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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

OPEN MEETING

Thursday, September 23, 1999

8:35 a.m.

CDER Advisory Committee Conference Room
Food and Drug Administration
5630 Fishers Lane
Rockville, Maryland

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STEPHEN R. BYRN, PH.D., Presiding

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MARY J. BERG, PHARM.D.

JOHN DOULL, M.D., PH.D.

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Consumer Representative

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Executive Secretary

C O N T E N T S

P R O C E E D I N G S

CALL TO ORDER/CONFLICT OF INTEREST

DR. BYRN: Okay, good morning everyone. I'd like to welcome you to the Advisory Committee for Pharmaceutical Science meeting, September 23 and 24.

Kimberly is going to read the conflict of interest statement.

MS. TOPPER: The following announcement addresses a conflict of interest with regard to this meeting and is made as part of the record to preclude even the appearance of such at this meeting. In accordance with 18 U.S.C. 208, general matters limited waivers have been granted to all committee participants who have interests in companies or organizations which could be affected by the subcommittee's discussion. They gave me the wrong date. Excuse me. I'll start again.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made as part of the record to preclude even the appearance of such at this meeting. Based on a submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of

conflict of interest at this meeting, with the following exceptions.

Since the issues to be discussed by the committee at this meeting will not have a unique impact on any particular firm or product but rather, may have widespread implications with respect to an entire class of products, in accordance with 18 U.S.C. 208(b), each participant has been granted a waiver which permits him to participate in today's discussion. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

Some administrative issues. These are new microphones. Most of our committee members have never used them before. You touch the dot, the red light will come on.

That means they're active. Everything you say will go over the speaker system. You just touch it again and it will go off. Please speak directly into the microphones. You can bend the mike down toward your face and it'll pick up. We need an accurate transcript of this meeting. Thank you.

DR. BYRN: The next order of business is to introduce the Pharmaceutical Science Advisory Committee. We have several new members and we'd like to welcome you to this committee. You'll find it's interesting and enjoyable, also. I think it's enjoyable, anyway.

We'll start with Vince. This is also a practice for use of the microphone.

DR. LEE: Why me first?

Vince Lee from the University of Southern California, Department of Pharmaceutical Sciences.

DR. BOEHLERT: I'm Judy Boehlert and I have my own consulting firm for the pharmaceutical industry.

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

DR. BERG: Mary Berg, University of Iowa College of Pharmacy.

DR. GOLDBERG: Arthur Goldberg, pharmaceutical consultant.

DR. BRANCH: Bob Branch, University of Pittsburgh.

DR. LAMBORN: Kathleen Lamborn, University of

California, San Francisco.

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

DR. PATNAIK: Rabby Patnaik, FDA.

DR. CHEN: Mei-Ling Chen, FDA.

DR. BYRN: And then I'll introduce Roger or Roger doesn't need an introduction but he's going to introduce himself and his two committees.

DR. WILLIAMS: Now did you want me to go into my talk now, Steve? I'm going to introduce them in the course of my talk.

DR. BYRN: Okay, that's fine. Roger will go ahead and begin with his overview presentation.

AVERAGE AND INDIVIDUAL BE CRITERIA

TO COMPARE BE MEASURES INTRODUCTION

DR. WILLIAMS: Thank you very much, Steve. I think we decided to allow first names.

In the next 30 minutes I'll be giving an overview of the first topic of this two-day meeting. I'd like to thank you all for coming and especially thank the committee for taking time to give us very valuable comments and conclusions and their expertise in some very exciting topics.

This particular committee has been in existence for about nine years. It started as the Generic Drugs

Advisory Committee in the heat of the generic scandal in the early part of this decade when I came to the center in 1993. Thereafter it was elevated to an Advisory Committee for Pharmaceutical Science. It's a very interesting advisory committee that generally deals with science and technical topics without focussing on specific drug approvals.

So I do thank the committee for giving us their time for some of the very interesting topics that will be discussed in the next two days.

I do see this as a critical committee meeting and in some ways a culminating meeting for topics in the area of bioavailability-bioequivalence that we have talked about over many years. We have made rapid progress, if you think of decade as a rapid period of time on many areas in the realm of bioavailability-bioequivalence, focussing, I think, on the how-to of measuring bioavailability and establishing bioequivalence. And these are in accord with our 21 CFR 320 regulations that came into being in 1977.

Now you all should have an agenda for the meeting. It's a three-page document. In the course of this two-day meeting you will see some very innovative uses of the advisory committee process here at FDA.

First of all, you see before you a meeting of the advisory committee itself. Tomorrow afternoon you will see a meeting of a subcommittee of the advisory committee that

will be led by Dr. Jim MacGregor. And then in association with the work of the advisory committee, you will see two expert panels.

Now first of all, I have to say I think we've pushed the utilization of these committees and panels about as far as they can go. And second of all, I would like to thank at the start FDA's advisors and consultant staff which is in CDER and in particular, Kimberly Topper, who's sitting there helping me with the overheads. Kimberly keeps us on track and on target.

Now I'm going to move into the agenda for the first day. What you will see as you look at the agenda is a series of presentations this morning that will deal with the concept of criteria for comparisons. And the focus here, of course, is on bioequivalence comparisons. And I don't have to tell you what a critical comparison that is for market access in the United States.

For generic substitution, we have to document bioequivalence, as well as pharmaceutical equivalence. But bioequivalence also attrudes itself in other ways that I'll talk about in the course of the meeting.

In the afternoon you will see a series of discussion topics for the advisory committee and I will introduce each discussion topic and then turn it back to the chair, of course, Steve, to lead the committee's discussion

of each topic. We look forward very much to the considerations of the committee for these six areas of focus on the first day.

I won't say anything about the second day except to note, if you could just show it briefly, Kimberly, you will see in the morning clinical pharmacology topics in the first part and the leader for that will be Dr. Larry Lesko, who is with us today and, of course, will be leading the discussion tomorrow. And then in the afternoon, as I said, you will see a discussion of a research subcommittee of the advisory committee that will be led by Dr. Jim MacGregor.

Now turning toward the topic for this morning, I will say that the Center for Drug Evaluation, which is where the agency people work for the meeting today, has formed a series of coordinating committees and you can see that there are quite a lot of them now and many of them are busily working on policies that provide recommendations to pharmaceutical sponsors on the information needed to satisfy our statute and regulations.

We have them in the areas of efficacy, safety and quality, and the quality ones are over on the right. And the particular one that I draw your attention to is the Biopharmaceutics Coordinating Committee, which focusses on bioavailability and bioequivalence topics.

In the course of future meetings, topics from

other coordinating committees in this picture may be presented and discussed, and that will happen, as a matter of fact, tomorrow when you see a discussion of clinical pharmacology topics led by Dr. Lesko, which are developed in association with the Medical Policy Coordinating Committee.

Now the Biopharmaceutics Coordinating Committee is working on eight core documents. I see these as how-to documents. And, as I say, they relate very clearly and very intimately to the 1977 bioavailability-bioequivalence regulations that were passed by the agency.

The two documents that we're going to focus on today are the first one, Bioavailability Bioequivalence Studies for Orally Administered Drug Products. You'll hear more about the specifics of that guidance from Dr. Vinod Shah in the course of the morning. And down at the bottom you will hear also in the course of the morning presented by Dr. Mei-Ling Chen an associated guidance that speaks to Criteria for Comparison: Average Population and Individual Approaches to Establishing Bioequivalence.

I will say that, speaking generally, sometimes the center is asked to show difference. A lot of times the center is asked to document sameness and I've always found that science and technical challenges associated with documenting sameness is quite remarkable. And we will be discussing that documentation in the course of the morning.

Now if I show you how these guidances stand in relation to one another, they do have a logic to them where we have a general guidance that focusses now on oral; we may incorporate transdermals in that. We have a Biopharmaceutic Classification System Guidance and a Food Effects Guidance that are in the works and it relates to the general guidance.

The next three guidances are for locally acting drug products. These tend to cause us special problems because we can't rely on systemic exposure measures, such as AUC and Cmax to document bioequivalence, and these guidances have been discussed before this committee and other committees in the center on many occasions. And I have a feeling they will be discussed again.

Down at the bottom we have two methodologic guidances. One is the Criteria Guidance that I already spoke to and the other is a Bioanalytical Methods Guidance that we hope will be finalized in the year 2000.

Now all those guidances to the left focussed in the preapproval period; in other words, how do you achieve market access in the documentation of bioavailability-bioequivalence? On the right you see a series of postapproval documents that provide how-to instructions on what kind of information and filing requirements are needed by the agency in the presence of specified postapproval

changes. And you all know the SUPAC story, which again has been discussed before this advisory committee on many occasions.

Now I will draw the committee's attention to a summary statement that occurred in February 1993. It is now six and a half years later. A lot of work, a lot of discussion have proceeded since that period of time six and a half years ago. And if you read this, and I do encourage the committee to read it, these were your predecessors speaking to us in that time period and I think many of those predecessors are here in the room today--Dr. Benet, for example.

And I think it was a very wise set of recommendations to the agency and we have diligently and with great effort, working collaboratively with many of you, worked to achieve understanding of some of the recommendations of the committee.

And I will draw your attention to the red box where it says "Encouraged the office to develop clinical trial designs and statistical procedures to assess individual bioequivalence." We have done that. I will not say by any means that the work is completed but in the course of the morning you will see six and a half years further effort that speaks to the recommendations that were given to us by this committee in its prior incarnation in

1993.

Now I want to speak to the point of bioavailability and bioequivalence. I hope this slide isn't too complicated. But the reality is that we establish bioavailability and we document bioequivalence--something like that. We measure bioavailability and we establish bioequivalence.

Bioavailability is something that occurs for a pioneer product in the IND period and information on bioavailability is submitted in NDAs. Bioequivalence is something that occurs, as I said previously, frequently in the course of both the pioneer and generic product. For example, questions of bioequivalence might arise as you go from pivotal clinical trial material to the to-be-marketed dose form.

Bioequivalence certainly arises as a stipulation of Hatch-Waxman for a generic product. And in the coupling with pharmaceutical equivalence, the dual documentation allows the agency to conclude therapeutic equivalence and market access.

In the presence of postapproval change for both pioneers and generics, sometimes the need to redocument bioequivalence arises. And examples of that need are specifically shown in the SUPAC documents that I already alluded to.

Now this is a very complicated picture and I think we should relish the complication. I actually think it's a beautiful regulatory system we have and a remarkable set of science and technical approaches that we use to achieve this regulatory system.

Now with that brief introduction, I'd like to turn to something else. I think as I speak now in the next few minutes I'd like to speak directly to the advisory committee but I'd also like to speak beyond the advisory committee to the roomful of people here and also to people who are in this country because I would say what we are doing when we talk about our topic this morning is we are talking about risk assessment, risk management and risk communication.

And you may all be aware that the agency in the last several months has put out a very important document on risk assessment, risk management and risk communication and I would say it's a core issue, what we will be discussing today.

Now what I would like to say is I would like to speak to one challenge we have received on the concept of the individual bioequivalence criterion, which I'm sure you all know, which is that it's not interpretable. It's very hard to understand. And I would like to counter that argument now and I would like to say not only is it fully comprehensible; I actually think it's comprehensible to the

American public.

And I would like to give you a few minutes to try an experiment where I try to explain it not necessarily to the committee, not necessarily to the roomful of experts who we have with us today but the people out there. So if you give me a few minutes here I'm going to try this experiment. Maybe at the end of the day the committee can give me a grade.

