new impurities which then will have to be qualified under pharm-tox.

Some additional examples that may be difficult to justify under a comparability protocol. A change in the synthesis from naturally sourced material to synthesis chemically or vice versa.

For synthetic peptides, a change from solid phase to liquid phase.

And lastly, a bullet about changes in manufacturing site if you change the manufacturing site, a facility, or the area when a prior approval supplement is normally recommended because a cGMP inspection is warranted. This is going to be difficult to do under a

comparability protocol because we would not be able to certify or agree that we would be able to do cGMP inspection that would be required and get that done before a minimum of 30 days, which is what a CBE-30 has as a cutoff, to the point which you can then distribute the product.

Going now on to some of the basic elements that are in a comparability protocol. This is what would be in a protocol that you would submit. It would include, of course, a description of the planned changes, the specific tests and studies and the analytical procedures and the acceptance criteria, which is part of the definition of a comparability protocol, and then what data would be reported or included with the comparability protocol. Sometimes there may be some developmental data which will help in showing that the protocol is in fact feasible and workable and up front there be data to support that.

And then the proposed reporting category, which is a matter of agreement between the industry and the FDA what is going to be the final reporting category for the follow-up supplement that will verify that the change actually had not an adverse effect on the product.

And an action which would be taken if equivalence is not demonstrated. This is a contingency. There are going to be some changes in which things are not

going to turn out as planned. So it would be good to have a contingency in the protocol what's going to happen at that point.

And then also a commitment that the protocol will be updated if it becomes out of date.

Specific issues to be considered when you have different types of changes. For example, here we're talking about for manufacturing process changes. Some of the considerations one might go into are effect on the physical characteristics, the effect on impurity profile, downstream process, and effect on the in-process controls.

For analytical procedural changes, effect on the characteristics used in the methods validation.

For changes to manufacturing equipment, some examples there, effect on the manufacturing process of changing that equipment.

And manufacturing facilities, for example, as I just mentioned, the cGMP inspection status and scope of the changes involved because in many cases when you're changing the facility, you're also in many cases scaling up and changing the process to make it more efficient. So the scope of some of these kind of changes is very large when you're talking about going to a new manufacturing facility.

Also container closure systems. This is one of the examples where repetitive changes may be particularly

useful, changing the container closure systems based on a comparability protocol.

And then there's process analytical technology, of course. Right now we haven't got guidance out, so we recommend early dialogue with the agency, and that's highly encouraged.

Then there are changes of a comparability protocol that's covered under a DMF. The issue there is the cross-reference to the comparability protocol.

I'll just summarize what Nancy and I have both said. Comparability protocols allow FDA and industry to agree early on about the specified CMC changes, the plan for assessing the effect of these changes, and the reporting category which will be made.

We hope that they will have savings in time of implementation of the changes and savings in resources for many of the changes.

This is a new regulatory mechanism. Therefore, industry and FDA are experiencing a learning curve. We have had quite a few comparability protocols that we've reviewed for biotechnology products, but we have very little experience for chemical drug products.

This guidance is hoped to stimulate interest in the use of comparability protocols.

DR. KIBBE: Questions, anyone? Efraim?

DR. SHEK: Just maybe a point of clarification. Reading the proposal, it's being envisioned that the sponsor will submit it at the time of filing an application or it can be submitted at any time?

DR. MOORE: A comparability protocol can be submitted in a new NDA or it can be submitted as a supplement postapproval.

DR. SHEK: Okay. So if it's being submitted as a supplement, that would be the time, right, for approval of their comparability? That would be like any other supplement?

DR. MOORE: The supplement has, yes, four months prior approval due date.

DR. SHEK: And just the efficiency we are going to gain -- I would assume both the agency as well as the industry -- is just moving things faster. But if I understand what is proposed, it always will be moved only one level. Oh, it can be moved more than one level?

DR. MOORE: It can be moved more than one level under certain circumstances, yes.

DR. SHEK: Okay. So whenever there is the agreement on the comparability protocol, it depends on the protocol whether it moves one level or two levels. Because the way I read it, I thought it says you can move only one level.

DR. MOORE: That's the usual type of reduction, is one level.

DR. SHEK: Thanks.

DR. KIBBE: We've got two here. Go ahead.

DR. KORCZYNSKI: I think there's a major opportunity in industry for a process comparability protocol. What I'm referring to is that major expense, labor-intensive activities center around validation, and prospective validation is validating your process at the beginning. But then every 12 to 14 months after that, you go through periodic validation. In many cases, certain processes have become so well established that it's becoming basically rote. The information is collected. You still go through that labor-intensive activity.

I haven't thought through it all yet, but there seems to be a tie-in of PAT and comparability protocols in the sense that why couldn't one use concurrent validation, utilizing all the good data that one collects throughout that 12 or 14 months, and then by some defined protocol, say I've re-validated the system by this new collection of data or new analysis of data?

I think that really needs to be thought about and addressed. I think it's a real opportunity because the industry in many cases is going forward just rotely collecting this data at major expense when they could

utilize some other systems. I think it's an opportunity to tie PAT into that approach.

DR. KIBBE: Gary and then Ajaz.

DR. HOLLENBECK: Well, that's perfect. I think, first of all, I speak in favor of this idea. I think it's a wonderful idea to put in the hands of industry this kind prospective approach to making your own SUPAC, one of Ajaz's favorite things I think. So in a sense I think that is very encouraging.

I just wondering how the agency is going to handle this. Who reviews comparability protocols?

DR. MOORE: The comparability protocols are reviewed by the chemistry reviewers and is signed off by the chemistry team leader, the same as supplements are being reviewed as of now.

DR. HOLLENBECK: So you wouldn't anticipate simultaneously submitting a comparability protocol with your application would slow it down?