Now as we begin I'm going to show what I always show, which are the Sheinerian questions--I give Lewis credit for this. What do we want to know? What are we willing to assume, rely on? How sure do we want to be? And when do we ask the question?

Now I've already talked on the issue of when do we ask the question--pivotal, to-be-marketed, generic, postapproval change.

What do we want to know is bioavailability and bioequivalence. That's the question. And what are we willing to assume and rely on? Now that is a very interesting question and, as you know, we have many modalities to assess bioavailability and bioequivalence. Of course, the most common are the system exposure measures, AUC and Cmax, but we also have pharmacodynamic in vitro comparative clinical trials that we can use to document bioavailability and bioequivalence.

How sure do we want to be I think is the core question that we'll be discussing in the course of the morning and the rest of the day.

So I think you can see that in terms of what we do, it relates very clearly to Lewis's questions and I will argue in the course of the rest of the meeting that it also relates very clearly to clinical pharmacology and safety and efficacy questions, as well.

Now I'd like to start this discussion with a picture that I show frequently, which I think refers very closely to what we do here at the agency. And if you'll allow me to start here with an active moiety in a drug product that is administered to patients by some route of administration which creates an exposure pattern either expressed in terms of dose or systemic exposure and then, in turn, produces a clinical response either in terms of efficacy or toxicity.

And I will argue that perhaps most of what my center does could be expressed in terms of this graphic.

When we get into the world of the chemist, and Dr. Byrn, of course, Steve is an expert chemist, we will talk about some of these topics before the committee. This committee has frequently talked about this topic. Tomorrow morning it will talk about the clinical pharmacology topic and Dr. MacGregor will also lead into a safety and efficacy

topic that I think focusses on this part of the loop.

Now I show this graphic because I would like to lead right away into the topics of goalposts. Now goalposts are an important aspect of what we do and I think they relate to regulatory standards.

The reality is regulatory standards is sort of what the agency does. A lot of people do a lot of other things but, as I always say to people in my center that I work with, it's what we get the big bucks for.

Regulatory standards and market access are what our Congress has given us with the power of the pen. And I'd like to talk about now the goalposts relative to this picture that will lead into the explanation that I'm about to provide to the American public.

Somehow we have an understanding of optimal dose and therapeutic window. And I would now like to talk about that therapeutic window, both in terms of a population therapeutic window, as well as an individual therapeutic window.

Now I will argue that these two windows are different and they are generated by different sets of data. The population window might be derived from the clinical safety and efficacy studies that we use to allow market access where you can show sometimes with a fairly broad range that the drug is safe and effective in the study

population.

Now we see dose ranges there sometimes from 1 to 1,000 that may be safe. So I would argue that the population window between these two goalposts can be wide.

If we go to an individual therapeutic window, my understanding of it is it tends to be narrower, and I use here the example of phenytoin, which of course is an extreme example, where you may want to titrate somebody to a level of 15 and ask that they not vary about that average value plus or minus 20 percent. And you can see that would give you 12 to 18, a much narrower range than what you might understand as safe and effective from your large-scale clinical trials.

So this curve is generated based on an understanding of the individual dose-response relationship for both efficacy and toxicity.

Now I will conclude this slide by saying we never see these data. The agency does not, for the most part--I want to say never but, of course, it's always dangerous to say never--see individual dose-response data in our marketing applications. And for that reason we use a default value of 1.25. So if you ever wonder where the 1.25 comes from, it's a clinical judgment that is not based on concrete data.

Now those windows that I showed you relate to

safety and efficacy information for the drug substance. The performance of the drug product relative to these windows--minimum effective level, maximum toxic level--are indicated by these curves. These curves are theoretical curves that should be construed to be representations of the distribution of a bioavailability measure, such as Cmax or AUC, for the reference and the test.

Now I said a mouthful just there and you may want to quiz the statisticians on what it was that Roger just said, but these are individual values. You can think of them as histograms where this is a dispersion of the bioavailability measure and this is its mode, the most common value, that is understood based on replicate or at least replicate data developed in a single individual. At least replicate means that you might need more than one replication to fully understand that individual's distribution of the bioavailability measure. But I have enough trouble asking just for replicate data. I'm not going to ask for triplicate or quadruplicate data.

Now I think you get a sense of what we're talking about here, of dispersion of the bioavailability measure in the reference and the test.

Now the individual bioequivalence criterion that we propose has three aspects of it. It allows a reward for reduction in variance of the test. It discourages the

presence of a subject-by-formulation interaction. And it allows widening of the goalpost for a highly variable reference product.

Now by taking into account these variances, we go beyond what we do now, which is a comparison of means. And I think there is a strong public health argument based on our understanding of what I might call absolute goods. I'm getting back to something I remember from my philosophy class, which is there can be absolute goods that we think about.

We do not think of subject-by-formulation interaction as good, and as a public health agency we would like to discourage it.

We do think of as reduction in variance of the test compared to the reference as a good that we would like to encourage. And we also believe that in fairness, it's not reasonable to penalize either a pioneer or generic in documenting bioequivalence to constrain the goalposts, if you will, if you're dealing with either a highly variable drug substance or drug product.

Now having said all that, I would like to now turn to the numbers here and what you see are numbers that I will talk about in more detail in my presentation later in the morning when I give you some evidence about our experience with these replicate studies. But what I want to show here,

and now I'm going to start communicating to the American public, what happens with the use of the criterion as compared to the average criterion.

These are real data that come from replicate datasets that the agency has. I'll talk more about the origin of these datasets when I speak later in the morning. But you can see here that the comparison of the means indicates that the mean comparison is quite close. The zero value indicates that there is no subject-by-formulation interaction.

You see here a comparison of the test and reference variance with a low number, .5, which indicates the test reduced the variance. The performance of the product made by the manufacturer of the test here showed a reduction in variance. And then you see here a value that's called PASS. And then you also see over here the possibility of scaling from a standard goalpost. And then here's a PASS value and I can't quite see it but I believe it passes over there for average equivalence, as well.

Now I haven't shown you the equation. I'm trying to talk it out first numerically and then graphically because the equation sort of looks awful. I want to talk about it conceptually before we get to the equation. But I think you can see by taking into account these variances we change the market access stipulations when it comes to

documenting bioequivalence.

And I will remind everybody that market access debates in this country have been extraordinary, starting in 1938 with elixir sulfanilamide, 1962 the Thalidomide crisis. And of course that raises the issue of justification as to why we would change the market access requirements for bioequivalence and that will be discussed in the course of the morning.

But now let me show you graphically, and I will thank Dr. Patnaik for helping me with these graphics and also Dr. Hauck, for showing to the consumer what seems to be happening here. This is the reference; this is the test. Graphically it's easy to see the dispersion about the mode for the test is less here. Graphically it's easy to see that we've widened the goalpost based on the performance of the reference. And there is also, because it doesn't have this offset, no subject-by-formulation interaction.

Over here I think you see an equivalent reduction in the dispersion about the mode compared to the further test, compared to the reference. The offset indicates that there is a subject-by-formulation interaction that may be important and because there's no dysjuncture in this line here, it indicates that no scaling took place.

Now I will argue that this simple graphic clearly explains in a risk communication way what the agency does to

first assess risk--the assessed risk is based on replicate study designs--manage risk in terms of comparison of means and variances, and then communicate risk to the public at large.

Now I'm not going to do this and I'm not trying to scare anybody but could you imagine this strip appearing at the bottle of every medication where a substitution arises? Would the American consumer be able to understand it? I don't think it's so hard. I think they could understand it. I think they could explain it. I could explain it, for example, to my parents, who are very interested in generic substitution.

I will leave you with that thought and you can give me a letter grade at the end of the day, but that's what I mean by risk communication.

Let's go on. I will wrap up with a few overheads.

I'd like to now show you the criterion. I will pause here for a little bit of nomenclature. We talk about the criterion itself. Right now we use an average bioequivalence criterion. We're talking about an individual bioequivalence criterion. You put a confidence interval around the criterion and it has to be less than some goalpost, which we term formally the bioequivalence limit. Let's go on.

You will hear much more about this sort of picture

in the course of the subsequent discussions. I'm now speaking to the advisory committee. Right now our goalposts have an upper and lower bound, which defines, if you will, the world of J versus B. I'm speaking regulatory lingo now. And it's based on a comparison of log transformed means using the two one-sided T test developed by Don Sherman, Don, who's in the audience.

Down at the bottom we come to a different approach that you'll hear more about, which is based on an individual distance ratio. This individual distance ratio relates very clearly to the individual therapeutic window that I talked about. It's a concept and I will give Lewis a lot of credit for this concept. It is based on a distance between the test and reference divided by the reference compared to itself. That is less than some goalpost. Through an interesting understanding that statisticians know, you get to the criterion, which has a different goalpost.

Now I took you through a lot of very complicated things that we'll be discussing in the course of the morning but I think you see perhaps conceptually the origin of this very complicated equation. Let's go on.

Now the motivation for the proposed criterion. I've already talked a lot about scaling, subject-by-formulation interaction, comparison of variability and rewards for reduction in test variability.

Secondary motivations are down in here. For example, we have a way now via scaling to deal with highly variable drugs. We encourage, as many of you know now, study in the more general population or perhaps even more specific populations, and I would argue that that has always been a criticism of generic substitution in the United States, which is that we tend to study it in young health males. The individual criterion encourages studies in more general populations to detect subject-by-formulation interaction because if you're going to see them, you would tend to think that they would occur more in the patient population.

Outliers, we can sort of deal with outliers perhaps better with replication. Narrow therapeutic range drugs and modified release products--there are some advantages to the criterion that we can talk about and I will talk about in the course of the morning. Let's go on.

Now also in the course of the morning we will get into a debate about justification. It's the justification to allow the agency to change the market access requirements. In that discussion you will sort of hear a debate between consumer risk and producer risk.

Over here if we think mostly about the consumers, perhaps you would argue you don't need any justification at all. You could just say if you see a subject-by-formulation

interaction it's up to the producer to prove that it doesn't exist, perhaps by reformulating, perhaps by doing another study.

Over here on this side we hear many people speak to the point that before the agency changes anything it better have a reason for doing it. That's sort of the elixir sulfanilamide-Thalidomide understanding that before we do something we need to have strong evidence to increase regulatory burden.

Now depending on where you sit here and how you think about what a regulatory agency does, you would say all studies should be replicated over here, perhaps few over here, and the committee will hear that debate in the course of the morning.

There are statistical issues that we have talked about before this committee on many occasions and I would like to argue that we should not talk about them in the course of today.

Steve, of course, that's your prerogative if you want to get into any of these issues but, for the most part, we believe these statistical issues are resolved. They're difficult and many of them are the province of expert statisticians and we certainly have many expert statisticians in the room today, should the committee want to ask questions about some of these issues.

Now here's a brief time line of where we've been and where we're going. As you can see, it's a long time. I've already alluded to that February advisory committee. Here we are in September of '99 for a further discussion. I do not think it's the final discussion but it's a further discussion of the approach. Let's go on.

And now I would like to say assisting the agency internally and externally and assisting the committee in its deliberations today are, first of all, a Population and Individual Bioequivalence Working Group. That working group functions under the Biopharmaceutics Coordinating Committee that I spoke about. The co-chairs of that working group are seated at the table--Dr. Rabby Patnaik and Dr. Mei-Ling Chen. I am chair of the Biopharmaceutics Coordinating Committee and the three of us will be here to assist the committee in its deliberations.

The other members of the committee are also here this morning and are here to assist the committee and some of them will also be giving presentations in the course of the morning.

Assisting this internal working group are Dr. Walter Hauck and Terry Hyslop and they also are here in the audience today to assist the committee as it goes into its discussions.

Now another thing that I mentioned early in the

morning was an expert panel. My section of the center, the Office of Pharmaceutical Science, likes to use expert panels as a means of drawing in stakeholders as we evolve regulatory policy. This is the particular membership of this expert panel, Population Individual Bioequivalence Expert Panel. Its chair is Dr. Les Benet. Les is certainly here today to present the views of the expert panel. And the membership is shown on this particular slide and some of these people will also be speaking in the course of the morning.

Both the internal working group and this expert panel have been tremendously value to the center, the Office of Pharmaceutical Science and the coordinating committee in moving forward on the proposals that we will discuss today.

Now Kimberly, I believe that's my last overhead.

Steve, thank you very much. I turn it back to you.

DR. BYRN: Thanks, Roger.

Are there any questions for Roger of clarification from the committee?

[No response.]

DR. BYRN: Okay, then we'll move ahead with Tom Gretter, who will make a presentation on clinical perspectives.

CLINICAL PERSPECTIVES

DR. GRETTER: Thank you very much, Steve.

Members of the committee, honored guests, it's a pleasure for me to be here. I will try to see whether we can make our slides work. Thank you.

I'm Tom Gretter. I'm a practicing physician. I'm a neurologist from Cleveland and I'm here to offer you today a physician's perspective, kind of an overview about this process of bioequivalence and bioavailability.

I think what we need to do is to step back a little bit and look at what the physician's responsibilities are. And I've listed them here and all of us know that physicians are responsible for evaluation, diagnosis, treatment, management, continuity of care. And when we get down into the treatment aspects of things, there are many forms of treatment but one of the things that we do use is we do use medication as a form of treatment.

And when physicians begin to use medication, what they want to do is to be assured that the medication will work and that it is safe. They want to know what the medication is going to do within a reasonable amount of assurance. And I think that the word for that is prescribability. And I must say that in this day and age, for medications, except for a few notable examples, we do have prescribability. We do know what medications are going to do and we do know how they're going to act. And we do

know the safety of them.

It's up to the physicians to establish what is the correct medication, and that's a whole elaborate process which we're not going to get into here, and what the dosage is. And we'll get into dosage a little bit later on.

As we begin to use medications, we now have to be aware of a whole host of things which can vary the therapeutic response of this medication. One of these, of course, is drug-drug interactions and now we also have to worry about drug-food interactions. Grapefruit now is a thing we all have to be careful about for various medications.

Banahan and Kolassa in their article, and I'll refer to this a little later on, again showed that there was again variations among patients. And I would have to say that one of the extreme causes of drug variable action is patient compliance. And were we to look at patient compliance, it would probably blow away drug variability that we're talking about today with regard to how often it does occur. One of the hardest things we have to do is to get patients to comply with the medicines which we will prescribe and give them.

But we also have to worry about how old the patient is and individual physiology. And I think when we use the words intrapatient and interpatient activity, I

think what we're talking about or what they're talking about, because I have difficulty in knowing what those words means, is what Roger alluded to, which is population and individual-based variability.

And now we get down to what we're talking about here today, which is the bioavailability and bioequivalence issues.

Now if we do a historical perspective, and having been involved with the history of this, it's kind of nice to do a historical perspective, when I was in my training, which was before 1970 in the beginning of this particular slide, we knew about differences among medicines when they were substituted. We knew that if we used generic drugs that there was a variability of it.

A particular medicine that we would refer to was Dilantin. We even called it diphenyl hydantoin then. We call it phenytoin now. But we all knew in the neurology aspects of things that when someone went to a generic medication that it would vary the drug level considerably in the patient and, in a lot of instances, throw them below the therapeutic level and occasionally cause a recurrence of seizures.

In the '70s there was physician resistance obviously to substitution, particularly among the generic drugs. And, as a matter of fact, there were anti-

substitution laws. And when we look upon this from the vantage point of substitution, we can say that that was the dark ages of substitution. History is interesting because we can look at it in different sizes and different perspectives.

In 1978, with the onset of state prosubstitution laws, became what we call the renaissance for substitution. Substitution began to reoccur. The FDA put out the Orange Book, which was an equivalence book on various medications, and the federal approval process for drugs began to ease a little bit.

Then about in 1986 came what I call the modern era, which is about where we are, where physicians begin to notice that there were specific substitution problems. A lot of this was pushed by the monetary issue with the advent of managed care--let's find the cheaper drug, irrespective in some instances as to what the effect is; let's use a cheaper drug. And then the generic drug scandal in the beginning of this particular committee, which evolved into the increasing surveillance by the FDA.

Now there have been some published materials for generic substitution and I think in order to write on this particular subject, at least according to this slide, your name has to begin with W. These are fairly well known examples of what will happen with generic substitution;

i.e., use of a medication will cause a significant lowering of the available medication.

At the same time that this has been happening, one would have to say that the science has also been progressing. It is now much easier for us to look at drug levels. This science of determining drug levels has come a long way in the last 30 years and is now much more reliable and goes hand in glove with what we're trying to do.

Going back to the Banahan article, which was in 1997, they did a whole series of interesting things, one of which was to ask physicians what they knew about the FDA and what their bioequivalence range was, as alluded to by Dr. Williams. And the range is listed there.

The physicians were not very good at this. Only about 17 percent of them in 1997 were able to come up with what the FDA ranges were. However, further with regard to this study, physicians were not to be denied. They didn't know what the FDA wanted but they had their own idea of what it should be and they thought that the variance should be plus or minus 11 percent for most drugs, which is a range which the FDA uses for a few choice drugs with a narrow therapeutic range.

Physicians also felt, according to that article, that for narrow therapeutic medications that it should be plus or minus 5 percent. The not-related-to-attitude group

was another corollary, which I'm not going to get into, that these authors used, and that is they were concerned about physicians by specialty and by location and what pressure they were under to prescribe certain medications by certain interested groups.

So now physicians overall do have, according to that article, substitution concerns and their substitution concerns were for this particular list of drugs, and this was two years ago. We can see in looking at these drugs that there are some of these medications that there really is some concern about substitution and there's been some evidence to show that with regard to some others of these drugs, that substitution really isn't so bad, that once bioavailability becomes available, knowledge of it becomes available, then we can substitute.

So overall, with regard to the physicians, physicians feel that drugs can be substituted, that they can be switched, and the word switchability is coming into being, but there has to be certain codicils with that. Physicians need to know when drugs are being switched. We want to be able to know, and I think rightly so, because of some variance in medications themselves, when the medications are being switched so that they can monitor it because of their responsibility toward the patients.

They have to be aware of the change because some

drugs really continue to have very critical therapeutic levels and some drugs need to be monitored. So medications can be switched if physicians are aware of them.

Physicians are responsible, as we talked about earlier, for diagnosis, for treatment and for management. And physicians are graded based on standards. Standards used to be community standards and now are extending to national standards, particularly in the malpractice era and in the quality era.

So physicians need to be able to have practice standards and part of the practice is to be able to be aware of those medications that we prescribe and that those medications that we prescribe are being given to that patient and that that patient, we'll know a little bit about what's happening to that particular patient.

So in summary, looking at where physicians are with all of this, physicians are well aware that there is both population and individual bioequivalence variance. We are looking for medications that we can prescribe safely. We're looking for medications that carry with it the overall broad term of prescribability.

We also know that occasionally it's necessary to switch drugs and we all will switch medications periodically for a variety of reasons, but we want to be able to know which medications we can switch and how switchable they are,

particularly among the generic group of medications.

So I want to thank you for allowing me to speak to you today.

DR. BYRN: Are there any questions of clarification for Tom from the committee?

[No response.]

DR. BYRN: Okay. The next speaker will be William Barr, who will give the pharmaceutical scientist perspective. We'll take a three-minute break to put the slides in.

[Recess.]

DR. BYRN: Okay, we're going to start if people could take their seats.

PHARMACEUTICAL SCIENTIST PERSPECTIVE

DR. BARR: Good morning. We're going to go ahead and get started again. We have one carousel so we've had to queue up for that.

MS. TOPPER: I'm sorry. I need to make an administrative announcement. The fire department requires that everyone be seated. You may not stand along the back of the room. We do have a room with a live broadcast on the TV right next door. For those of you who come in and stand, you'll be asked to leave to go to the other room.

So there are seats vacant down here. If you sit there you might be asked to be an expert but that'll be all

right, but please take those seats. And there were two seats over in the FDA section so please take those seats. If you're saving a seat for somebody, sorry, too late. Whoever's standing gets to sit first. They'll have to just stand or move into the other room.

So those of you walking around, please find a seat.

DR. BARR: I'll be reviewing some of the clinical pharmacology pharmaceutical aspects of individual bioequivalence. Specifically, as we talk about individual bioequivalence, there are two major areas that are additional considerations that we have through the replicate design that we see in individual bioequivalence.

One of these is whether or not two products have greater variability with respect to the intrasubject variability. The other that I'm going to spend most of my time on this morning, the 15 minutes or so that I'll be talking to you, is relative to the question are there absorption subsets and are there physiological mechanisms that would explain why we should be concerned about subsets?

The subsets, of course, relate to the treatment, the subject-treatment interaction, the SF interaction that most of you have heard a lot about, which is a major new addition to the concept of individual bioequivalence. Through replicate design, we can actually determine whether

or not there are some groups within the population that may, in fact, show differences to two products, even though the average person does not, as it would be determined by the usual methods by average bioequivalence.

So the real question comes up and has been raised by many people, well, that's great; it's nice that we're able to do that but does it mean anything? Are there any out there? We've never seen any evidence. There's no reason for fixing it because it's not broken; there's no dead bodies in the street; there's no evidence that this has any relevance to anything, so we probably ought not to do it until we have some evidence that there's really absorption subsets and they do exist.

It's kind of strange to me that this mentality exists still today because in every other area of pharmacology we finally realize that there are tremendous examples and numbers of examples and reasons for examples for individual differences between people.

When we talk about patients we all know that we have to individualize therapy. Anyone that's ever been involved in any aspect of therapy knows that that's true for every area except absorption. Absorption, somehow we're very monolithic. Everybody absorbs a drug exactly the same. We know there are differences in metabolism and excretion and we look at special populations when we at patients with

renal disease. We have a drug that's absorbed and excreted primarily by the renal pathway. We look at metabolism and we have subsets when we look at that and we take particular attention to these groups of individuals by doing specific studies in order to determine whether that's important for a drug.

Absorption, on the other hand, has been the stepchild. Absorption has been totally neglected because we've made the assumption that all people absorb all products exactly the same, that there are no mechanisms for any differences. So I'd just like to take a few minutes to show you that just isn't true, and probably many of you have suspected that in the past anyway.

There's many reasons, theoretical or hypothetical reasons. Gastric pH, and there are actually some studies showing that there are some very nice examples--one was presented in Montreal at the last meeting on individual bioequivalence--and there are other reasons to believe that other physiological variables may be important, things like luminal enzymes and digestive enzymes that we have in the lumen that also affect certain drugs.