DR. MOORE: It is conceivable that it could if it caused us, of course, more effort in meeting the user fee goal date for the application, if there are one or more comparability protocols in the application. But if they are valid protocols and appropriate protocols, I see no reason why we couldn't --

DR. HOLLENBECK: I know that developing SUPACs

has been a major challenge, but you could be actually transferring that to a gazillion SUPACs, you know, one submitted with every product. One would hope that a process like, if good comparability protocols came out of it, that they could sort of rise to the top and become generally applied.

DR. HUSSAIN: There are sort of two parts. I think the proposal for looking at concurrent validation, process validation, and then the linking I think is an excellent topic for a Manufacturing Subcommittee discussion, and maybe we'll capture that and take that to that discussion. I think it's an excellent point.

The comparability protocol I think doesn't come close to what I think the make your own SUPAC concept essentially is. And I think if I go back to that concept, essentially that is the University of Maryland-FDA research model where you have a set of designed experiments which could be part of the development. See, I think we don't use all the know-how and knowledge that is present in the development reports. I think at some point we'll have to bring this committee to discuss how best to use all the available knowledge, and then say, here, for this particular formulation, a .2 percent or .3 percent magnesium stearate change had no impact, we have this data, but SUPAC says it's a level 2 change or a level 3 change.

Why don't we sort of use the available data to make those decisions? I think that's the next step in the discussion that we want to get into.

But I think going back to the question raised on will it slow down the new drug review process when it gets submitted, I don't think that should happen at all. In fact, I think that would be counter-productive to the whole situation.

So in many cases, I think these might be after approval. These protocols will be submitted in the postapproval sort of scenario.

MS. SAGER: Just to follow up on that issue, I don't think Steve was aware of this but I was at a meeting where we talked about comparability protocols and how to handle them as they were coming in. As Steve indicated, they would be assigned to the normal reviewer and team leader, but we are anticipating that we would have some kind of scientific rounds and discussions on the initial protocols coming in, trying to get consistency and standards.

There's certainly a good opportunity for kind of a lessons-learned exchange. We could blind protocols or we could issue some kind of guidance document on what are the problems we've seen in comparability protocols, trying to exchange information in a way that we can get everybody

on the same level playing field so they're not trying to do a comparability protocol and having the same deficiencies that we've seen in previous ones.

So we're both on a learning curve, and I think we're going to have to take this opportunity to find a way of communicating. If we get good protocols in, there is always a possibly of, like I say, communicating some kind of lessons learned in a document.

DR. KIBBE: Dr. Bloom?

DR. BLOOM: Yes. Maybe it's out of ignorance. Does the industry select which kind of supplement they should submit?

DR. MOORE: I'm sorry.

DR. BLOOM: I mean, can they submit like a PAS or a CBE-30?

DR. MOORE: The comparability protocol itself is a prior approval supplement in all cases unless it's also part of a new drug application.

DR. HOLLENBECK: I'll ask his question. We'll see if it's the same question. I think his question is who determines what filing has to be made by the industry? How would you decide one is supposed to come in as a CBE or a CBE-30 or an annual report?

DR. MOORE: You're talking about the follow-up submission at this point.

DR. HOLLENBECK: Yes.

DR. MOORE: If the comparability protocol itself is prior approval, then one has to make a proposal what is going to be the category for reporting that change. We have a lot of guidances out there. We have the SUPAC, the BACPAC, and the Changes to an Approved NDA and ANDA that talk about general types of changes and what are appropriate categories for those changes. That's a good starting point for gathering the information on what is the change by itself without a comparability protocol. That's the starting point. Is it a prior approval change? And then with a comparability protocol, you might be able to reduce it to a change that's being effected or a CBE-30 change.

DR. BLOOM: Let me ask another one. What if the company submits a CBE-30 and then the agency can change that?

DR. MOORE: Well, the category for reporting will be a part of the approval of the comparability protocol itself. So that will be agreed upon at the time that the comparability protocol is approved.

DR. KIBBE: Anybody else?

DR. SHARGEL: I think the idea is very good and allows a lot more flexibility for the industry.

I'm curious. Is this a requirement for those

manufacturers who are making more or less standard dosage forms? By that I mean usually solid oral dosage forms. And there are SUPAC guidances out there. Would there be a need to put in a comparability protocol if they followed the SUPAC at this point?

DR. MOORE: Well, comparability protocols are not required. They're an option. So if you can plan far enough ahead what specifically is going to be change -- and you have to factor in there's going to be a four-month review of the protocol itself, and then that's followed by gathering the data and then submitting the follow-up submission. If that time line is shorter on the basis of a comparability protocol, then it could be useful for that kind of change. But it's not required by any means.

DR. KIBBE: Anyone else?

DR. HUSSAIN: If I understood the question correctly, if I have a SUPAC change right now, which may be a prior approval supplement, I could use a comparability protocol to downgrade that reporting requirement.

DR. SHARGEL: That's one possibly or just report it as a SUPAC, since I've already done that. That was a question.

DR. KIBBE: Anyone else? Wrap-ups, thoughts? Kathleen, do you have something? Business announcements?

MS. REEDY: A couple of things. Those purple

folders in front of you are for both days, so please leave them at the table in front of your seat, and they will be there for you in the morning, along with the slides for tomorrow.

The second thing is please leave your name tag with the colored stripe across the top, and it will be at the table by the x-ray machine in the morning and you will not have to pick up an orange one, but you will pick up the one with your name on it. And that will be your badge to stay here.

DR. KIBBE: Seeing no one else looking to discuss real business, I guess we are adjourned.

(Whereupon, at 4:07 p.m., the committee was recessed, to reconvene at 8:30 a.m., Thursday, March 13, 2003.)