We have mucosal enzymes, which are probably more important.

Gastric emptying and intestinal transit. I'm going to take just one of these. We could go down and

probably find examples for all these but in the last couple of years, while we've been doing studies, we've actually been looking to see whether there's any indication that these things are real and like most things, once you start to look, you find out there may be something there after all.

So I'm going to show you two examples that we've picked up within our research in the last couple of years and just take one of these, intestinal transit, and show how this may be one factor and probably a very important factor, that will distinguish between certain dosage forms because there are individuals that have differences in intestinal transit time.

So I want to talk about two drugs, Levothyroxine and Cyclosporine. Now these drugs are particularly important because they also are classes of drugs which are called clinical dose drugs or the old terminology, narrow therapeutic index drugs. The critical dose classification I think is a much more realistic one.

The important thing is that relatively small differences in the amount of drug absorbed can, in fact, have differences in the clinical effect of the drugs. So if we are going to look at any class of drugs, it makes sense to look at those drugs where small differences in bioavailability have some relevance in terms of the ultimate

clinical effect, and these two, I think, are very good examples of that.

We did a relatively standard type of bioavailability study a couple of years ago on a generic brand of Levothyroxine compared to what the market standard is today, although there's not an NDA-holder, but most people consider Synthroid the market standard.

We did a multiple-dose study in which we compared both T4, the Levothyroxine, at steady state. This was actually a marketing study so they wanted to show it under more clinically realistic conditions; namely, this was in patients. These are hypothyroid patients who had been treated with 100 micrograms of Levothyroxine and been stabilized and we just simply switched them over in a switch study.

And this shows that the Levothyroxine in the generic brand was slightly higher but met all of the requirements in terms of area under the curve for a confidence interval, log transform confidence interval, bioequivalence standards for average population difference. That was also true for the active metabolite T3, the triiodothyronine, which would be considered bioequivalent under the average conditions, as well.

Now what we found though, is that when we looked at TSH, the thyroid-stimulating hormone, which is the index

that clinicians use to determine whether or not a particular medication has the right dose, and we happened to take this on two replicate samples--we took it at two different times about two or three weeks apart and when we compared that, now that we had a replicate design, we looked at this statistically and all of a sudden we found it was statistically different.

We took a look--which was interesting because none of the others were statistically different or bioequivalently different relative to the confidence interval but this was. It turns out TSH is a very exquisite measure in the body of circulating levels and effective levels of T3 and T4, and that's, in fact, why it's used by clinicians rather than direct measurements of T3 and T4.

And when you look at the replicate design of this, we found something very interesting. We found that indeed if you look now at test 1 versus test 2 in a given subject versus now reference 1, reference 2, where we have now replicate measures, where we have two chances to look at the two products, in most cases, this bottom group down here, you can see that most individuals, there's no difference between T1 and T2 and the reference over here. This group is kind of the average. But there are patients who whenever you go from the test to the reference that now jump up and have very high levels of the TSH.

Now about 5 or 6 is actually where most clinicians would actually start to change the dose of the drug. In other words, this is going to be relevant when you see this. In most cases whenever you get to levels of 5 and 6 on TSH, clinicians would then consider changing the dose of the drug. So that these changes now, whenever you go from test 1 to the reference product, the Synthroid, are, in fact, clinically relevant to the point that that would result in a change in the drug normally.

Now we found this is only about maybe 10 or 15 percent of the population, that every time whenever they changed the Synthroid, the TSH levels went up. I thought this was curious. I thought it might be anomalous and we went back and there was another student that had been done by Forest, another company that just was in my files because I was on the Virginia Voluntary Formulary, and went back and looked on this and found that they had almost identical results. They had a multiple dose study. They had tested their generic drug against the Synthroid.

These are the TSH levels that they had whenever they used the generic drug. These are the ones that they had when they used the Synthroid. And again you can see the outliers. You can see these groups up here where the TSH levels are high.

Now what does this mean? Well, the data were not

reported in quite this way. When they saw the outliers, I talked to the people who actually did this study and they thought these were simply outliers, so they went ahead and did a median evaluation rather than an average and they then determined that these were outliers, so that they were excluded by using the median analysis.

I talked to Jerry Skelly. He thought that perhaps this was a food effect, so that they kind of dismissed this. They just felt that this probably wasn't relevant. But indeed it seems to be the same thing.

Let me give you a probable mechanism why this works, what happens with this. These are the in vitro dissolution data for the generic drug.

Now it turns out there are three or four major generic drugs on the market and all of them have almost identical in vitro dissolution standards. The in vitro dissolution standard for the generics is that most of the drug, about 90 to 100 percent, is actually dissolved and is available for absorption within 10 minutes.

On the other hand, the standard drug is an old wet granulation method that these are three different lots of the in vitro dissolution and you can see that about four hours here, only about 50 percent of the drug is dissolved. Over here at about two hours or so then we're getting closer to 100 percent.

Now interestingly enough, the USP has looked at the in vitro dissolution. At one time there was the thought that they would have two individual in vitro dissolution tests, one for all the generics and one for Synthroid. They decided that that probably wasn't a good idea so they made the test bad enough that everybody did, in fact, get underneath, and that's what we have.

We have one in vitro test. Very often I've seen statements by the USP stating that they've never seen a case of bioinequivalence provided that they meet the in vitro standards, and this is also an example where that just isn't true.

Most of the population have intestinal transit times somewhere about two to about six hours on the average. This is classic data by Davis in which they looked at about 200 studies that they had done using centrifugy to look at intestinal transit time and you can see each one of these represents an individual study and each one of these points represents an individual person. You can see that on the average, most of the people had transit times somewhere between about two and six hours, averaging somewhere around four hours or so.

But there is a distinct group of people in the population that have transit times somewhere between one and two hours and they seem to do this repeatedly. They may be

vegetarians. There may be other reasons for that. There may be drugs that they're taking, something like some of the propopulsive kinds of agents. We don't know all the variables but indeed if you have a transit time of one to two hours, you will simply not absorb all of the drug because it won't be available because of its solubility reasons.

So this is one example of an interaction between a physiologic mechanism and a formulation difference between these two products. Now it won't show up in all people but if that drug stays around for four to six hours in the intestine, then it's going to get absorbed by either method and the rate of absorption for Levothyroxine is unimportant; all that matters is how much finally gets in there.

So the average patient with an average transit time of four hours is going to absorb both of these drugs and they'll be completely interchangeable. No problem.

On the other hand, if you happen to have a person who has a transit time below four hours, on the order of three or two or one, then they will not absorb all of the drug; it simply won't be available because the drug won't be dissolved.

Let me show you one more example of this very quickly. Cyclosporine is a drug that we all know is a narrow therapeutic index, critical dose drug--no question

about it. It's use for life-saving situations. If the drug doesn't work, you lose a kidney or a heart or a major organ, and it results in hundreds of thousands of dollars, if not increased morbidity and mortality whenever things like this happen.

Just to show you that it is also a critical dose drug relative to changes in the plasma levels--not changes in the dose but changes in the plasma levels can be directly related to the percent of incidence-free individuals within a given year. That is, this is a direct clinical endpoint that you're looking at how many people have indications of rejection during a year and it's directly related to the plasma level.

Now we don't need to go back, as some people have suggested, and actually take two bioinequivalent drugs and put them into the population to see whether we're going to get clinical effects but a lot of people say well, we've not seen the clinical result of this. And the idea of actually taking two generic drugs or two bioequivalent drugs and putting them into a population to see whether we're going to have an increased incidence of rejection is obviously a foolish and dangerous one.

What we need to do is to find out what amount of change is likely to cause this from one or two major studies in which you got more like a dose-response curve and use

that as your critical evidence, not the idea that you have to put two drugs in this population and see it directly from the drugs.

Let me show you one other thing that makes this, I think, a pretty interesting drug to take a look at. Not only is the blood level important but the variability of the blood level is very important. This is a little busy slide but let me just walk you through it very quickly.

Basically what this says is that in terms of those who have had no rejection, that they took people who had the same average blood level but differed in the variability of the blood levels and found that those that had more variable blood levels, in fact, also had a greater incidence of rejection within the year.

Now what that means is it gets back to this intrasubject variability that we're talking about with this particular product. If you have two drugs that have the same bioavailability but have a greater intrasubject variability, then according to these studies by Cohen, they would be more likely to have an increased incidence of rejection during the year.

Cyclosporine is a drug which has interesting and troublesome absorption characteristics, as well. You can see on this slide whenever you do an intubation study you find that the drug is well absorbed in the duodenum, the

jejunum, decreases as we get to the ileum and when it gets to the colon it's not absorbed at all, or very, very small amount is absorbed.

This is a direct giveaway saying this is a drug that's going to have intestinal transit problems. Once you see a drug like this, you know it's got four hours to be absorbed and if you've got problems between formulations that may be transit time-dependent, these are the kinds of drugs you're going to have.

In addition to that, the regional absorption is interesting because these are probably related to at least two mechanisms. We know that the P-glycoprotein and the metabolism of this drug, the P-450 metabolism by 3A4, has different amounts in different regions. We have the P-450 enzymes, the 3A4 and perhaps others that seem to be to a greater extent in the proximal part of the small intestine.

On the other hand, the P-glycoprotein, this efflux mechanism that we've just started to become more familiar with and understand, is, in fact, one of the things that relates to the grapefruit that we talked about. Both of these mechanisms are affected by grapefruit juice.

This one tends to be greater in the distal parts of the intestine. We've seen different regional differences for drugs, as well, as we've done intubation studies, which we don't have time to go into, but these can also be

important relative to transit time.

Now there are two drugs--we don't have examples in generic drugs but there's a couple of drugs that are interesting to look at. Neoral and Sandimmune are two dosage forms from the same company. They differ somewhat by not the total amount absorbed in most people but by the rate of absorption, the initial rate of absorption, and this is the input function, the fraction absorbed for these two, and I've blown this up a little bit just to emphasize the differences in the first four hours. By the time you get out here to about eight hours, the fraction absorbed gets to be pretty similar in most people.

Now interestingly enough, there have been a few studies that have looked at these two products in different groups of people. And the group that is probably most critical are there are a group of people who were poor absorbers of Sandimmune, the original product. And so if you look at the AUC versus dose in Sandimmune and you find that these people are down below about 20 in terms of the AUC-dose ratio, and then what you find is that the difference between these two products is indeed greater for the poorer absorbers.

For good absorbers, which are probably people with, in my estimation although there may be other mechanisms, may simply just be something as simple as a

transit time--these are people that have transit times of four to eight hours and have no problems--then you get no differences between this. The difference between the two products is very small.

On the other hand, if you get people that are poor absorbers of one dosage form, the difference between the two becomes magnified and gets up to as much as 250 percent differences between these.

Now what this means is if I were doing a bioequivalence study and I wanted to show that these two products were the same, all I would have to do is go out and select a group of people who are good absorbers, who probably had slow transit times, and I would do the study in this group of people and they would probably be bioequivalent.

On the other hand, if I wanted to show that the two products were different, I could also do that. I'd just go over here and take all of these people over in this group and I would get over here and they would be bioinequivalent in this group.

So depending on what you want to do, you've just got to select the right patients.

Now, in fact, there was a study, which I don't have a slide on but there was a study that there was a recent abstract--I don't know if it's published--in which

they did exactly that. They took two products. The old, the Sandimmune solution, which is actually an oil, and the Sandimmune capsule, which is a capsule containing an oil, a soft gelatin capsule containing an oil. These two products were shown to be bioequivalent in previous studies and, in fact, the capsule was approved based on the bioequivalence. The FDA accepted the capsule based on bioequivalence to the solution in a previous study.

And what they did, they went out and they screened subjects and they screened about 60 people. Of those, they found about 20 were poor absorbers of the Sandimmune, did the bioequivalence study in the poor absorbers and found that they were bioequivalent.

Now what this means is that there are subject-treatment interactions and that they can greatly influence the outcome, in fact, if you choose particular groups of people. The FDA in the past has allowed preselection. In fact, I was told that one study that I to do with Propranolol, that we ought to go ahead and screen all the people because there's a great deal of polymorphic variability and that we ought to get the metabolic group that had the rapid metabolism. So that is permissible.

Now what I'm suggesting is that there's a couple of ways that we could do this. We could hope that these groups of people would be in the population that we studied

that accidently were in the Levothyroxine. Or indeed if we know that there is a particular group that is likely to show differences--this is, an achlorhydric or people with rapid transit time--that we might simply insist that some of those be included in the particular group that is being studied so that we would be able to pick this up.

If we only have one or two of these people, we're not likely to pick this up in 24 unless it's a very, very large effect, similar to ones I've seen before.

So there may be some alternative ways that we attack this but the most important thing is that we recognize, I think, that, in fact, subject-treatment formulations do exist. This is just another example of the same thing. And let me just point out that they may exist in different populations, as well.

These are Cyclosporine dose that's required in children who have had hepatic transplants. Whenever you do a liver transplant, you also have to take out some of the intestine, as much as 30 or 40 percent of the intestine. And it turns out that the dose that you have to give in this, that the doses required to get therapeutic levels is inversely proportional to the length of intestine in these children, which is the same thing instead of transit time, it's residence, depending upon the length of intestine.

It's also well known that the transit time and the

length of the intestine, the relative length of intestine in children decreases as we go down. So this would indicate that drugs which have these formulation differences which are dependent upon transit time are going to have greater differences the smaller the child.

In addition to that, we know through some of the studies that the FDA has done that there are subsets that have turned out, when they've looked at replicate design studies. Interestingly enough, often what pops up are women, that women become the subset. This is kind of interesting because not very long ago many of us were saying we don't think there's much problem of putting women in bioequivalence studies; that shouldn't mean that we're going to get different results. And, of course, as we all know, for 20 or 30 years we did all of our bioequivalence studies in young, healthy males. It was more convenient. We were very protective of the women because they ought not to be taking more drugs, and all of these reasons. But basically it was more convenient and the distribution was about the same and it was easier to put males all in one place rather than having to separate them.

And so for 20 years we went with the assumption that, in fact, young, healthy males were completely predictive of females. We disenfranchised 53 percent of our population with that particular assumption.

There's some evidence that there may be differences in transit time at different times in the menstrual cycle. These are some studies from Wald that shows transit time in the estrogen phase and the luteal phase and you can see that this is the measurement of hydrogen whenever you give a lactose test, that the lactose that's unabsorbed gets to the colon, where it's converted rapidly to hydrogen, which is picked up by a detector. So it's a measure, although a crude one and has some faults, but it's one measure, of transit time.

And you can see in these two individuals that the transit time in this case in the estrogen phase is picked up--is relatively brief, only about 50 minutes. On the other hand, in the luteal phase it's fairly long on these two individuals, about what you would expect, at least two hours.

Now the reason that these are a little smaller values than normal is because unfortunately, lactose is an accelerator itself. It increases its own transit time, so it's not a very good measure of transit time, but I points out that many compounds, like Mannatol and lactose will, in fact, increase transit time. And I think the FDA has a study right now looking at Mannatol to see the effects on this and my prediction is it's going to increase transit time, like lactose, and that for some formulations we will

see those kinds of differences happening.

Now one final comment. One final comment. Why haven't we seen all this before? Why are we just finding there's differences? Because we've had the assumption there are no differences. We've gone with the assumption and there's an old dictum, I guess, that the physicians use that the diagnosis, if not suspected, isn't detected. And I think that's very true in this case.

I'm just going to end with one final comment. You can't find termites unless you look under the floor, until it's too late. So I think we'll find a lot of these when we look. I think the assumption that there are no examples of subject-treatment interaction is just, at this point, a marker of our present ignorance and clearly within the next two or three years we'll have many examples. Thanks for your attention.

DR. BYRN: Are there questions from the committee for clarification? We have two questions, Mary and then Arthur.

DR. BERG: Dr. Barr, getting back to your data on Levothyroxine and Synthroid, I just wanted to clarify. Did you have a gender analysis of that data? The reason I ask that question is that hypothyroidism occurs roughly 15 times more in women than in men.

DR. BARR: Yes.

DR. BERG: I didn't catch it if there was.

DR. BARR: We didn't look to see if there's a gender interaction in that. When we looked roughly at the data, there was only about, as I said, I think we did 24 subjects in this, so that we were looking at about four people and we didn't really have enough to be able to detect. I think there was one woman--we had women in the study but, like many studies, we had some women but not half of them being women. So we really weren't able to look at that statistically. But that's a very interesting question and probably ought to be examined.

Art?

DR. GOLDBERG: The slide you showed on the subject formulation differences between the reference and the test, did I read that correctly? There was a higher level of the reference product?

DR. BARR: That's correct.

DR. GOLDBERG: Despite the fact that the generic dissolved at a more rapid rate?

DR. BARR: I'm sorry; there was a slightly higher level of the T3 and T4 for the generic product compared to the Synthroid.

DR. GOLDBERG: Not the T3 and T4 levels but the marker.

DR. BARR: Oh, the TSH.

DR. GOLDBERG: Right.

DR. BARR: The TSH was a higher level of TSH for the reference product; that's correct. That's TSH. Now this is a thyroid stimulating hormone which, when the levels of T3 and T4 go lower, then the TSH level goes higher.

So this was an indication of lower circulating levels that are acting at the pituitary level of T3 and T4 for the product for those individuals.

DR. GOLDBERG: And the lower levels came from the--

DR. BARR: The lowers levels of TSH were the generic drug and most of the individuals on the reference drug, those that, I believe, have longer transit time, so the same amount was absorbed.

When less drug is absorbed and is detected at the circulating level at the pituitary level, then the TSH levels will go up as an indication of decreased bioavailability at the site of action in this case.

DR. GOLDBERG: Thank you.

DR. BARR: Sure.

DR. BYRN: Okay, the next speaker is Les Benet.

EXPERT PANEL REPORT

DR. BENET: Thank you, Steve. It's always a pleasure to speak continuously at these meetings over the last--let's see, Roger. The time line started in '93 when I

was 32, but I think we've been talking a lot longer than that.

I've had the pleasure over the last couple of years to be the chairman of the expert panel and Roger showed you the membership of that expert panel. I'm going to report today the latest discussions and recommendations of the expert panel and to also give you some feedback concerning various aspects that have been discussed at the last few meetings, not only the expert panel but of the individual bioequivalence workshops, the last one held a few weeks ago in Montreal.

I'd like to first though, Dr. Gretter's earlier talk, to reflect on something that I have said at least once before at one of these meetings that I think is very important. Dr. Gretter reviewed with you the Banahan et al. article that appeared in Annals of Internal Medicine in 19907.

When I first read that article and the previous article that the authors wrote, I felt it was a very prejudiced article. It was funded by a major pharmaceutical company and I felt that it took a perspective that was unfair. But in fact, I now agree that it is not unfair.

And I want to point out that when Banahan and his colleagues went to physicians who did not know the law, did not know the rules--there were 83 percent of them, as Dr.

Gretter showed--they showed them what is written in the Orange Book. And what is written in the Orange Book is not what we do today. Therefore, if the FDA is going to help the community to understand what we do, it would be very useful to list, especially in a context like the Orange Book, exactly what we do because what the Orange Book says and what the law says from 1977, when it was first written, that Cmax and AUC are a measure of--rate of availability in AUC must not differ by plus or minus 20 or 25 percent. It doesn't say anything about confidence intervals.

So when the physicians read what we write today, they were under the assumption that under all conditions, the law, as it's presently written, allows innovators and generics to compare in terms of means. And I think it would be incumbent upon the FDA to actually, in their publications, say what we do because the physicians are not misinterpreting what is written; it is we are not writing, in fact, what we actually do, what today is we say that we want confidence intervals around those means for a measure of the rate and extent to be plus or minus 20 to 25 percent in terms of our view.

So I think, Roger, in terms of explaining to the American public, a very first step is to say, in fact, what we really do so that when Banahan and his colleagues go out and show the clinical community, they can read what's in

fact true.

And, in fact, my position is that we do exactly what the physicians want. The physicians say we don't want those products to differ by more than 11 percent. My view is that they don't differ by more than 10 percent and, in fact, my recommendation is in terms of the number that physicians look at, that we should have a point estimate criteria, in addition to the statistical criteria.

And Kimberly, if you would show this slide, which I presented a couple of years ago, I believe that it is important for confidence of patients and clinicians a parameter that is readily understood. I give Roger an A+ in his explanation but just in case there's somebody that wouldn't understand that, I think it would be very valuable to actually say, no, we don't allow products in terms of the point estimate that are outside this range. No statistical basis. No worrying about it's strictly political. Strictly from a point of view that we want patients and clinicians to be confident that the products that they take do not differ.

So I think that, in fact, we already do meet that criteria. I believe, as I said before, if we had the data, all we have is data from 20 years ago. I know the agency's looking at this data. If we actually look at the means that are presented to us in terms of approved products at the present time, I think we meet the criteria that the

physicians, in response to Banahan and his colleagues, want. So let me on though from there.

The first couple of slides are going to be slides that I've shown repeatedly but they still reflect a view that you hear often from the scientific community, knowledgeable scientific community, about the criteria and the information that we're presenting today.

I believe, I believe everyone on the expert panel believes that individual bioequivalence is a promising, clinically relevant method which should theoretically provide further confidence to clinicians and patients that generic drug products are indeed equivalent in an individual patient. And we do want the patients and the clinicians to have this confidence.

However, as of this time, and this is a slide that so far I've been able to use about six years and I can still say "as of this time," as of this time, little perspective data exists which may serve to validate the theoretical approach and provide confidence to the scientific community that the methodology required and the expenses entailed are justified. And that is what we hear a great deal in terms of concerns particularly of the generic industry and the brand name industry, also, in terms of the expenses that would be required in doing any type of bioequivalence criteria--are they justified? Do we have a basis? Do we

know that it's useful?

So this is a statement that I've made. Individual bioequivalence is a theoretical solution to solve a theoretical clinical problem and I agree with what Dr. Barr said; I agree with what everyone will say here. We don't know that just because we don't see bodies in the street doesn't mean we have a problem. But it is a theoretical problem. And we don't know whether the new criteria would solve that problem, if we do have a problem. And that again is what everyone that gets up and has concerns about the methodology suggests--we don't have enough information at the present time because we don't know that we have a problem. We're beginning to see some information and we don't know for sure whether we would solve this problem.

So what is needed? And I think everyone agrees on this. What is needed is generation of a large database which will provide the FDA and the company scientists with necessary information to make a reasoned consensus judgment as to the appropriate criteria for individual bioequivalence.

Now everyone agrees with this but the methodology of getting that data is what is being disagreed with. Do we have a requirement that certain data be submitted to the agency using cross-over repeated measure studies? That's what the issue comes down to.

Now let me go, leaving this slide on, briefly to some of the questions that Roger pointed out. I think the expert panel feels that we have solved most of the statistical issues. We've raised a couple of others but I think the expert panel believes that all of those statistical issues and our outstanding expert consultants can solve those statistical issues.

The expert panel also, and I think the audience in Montreal was impressed on the last day with some of the real data that we saw, presented both by the brand name industry and the generic industry in terms of studies that had been carried out, some of which have been made available to the agency and some of which were presented for the first time.

It was obvious from seeing these studies that we were seeing results or outcomes that we would not have put into simulations, that we were seeing things that were the unexpected, and that's why we needed real data. I think most of us in the room at the time thought that what we saw in some of those real studies would not have come about with multiple, multiple simulations of the data because we wouldn't have expected to see it. And, in fact, that's why we do studies, to find out real data.

So what the expert panel and what we, as a scientific community, have been struggling with is how do we get that kind of data to the agency and to ourselves so that

we can move forward in a reasoned way?

Now we have seen the second version of the proposed guidelines from the agency and it incorporates many of the suggested comments from the first version but there still is great concern that this yet doesn't meet the needs of showing that the experiment justifies the expenses.

So what the expert panel struggles with all the time is what can we agree on? Now you saw the membership of the expert panel. If we can get consensus of that membership on any issue, I'm terrific. So I'm terrific because we do have some consensus on some issues. Because we represent, in fact, the diversity of everyone that comes to the picture in terms of academic and in terms of industry perspective. But we do have some consensus and I'm very proud of that and I think we can move forward and the recommendation that I'm giving to the advisory panel is that you concur with our recommendations in terms of this. So let me show you the next slide.

First of all, when the expert panel meets, we have a way of doing this. We meet at these workshops. In fact, there's going to be another one in London in two weeks or one week--I'm not really sure. We meet--the expert panel meets on Sunday evening before the workshop. We spend about three hours discussing all the issues and we reach absolutely no consensus on anything.

Then we schedule a breakfast meeting on the last morning and in that one hour we hammer out some consensus. A lot of people show up for the first meeting, which is the detailed scheduled meeting with a big agenda. In fact, most of our committee members when they're not there are also available by phone. But nobody shows up for the breakfast except the really dedicated people.

So here are the people that showed up at the breakfast meeting on Wednesday morning. So when I give you the votes, these are the members of the expert panel that were, in fact, at the breakfast meeting. But, of course, all of the working group show up because they're forced to by their bosses. So the whole working group is there and these expert panel members who can get up early in the morning on Wednesday are there.

Now let me show you the first recommendation. What everyone is concerned about is can there be a carrot that we can give the group of people submitting data to the agenda that would allow them to think that it would be worthwhile to carry out these individual bioequivalence repeat measure studies so that there is, in fact, some trade-off? They get some benefit, not just in terms of the approval process, which Roger tried to point out, but some benefit even in providing the data. And we think we have one.

So what we've recommended in this particular category, modified release drug products, where sponsors are now required to provide multiple dose data for these modified release products, we recommend that for a two-year period, all modified release drug products should be approved based on fasted, single-dose, four-way replicate design studies, powered and analyzed for average bioequivalence.

Now what are we saying? We're saying that we want to give the agency and the industry more of a database. Therefore, we want this class of studies to be carried out in this way--single dose, replicate design, four-way cross-over--so that the information is available to the FDA. But we're going to analyze the data just like we do now.

So instead of 48, for example, 48 subjects, two-way cross-over, it would be 24 subjects, four-way cross-over and the statistics--consultants have come up with a methodology that will allow us to use that data.

So the same number of dosings but, in fact, less dosings because it's not multiple dose in this particular case.

Now at least 40 percent of the analyzed subjects must be either males-females, if the drug product is intended for use in both genders. And if the drug product is to be used predominantly in the elderly, at least 40

percent of the analyzed subjects must be 60 years or older.

Now the expert panel here is punting. We're not going to define "predominantly." We say that this would be some discussion between the agency and the sponsor in terms of what that means.

In addition, because we believe strongly that for these modified release dosage forms, a great deal of useful information comes from dissolution profiles, and dissolution profiles at more than one pH, that as a requirement, not just as a recommendation, that also dissolution profiles be submitted in three media at pH 1, 4.5 and 6.8. That will allow the agency to get some information.

Now up on the top I say powered and analyzed for average bioequivalence. Now my comment on the bottom--the vote. In fact, of the nine members there that were present, three of the members of the committee, and it was Drs. Bolton, Barr and Benet--you had to have a letter B--thought that it would be useful to use the suggested scaled individual bioequivalence method that is proposed in the guidelines. Six said no, use average bioequivalence, but the entire nine members there agreed that we should use--there's no disagreement on this recommendation using average bioequivalence. Three would have preferred scaled individual bioequivalence but, in fact, the recommendation of the committee is that we use our standard statistical

criteria and all nine members voting at that time agreed with this, even though three would have preferred--so that's a concrete recommendation to the advisory committee.

We don't have as concrete anything else. What about highly variable immediate release dosage forms? And we say particularly Class II in the Biopharmaceutical Classification System--it could be Class IV also; those are compounds that have poor solubility characteristics--the committee unanimously agrees that drug sponsors are encouraged to conduct single-dose, four-way replicate design studies, but that's the best we can do. We encourage that kind of information. And, in fact, there are a number of people carrying out such studies and that is useful information and that's why we had such good useful information at the workshop that showed us some new understandings of what was going on.

When we looked at this kind of criteria, if we were going to use this method for approval, if we were going to use the recommendations for approval in terms of what is presented, five of the nine members voting said scaled individual or scaled average bioequivalence would be a useful way to analyze this data.

Now the reason we changed here from the six to three number is because this is an "or." You could use scaled individual or scaled average.

Now scaled average has not been statistically provided to us by the working group consultants. It was a recommendation of the expert panel that such a methodology be viewed. And four of the nine members said still average bioequivalence, not scaled, but this just for your information because all we're doing is recommending that studies be carried out, encourage studies be carried out. We're not recommending at this time that the agency require these studies to be carried out.

This is an important piece of criteria for the scientific community. It is recommended that parameters, including relevant covariates from replicate design studies, which the FDA--it should be "that;" sorry; you know I'm an English major undergraduate--that FDA analyzes for the determination of population and individual bioequivalence be placed on the Internet at regular intervals in order to make them available to the pharmaceutical scientific community. Just that this is the kinds of data that can be very useful to all of us out there who are trying to develop this new methodology.

So in essence, we have a concrete recommendation on the modified release dosage forms and that is what the expert panel is recommending to the FDA and to this advisory committee; would at least be a first step in implementing these guidelines and we believe that we would have general

consensus from all aspects of the industry in terms of this, not unanimous consensus but general consensus because there is a carrot that these studies could, in fact, be not necessarily as burdensome as the present studies in modified release.

Thank you, Steve.

DR. BYRN: Questions for clarification for Les? Arthur?

DR. GOLDBERG: Hi, Les. If the N is selected based on the number of subjects you would require for an average bioequivalence and you split it into two groups?

DR. BENET: That's correct.

DR. GOLDBERG: Does the N stay the same?

DR. BENET: No, the N goes in half. Well, the number of dosings stays the same.

DR. GOLDBERG: Yes, but you expect the same statistical power?

DR. BENET: Well actually, that is--I'm not going to address that issue. I mean I know that there are some people that believe yes. I know Sandy Bolton is going to say no, that there's not, because we've discussed this recently. I think that's a different issue that really should be the issue of the consultants.

The idea was that you should be able to treat it as if it was a two-way cross-over. That's the idea of the

recommendation. You should be able to treat it as a two-way cross-over. And we have been provided by our expert panel, working group and statisticians a methodology to do that.

DR. GOLDBERG: One last question. One of the advantages supposedly of using an IBE versus the average bioequivalence would be for highly variable drugs. How would you define a highly variable drug in terms of coefficient of variation? Thirty percent? Sixty percent?

DR. BENET: I would take the definitions that have come out of these workshops that say within-subject variation of 30 percent or greater is a highly variable drug.

Now there's a very good question of whether some drugs that we think are highly variable really are highly variable and there was a lot of discussion in Montreal about Cyclosporine, for example, that there is data in the literature and also from the company, at least in healthy volunteers, that suggests that Neoral is not a highly variable drug under those criteria in this Cyclosporine situation. There are other studies that show that it would be.

DR. BYRN: Okay. Let's take a break until 10:45.

[Recess.]

DR. BYRN: Okay, if everybody could take their seats we could begin the next session.

Les Benet would like to make a clarification based on his earlier discussion and then we'll begin with the second session.

DR. BENET: A number of people have asked me in the recommendation on modified release, are we not making a recommendation about food effect studies? We're not paying any attention to the food effect studies. The food effect studies are still there. All we are making a recommendation is on the approval base on the statistical criteria.

So we are not making any recommendation about that there should or should not be a food effect study. There's now a required food effect study. That, as far as the committee is concerned, was not an issue. So we are not recommending that that food effect study go away.

DR. BYRN: Okay, we will begin with the next session, the first speaker. This is the report of the Population and Individual Bioequivalence Working Group and Walter Hauck will make the first presentation.

POPULATION AND INDIVIDUAL BIOEQUIVALENCE WORKING GROUP

DR. HAUCK: I'm leading off this session with what will be a brief review of some of the key concepts underlying particularly individual bioequivalence and then I'll be more than happy to answer any questions the committee has, whether now or at other times during the day,

as you wish.

It seems that there's kind of an underlying question to be addressed and I think Bill Barr particularly touched on that in his presentation. In current bioequivalence practice we focus on the average bioavailability of the test in compared to the average bioavailability of the reference, and the underlying question is what does this tell us about what happens at the level of the individual patient who switches from one formulation to another? And it seems to me that is kind of the clinical public health question that we need to keep in mind.

Now there was a letter in J. Pharm. Sci. back in '78 which usually is given credit as the first at least published reference referring to this problem. They actually called by subject-by-product interactions but a number of different terms apply. You've already heard a couple of variations of them today. So I thought it would be worth putting down a definition.

The term that you'll be most commonly hearing, at least in the next set of presentations, is subject-by-formulation interaction and what we mean by that is we're looking at the extent to which individuals differ in their test reference comparison.

So if the test reference difference is the same

for everybody, there is no interaction. If it varies from individual to individual, there is an interaction of some magnitude.

As an example, one of the datasets you'll be seeing in a later presentation is a calcium channel blocker where the test reference difference in women is different than it is in men. That's an example of a subject-by-formulation interaction. Or you could be more specific and say it's an example of a gender-by-formulation interaction. That's just indicating it's a special case.

So whether it's subject-by-product or whatever other terminology, we're really talking about the same thing. Hopefully that won't be too confusing.

Now actually although we're talking individual bioequivalence now, this idea does go back a way and the FDA did have a rule in place referred to as the 75/75 rule that was intended to address the issue of within-subject comparison of test and reference. And that rule was that at least 75 percent of the individuals had to have their individual test reference ratio fall within 75, 1.25. And that rule was later dropped because of its bad statistical properties and the paper by Haynes is a good source on some of the information on that.

And the other bit of history I want to mention is the paper that Sharon Anderson and I published in 1990,

which was actually originally motivated by the 75/75 rule because we thought that that did, in fact, capture something worthwhile. It did capture the notion that one needed to look within an individual to have some notion of what's appropriate for bioequivalence.

Now we've also identified two different clinical contexts and most of the discussion today will really be the first one. Terminologies--we're usually using a switchability, and have in mind that a patient has been successfully controlled on a pioneer or reference product and that they're now switched to another formulation. And switchability would mean that they retain essentially the same efficacy and safety on that switch.

So the clinical context, at least in this country, is that the switch is transparent, usually to the physician, maybe even to the patient, and what we're asking is that the actual formulations switch, so what we ask is the switch is also transparent in terms of the safety and efficacy that that patient sees.

Second clinical context is the different one where you have a drug-naive patient who's starting on a formulation. Can they take either one with the same expectation? I tend to think of this as asking whether or not a physician's experience initiating treatment on one formulation can be carried over to new patients initiating

treatment on the second formulation. And that would be what we'd typically call prescribability.

Now a key concept, and you've already heard some of this from Roger, that kind of motivates what we do for a criterion, how we think about individual bioequivalence, is the individual therapeutic window. Now the motion of the individual therapeutic window is that each individual has an interval in which their bioavailability must be retained. And I think Roger is very clear about the fact that there could be an individual window that would typically be much narrower than the population window or the therapeutic index, as I think it used to be called.

Now one of the things that's nice about the window, I think, is that it helps you in terms of what you need to know and what you don't need to know or what you need to show and what you don't need to show.

I want to repeat here one of Roger's graphics. Particularly if we look at the top one, this is actually--the curves correspond actually to one of the datasets that's already out on the website from the FDA. The test product has an average bioavailability that's 15 percent higher than the reference but a 40 percent reduction in CV. So it's a less variable, more bioavailable product. We can see that the two curves are clearly not identical.

But if you had a wide therapeutic index or wide

individual window situation, as shown in the graphic with the maximally tolerated and minimally effective, fairly widely separated, there'd be no reason to say that there's anything wrong with--if this reference product is fine, then this test product should be fine, as well. The patient is being retained very well within that very wide interval.

So you have a nice wide target. You should be able to be more flexible in your criterion.

The bottom one, of course, is the opposite situation where you have a very narrow window and that would tell us that that's the situation where you can't be as flexible.

The last bit of terminology and then I'll turn it over to Mei-Ling to continue this. When we talk about individual bioequivalence criteria, what we mean is a criterion that's developed to address that switchability issue that I talked about, and that's really what we'll be primarily discussing today. And then population bioequivalence criterion, the one developed to address the prescribability context that I mentioned.

DR. BYRN: Any questions for clarification for Walter?

[No response.]

DR. BYRN: Okay, thank you very much.

The next speaker will be Mei-Ling Chen, who will

cover criteria and update of the guidance.

CRITERIA AND UPDATE OF GUIDANCE

DR. CHEN: Good morning. My assignment today is to provide you an overview of criteria for bioequivalence determination and update of FDA's draft statistical guidance that was published in August this year.

This is the title of the draft statistical guidance: "Average, Population, and Individual Approaches to Establishing Bioequivalence." And on the bottom of this slide is the website address for the guidance.

You may have seen that the new guidance has covered three bioequivalence criteria. It's a revision of the 1997 preliminary draft guidance that outlined the statistical concepts and methodology for population and individual bioequivalence approaches.

The guidance has been updated based on the public comments to the 1997 preliminary draft guidance. It also incorporates and updates the 1992 guidance for statistical procedures on bioequivalence studies using the average bioequivalence approach.

I would like to point out that the new guidance focusses on the statistical methods, so it talks about how to use the criterion once a specific criterion has been chosen by the drug sponsors. It doesn't, however, address the question of when to use the specific criterion. And

that will be addressed and discussed by Dr. Vinod Shah in his talk for the general bioavailability-bioequivalence guidance for orally administered drug products.

This slide is the outline of the statistical guidance. The guidance starts with the general statistical model followed by the description for three bioequivalence criteria. The statistical criteria proposed in this guidance remains the same as proposed in the 1997 guidance. This guidance describes all the possible study designs for the three bioequivalence criteria. The guidance also describes statistical analysis for all the possible study designs.

In essence, there are three types of bioequivalence criteria that have been developed over the years. Average bioequivalence focusses on comparison of population means between the test and the reference product while population and individual bioequivalence focus on both means and the variances.

The distinction between population and individual bioequivalence is that population bioequivalence addresses the question of prescribability and so it deals with total variances between the test and the reference product, yet individual bioequivalence addresses the question of switchability, so it deals with within-subject variances and subject-by-formulation interaction.

The thesis here is that the assessment of subject-by-formulation interaction is important in the consideration of whether an individual could be switched from one formulation to another while maintaining the same safety and efficacy of the drug.

Some concerns for using individual bioequivalence lies in the fact that replicated cross-over designs are needed in order to estimate these variance components separately.

So except for average bioequivalence that focusses only on the comparison population means, a general principle for population and individual bioequivalence is to compare the difference between the test and the reference product in the bioavailability measures with the difference between the reference and the reference formulation.

For individual bioequivalence, the test and the reference product will be administered to the same individual. For population bioequivalence, the test and the reference product will be administered to different individuals.

So we call this comparison a difference ratio and the goal of bioequivalence demonstration is to show the difference ratio is not substantially greater than 1.

Based on the concept of distance ratio or difference ratio, we have developed a general form of

bioequivalence criteria that combines the average bioequivalence criterion and the variance terms, which is then normalized by the variance of the reference product.

So depending on the variance terms, you have two distinct bioequivalence approaches. One important feature of these approaches is that with reference variance in the denominator, now we are talking about a scaling approach where the bioequivalence criterion will be scaled based on the reference variability.

The reference scaling approach comes from the understanding that the pioneer or reference product has been demonstrated to be safe and efficacious clinically. The variability of the reference product well defines the therapeutic window and therefore should set or otherwise adjust the public standard; for example, the bioequivalence limits on the right-hand side of the equation.

The reference scaling approach, in fact, will take us away from the current practice and that is a one-size-fits-all approach. So this approach will offer us flexible criteria for variance causes of drug products. We may widen the goalpost for highly variable drugs or drug products and we may narrow the limits for narrow therapeutic range or index drug products.

The proposed criteria for population and individual bioequivalence have both means and variance in

one equation. As such, it's called aggregate criteria. The aggregate criteria will provide the agency a mechanism for rewarding the drug sponsors for manufacturing a less variable formulation. Also, he can have a trade-off between the difference in the means and the difference in the variances.

On the other hand, concerns were raised regarding this criterion that a substantial reduction in the variability of the test product may permit or allow products with a large difference in the means to enter the marketplace.

So in view of that, some have suggested disaggregate criteria. The disaggregate criteria consider the means and the variances separately. That is, you may have a criterion for the means and then you may have another criterion for the variances.

Intuitively, the reasons for using disaggregate criteria is that they offer the advantage of preserving the current average bioequivalence criterion for the difference of means and thus avoids the mean variance trade-off concerns. However, with separate comparisons for means and the variances, we are talking about a criterion with a multiplicity of tests and thus it increases the regulatory burden.

The disaggregate criteria ignore the fundamental

switching concept, as described by Roger and Walter, that the distribution of the bioavailability matrix for the reference product should define the therapeutic window and drive the bioequivalence limit. In addition, there will be no reward or encouragement for reduced variability in the test product.

So the current draft guidance issued by the FDA recommends an aggregate criteria.

Regarding the mean variance trade-off, the working group so far has considered various approaches for resolution of this issue. One option is to control the trade-off by weighting of the appropriate variance terms. However, it disturbs the distance ratio concept which underlies the individual or population bioequivalence criteria.

Another option is to impose a constraint on the allowable mean difference, for example, 10 to 20 percent, on the point estimate. This is for reasons that are more political than scientific, just as indicated by Dr. Benet, but the working group is prepared to have this proposal on the table for the advisory committee's input and advice today.

This is my last slide. I would like to point out that the current guidance has two major improvements over the 1997 preliminary draft guidance on the statistical

issues. One improvement is the estimation of variances and the second improvement is the computation of confidence intervals.

The 1997 preliminary draft guidance recommends restricting maximum likelihood method for estimation of variances, and that involves normality assumptions and also constrains Signa D squared to be nonnegative.

The current guidance has changed to the method of moments that doesn't make any assumptions for normality and doesn't assume Signa D squared to be nonnegative.

The 1997 preliminary guidance has proposed bootstrap method for computation of confidence intervals. The current 1999 guidance has a much simplified non-bootstrap method and that could achieve the job in a very short period of time.

This concludes my presentation. Thank you.

DR. BYRN: Questions for Mei-Ling? Yes, Arthur?

DR. GOLDBERG: Mei-Ling, you suggested that the goalposts be widened for highly variable drugs and narrowed for NTI drugs. If you base it all on the variance found within the reference, why should there be a difference between NTI and other drugs?

DR. CHEN: Well, historically, we have observed that most NTI or NTR drugs have lower variability. So by reference scaling approach, you would effectively tighten

the bioequivalence criteria for NTR drugs.

DR. GOLDBERG: But that's just luck of the draw that the NTR drugs happen to be less variable. You could have highly variable NTR drugs, as well.

DR. CHEN: So far, we haven't seen NTR drugs with high variability except Cyclosporine that Dr. Benet mentioned but a new formulation for Cyclosporine, in fact, has low variability.

DR. BYRN: Okay, thank you, Mei-Ling.

Our next speaker is Larry Lesko, who's going to discuss a mechanistic understanding.

MECHANISTIC UNDERSTANDING

DR. LESKO: Good morning. I'm going to have to have an assistant here because we have a multi-media presentation. I'm going to combine some slides from my computer, as well as some overheads and hopefully it'll all go smoothly.

My mission here this morning is to provide the advisory committee some rationale to explain subject-by-formulation interactions and provide some insights into a mechanistic understanding of why these subject-by-formulation interactions emerge.

The flow of this presentation is going to move from a mechanistic definition of subject-by-formulation interaction to a general paradigm for gaining insights into

the interactions and why they're occurring. To illustrate the principles of the paradigm we'll present a case study and we'll walk through a stepwise analysis of that case study and then finish up with some conclusions from our deliberations.

We weren't happy with Sigma D as a definition of subject-by-formulation interaction and since we're talking mechanistically, we wanted to get into something that's more biopharmaceutical in terms of a definition. So when we talk about a subject-by-formulation interaction in the mechanistic world, what we're talking about is the in vivo dissolution of a formulation and the absorption of its drug, display sensitivity to the physiological variables in the gastrointestinal tract. And those variables have a range which we find in healthy subjects or in patient volunteers that participate in these subjects.

Furthermore, there's a second part to the definition. When the excipients in a formulation can influence those physiological variables or the physical chemical properties of a formulation or its drug in the GIT, we have a subject-by-formulation interaction.

This is a very key set of concepts here and you can see what I've highlighted in blue and those are the components of the subject-by-formulation interaction that come together to produce the attribute of this system, which

will be the S by F.

I presented the same concept in this paradigm and we approach the paradigm as a complex system from which emerges a property or an attribute we call the subject-by-formulation interaction. In a complex system we generally have a hierarchy of systems. We have subsystems that are relatively simple but when you combine some simple subsystems, they produce a more complex system and you end up with a sequential hierarchy.

I don't have a pointer but if you sort of walk through from the top, you take a simple subsystem like a drug that has its own physical chemical properties, you take an excipient, it has its own physical chemical properties, and when you combine that drug and excipient you end up with a formulation that has its own properties. And that formulation, by the combination of properties from this and that, has a new set of properties that are inherent to that more complex system.

And as you move down this hierarchy of subsystems, you get into the more complex system of putting that formulation into the gastrointestinal tract with its own variables and then that gastrointestinal tract is part of a complex whole body system from which emerges measures of bioavailability.

So it's the whole process and the interaction

between the things I've highlighted in blue that we think produce, at the end, a subject-by-formulation interaction.

Now the way we characterize the subject-by-formulation interaction is in terms of risk factors. We found that it's not easy to simply say one's going to have or not have a subject-by-formulation interaction. Rather, we think that there's a continuum of risk factors associated with those four elements of the subject-by-formulation interaction that eventually contribute to what we observe in the replicate design studies. And I'll walk through both the properties of the drug, the excipient, the formulation, to give you a sense of what we're talking about.

I'm starting out with the drug properties and based on risk factors, one would conclude, I think, that subject-by-formulation interaction is unlikely to occur when I have a simple drug substance, a highly soluble, highly permeable drug that has rapid intrinsic dissolution. Because of its high solubility and high permeability, there is no site- and transit time-dependent absorption.

I would say a simple situation is where we have no physical or chemical incompatibilities. It's not an achiral substance so we have any risk of enantiomer differences. And its pharmacokinetics are uncomplicated and there's no intrinsic pharmacological properties that can affect the gastrointestinal tract.

Compare that to a more opposite situation. I would say for that drug substance when we have a likelihood of a subject-by-formulation interaction we're talking about something that is in the low solubility/low permeability class or the low solubility/high permeability class. Because of those properties, it has slow intrinsic dissolution. Because of low permeability it may have site- and transit time-dependent absorption. There could be some physical chemical incompatibilities, perhaps some complicated pharmacokinetics and maybe the drug itself exerts an effect on gastric pH or on the intestinal transit time or gastric emptying.

So this is a range of properties, like I said, a continuum moving from low-risk to high-risk.

I can do the same thing with the excipient properties. They're unlikely to contribute to a subject-by-formulation interaction when these conditions hold: no effects on pH, no effects on permeability, transit time, no interactions with the drug substance, no effects on presystemic CYP 3A4 or PGP transport processes.

Now going to the other end of the spectrum, one would say, I think, that excipients are more likely to contribute to a subject-by-formulation interaction when they have the ability to alter pH, promote permeability or perhaps inhibit it, have a pharmacological effect on

motility themselves. Maybe they have some interactions. And then when we get down into the enterocytes perhaps they inhibit presystemic 3A4 metabolism or somehow reduce the PGP transport or perhaps other carrier efflux systems.

Now I want to use one example that we recently have of excipient properties to give you a sense of how an excipient can influence bioavailability. The data that we're going to show on the overhead comes from a study that's currently under way at the University of Tennessee. It's an FDA-sponsored study and we took a fairly simple dosage form. We took Ranitidine.

Now we picked Ranitidine because it has high solubility but it has low permeability. Having low permeability, it's going to be in that higher risk category that I mentioned for the drug substance.

We took this substance and put it in a relatively simple vehicle--a solution. There was no manufacturing tableting, capsule or whatever. And the vehicle was one that contained either sorbitol or sucrose.

Now one would say the bioavailability of an oral solution is self-evident and what we demonstrated with some preliminary data on a couple of subjects is a marked difference in the bioavailability of Ranitidine when it's combined with sucrose or sorbitol. These aren't large amounts of sorbitol and sucrose but they illustrate the

effect that an excipient can have on physiological variables.

The explanation for the higher blood levels here of Ranitidine with sucrose is that when you give sucrose orally, it in a sense tricks the body into thinking it's in a fed state. It reduces gastric emptying and increases the absorption in the upper part of the GI tract.

When you give sorbitol, sorbitol has an osmatic effect on the intestinal tract. It speeds up intestinal transit, reduces the residence time in the gut, and that's important for a low-permeability drug because the overall absorption is going to be reduced.

We can show you two more subjects to illustrate the point. I don't have to say much more about that one, other than you can see the same trend. And then the third subject shows something very similar, a little more erratic.

This study is conducted in 24 subjects, male and female in the population. We don't have complete data on the study but it gives you a sense of what we're talking about when we talk about an excipient having an effect on bioavailability.

We talked about a formulation. Now we've taken the drug and excipient, put it into the formulation, and what kind of formulations will be unlikely to have a subject-by-formulation interaction?

Well first of all, if I'm comparing pharmaceutical equivalents, I don't have any complications. I'm not comparing tablets to capsules. I'm comparing tablets to tablets, qualitatively and perhaps quantitatively the same.

I wouldn't expect any problems with simple formulations if I had a solution, assuming I had no active excipients. If I had a solid, oral or immediate-release dosage form I'd expect less of a problem.

If my excipient-to-drug ratio is low--that is, most of the dosage form is drug--I'd have less of a problem. And if I had uncomplicated manufacturing and rapid and pH-independent dissolution of the formulation, one wouldn't anticipate many problems.

At the other end of the spectrum, a likely contributor to subject-by-formulation interaction is when I'm comparing two products that are not pharmaceutically equivalent. I may have complex formulations, such as a transdermal product or a modified release product. I might have high excipient-drug ratios, where excipients can play a bigger role. And I might have more complicated manufacturing, perhaps some wet granulation compression, that sort of thing. And perhaps that formulation might have low and pH-dependent dissolution.

So again the idea here is to compare and contrast the spectrum and continuum of risk factors.

And then finally, you take that formulation and put it into the test subjects and we encounter a number of physiological variables that can complicate the picture even more. And those physiological variables that we think are important to emerging subject-by-formulation interactions include the pH gradient along the gastrointestinal tract, the gastric emptying time, which can have a tenfold or larger range, small intestinal transit time, colonic residence time, particularly for extended release or modified release products.

There's an intestinal permeability gradient. There's a gradient of activity and capacity of CYP 3A4. And there's also an activity and capacity gradient for the transport processes.

Now we think about a subject-by-formulation interaction and I think we have to reflect upon the physiological range of all these properties that you see in test subjects in bioequivalence studies, even if they're homogeneous test population, all males, but even more so if it's male and female or people with disease states because we get physiological ranges under genetic or environmental control, so we know there's going to be differences inherently and extrinsically. We know gender from the literature affects these physiological variables; so does age, race, disease states. We all know about diet affecting

transit time. And certainly if the protocol had any co-administered drugs, there's a potential there.

So as I said in that mechanistic definition of subject-by-formulation interaction, it's when formulations, two formulations, are sensitive to the range of variables in physiology that one encounters in test subjects.

Now this working group that's been looking at mechanistic understanding has taken a classical case method approach to trying to gain insights into the subject-by-formulation interaction. What we've done is take actual examples of bioequivalence studies that have shown subject-by-formulation interaction and we conduct a stepwise analysis of that data.

We determine the risk factors that are included in the example in terms of drug, excipients, the formulation and the test subjects. And then from those risk factors we obtain insight in a retrospective way into the possible mechanism by which a subject-by-formulation interaction is occurring.

What we've learned from the experience is that when one has multiple risk factors, as described on those earlier slides, the probability of observing a subject-by-formulation interaction increases.

I'm going to walk through an example to illustrate this stepwise case study method of analysis and I've picked

a calcium channel blocker, which is the well known drug X, and I'll walk through some of the observations from the study and then some of the mechanistic insights.

This study was a two-way cross-over study. I emphasize it was not replicated. It wasn't one of these four-way cross-overs. It was a single-dose, fasting bioequivalent study. It was conducted in healthy young males, 12, and females, 13, so we had that diversity in the test subjects.

These were oral capsules. They were plasma levels measured of parent and metabolite, and there was a standard analysis of the study looking at not so much the subject-by-formulation interaction in this case but the group-by-formulation or gender-by-formulation interaction.

I might point out that the formulation was complex. It was a modified release formulation.

And the data from the study looks like this. This is product A. And what it shows is the pharmacokinetic profiles in female and male test subjects. And this is somewhat of an uneventful profile. There's a short lag time here. Relatively early, three to four hours, there's a certain rise in the blood concentrations. They dip down and then they continue with absorption in the latter part of the transit time.

Again what this shows is the modified release

nature of these products, product A, where you have some early release and then some later release and, as you can see, no difference between female and male subjects.

Product B shows a little different profile and this is what's interesting in terms of subject-by-formulation interaction. Here again we have a little bit of lag time but you can see the products differed in the way they rise up to a peak. They come down and you can see a fairly large chunk of area under the curve right here in the female subjects and then they go down in a terminal decay with no difference in half-life.

So the key part of this slide is a difference in the area under curve and in the Cmax for one product but not the other product when you look at male and female subjects.

When you look at the BE data, you can get an insight into what's going on in terms of the numbers. First, with the male subjects, I'm going to compare Cmax and area under curve and look at the product A-to-product B ratio. And you can see that it's pretty much uneventful. It's close to 1, not much difference. This would pass the typical bioequivalence criteria of the 90 percent confidence interval being between 80 and 125.

Different story when we look at the female subjects in this study. When we look at Cmax and area under curve you can see the big difference in the ratio of A to

B--.62, .77. They would obviously fail if we applied a bioequivalence test to that. And the reason it's so low, of course, is the higher area under curve and Cmax that was observed for product B.

We get a visualization of subject-by-formulation interaction via stick plots, and this is a stick plot for all of the subjects in the study, male and female. And it isn't all that dramatic, so on the overhead I'll show you a slide of the stick plot for the male and female and you can see how consistent this observation was and that it wasn't an artifact of the methodology.

This is the same sort of thing. It's a stick plot. Look at the males. Random variability--what are we looking at here? I think area under curve. But anyway, you can see some go up, some go down, some stay the same. The overall mean is the same. So there's nothing going on here with product A and B in the male subjects.

When you look at the females you can see some consistent trends. They're low on A, high on B. We observe that in the pharmacokinetic curve. The means are different. We know that to be the case. And, of course, when you compare the ratios of means, you have your subject-by-formulation interaction pretty evident. It happens not only with area under curve but it also happens with Cmax.

Back to the slides. So I showed you stick plots

and let's go on to the next one.

Now let's take a stepwise analysis of this example, and I think we can do this with every example that shows a subject-by-formulation interaction. And if we have access to a large database, this is the process by which we would analyze it.

First of all, it's clear from this example that we have the multiple risk factor profile. It's not a simple case. We took a drug in this case which was actually a Class I drug--highly soluble, highly permeable--and we made it a Class II drug by the formulation, making it modified release. So it's functioning in the gastrointestinal tract as a Class II drug--low solubility, high permeability.

It wasn't difficult to look at the excipients in this product that are prolonging release and realize that they're pH-sensitive in the way they act. The formulation was complex in each case--extended release.

The drug in this case was complex because it was a substrate not only for local 3A4 metabolism but it was also a substrate for the efflux in the lower intestinal tract PGP. And both of these processes were significant in terms of the drug's absorption and they both have the potential to be easily saturated.

The absolute bioavailability, because of these factors, was less than 50 percent. And the study was