

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF  
THE ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

8:36 a.m.

Friday, December 12, 1997

Maryland Room  
Quality Hotel  
8727 Colesville Road  
Silver Spring, Maryland 20910

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## P R O C E E D I N G S

(8:36 a.m.)

1  
2  
3 DR. ZIMMERMAN: Ladies and gentlemen, I think  
4 we'll get started.

5 Good morning. This is the second day of the  
6 meeting of the Advisory Committee for Pharmaceutical  
7 Science. I'm Cheryl Zimmerman from the University of  
8 Minnesota, and I'm the Acting Chair today because our real  
9 Chair was called away on an emergency.

10 Before we get started, I'll ask Kimberly to  
11 read the conflict of interest statement.

12 MS. TOPPER: The following announcement  
13 addresses the issue of conflict of interest with regard to  
14 this meeting and is made as part of the record to preclude  
15 even the appearance of such at this meeting.

16 Since the issues to be discussed by the  
17 committee will not have a unique impact on any particular  
18 firm or product, but rather may have widespread  
19 implications with respect to entire classes of products, in  
20 accordance with 18 U.S.C. 208, waivers have been granted to  
21 each member and consultant participating in the committee  
22 meeting. A copy of these waiver statements may be obtained  
23 from the agency's Freedom of Information Office, Room 12A-  
24 30 of the Parklawn Building.

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

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

11           Thank you.

12           DR. ZIMMERMAN: Our order of business today for  
13 this morning and a good part of the afternoon are  
14 presentations from the Clinical Pharmacology Section of  
15 MPCC. The moderator for this is Dr. Larry Lesko, and he  
16 will be giving us an overview.

17           But first, let me ask the committee to  
18 introduce themselves and their affiliations once again.  
19 Dr. Lesko?

20           DR. LESKO: I'm Larry Lesko, Director of the  
21 Office of Clinical Pharmacology and Biopharmaceutics.

22           DR. WILLIAMS: Roger Williams, Deputy Center  
23 Director, Center for Drug Evaluation and Research.

24           DR. CANTILENA: Hi. I'm Lou Cantilena,

1 Clinical Pharmacology, Uniformed Services University.

2 DR. FLOCKHART: I'm Dave Flockhart. I'm  
3 Assistant Professor of Medicine and Pharmacology at  
4 Georgetown University.

5 DR. PARKINSON: I'm Andrew Parkinson. I am  
6 Professor of Pharmacology and Toxicology at the University  
7 of Kansas Medical Center and CEO of Xenotech.

8 DR. WATKINS: I am Paul Watkins. I'm Professor  
9 of Medicine and Director of the General Clinical Research  
10 Center at the University of Michigan.

11 DR. BYRN: Steve Byrn, Professor of Industrial  
12 Pharmacy and head of the Department of Industrial Pharmacy  
13 of Purdue University.

14 DR. MAYERSOHN: Good morning. Michael  
15 Mayersohn, Professor of the College of Pharmacy, University  
16 of Arizona.

17 DR. GOLDBERG: Arthur Goldberg. I'm an  
18 independent consultant.

19 DR. LAMBORN: Kathleen Lamborn, Professor of  
20 Neurological Surgery and Director of Biostatistics Cancer  
21 Center Corps at the University of California, San  
22 Francisco.

23 DR. BRAZEAU: Gayle Brazeau. I'm Associate  
24 Professor in the Department of Pharmaceutics at the

1 University of Florida College of Pharmacy.

2 DR. STEWART: Jim Stewart, University of  
3 Georgia, College of Pharmacy, Professor.

4 DR. ZIMMERMAN: Thank you.

5 We'll start with Dr. Lesko then.

6 DR. LESKO: Thanks. Good morning, everybody,  
7 and I'd like to welcome the committee and guests to the  
8 second day of our advisory committee meeting.

9 I'd like to direct your attention to a fresh  
10 topic for today, one that I think everyone can relate to,  
11 drug-drug interactions, as either a clinician, scientist,  
12 or even a patient. What we're going to present this  
13 morning is a series of hopefully interesting subtopics on  
14 drug-drug interactions that we'd like the committee to  
15 direct our comments towards. These comments and questions  
16 will be related to the subsequent development of a guidance  
17 on the in vivo drug-drug interaction area that we hope to  
18 develop in the upcoming future.

19 I'd like to acknowledge the invited experts and  
20 guests that are with us today. The committee members  
21 certainly recognize their role in the proceedings here  
22 today, and I just want to encourage the invited experts and  
23 guests to direct any comments or questions that they have  
24 to the FDA speakers that they'll hear this morning. We

1 hope to get again some specific questions on the agenda for  
2 our discussion and look forward to the comments of the ACPS  
3 members, as well as our invited experts and guests.

4 I'd like to introduce a little background.  
5 Roger did a good amount of background yesterday, but this  
6 slide represents what I think is the mission and goals of  
7 the Office of Clinical Pharmacology and Biopharmaceutics  
8 and provides a backdrop for why we're leading the  
9 discussion today in the area of drug-drug interactions.

10 The segment of this slide above the dotted line  
11 is what we might call the area of phase III or late  
12 clinical trials where the goal of those studies is to  
13 document the safety and efficacy of the drug product.  
14 Within the context of these clinical trials, we recognize  
15 that there's a fair amount of variability in response in  
16 the cohort of patients in these trials, and that  
17 variability in turn comes into play when we look at the  
18 label and recommend a dose range for the projected target  
19 population.

20 When we get below the line, we move into the  
21 two areas that come under the Office of Pharmaceutical  
22 Sciences. One of those areas I might call  
23 biopharmaceutics. It's an area that focuses primarily on  
24 the drug product and in particular getting the drug

1 substance from the product into the general circulation.  
2 The topics covered here would range from bioavailability,  
3 food effects, down to dissolution, and we heard some of  
4 those topics yesterday with regard to the Biopharm  
5 Classification System and with regard to individual  
6 bioequivalence.

7 So, the purpose of this science and the purpose  
8 of what the office does in the review of NDA's is to  
9 understand these issues of the drug product and how they  
10 contribute to variability and response.

11 On the other side of the slide is the area we  
12 might call clinical pharmacology. In contrast to the  
13 clinical science up here, this area is focused primarily on  
14 the PK and PD of the drug substance. Again, the goal of  
15 our review of this information is to understand their  
16 contributions to the variability in response in terms of  
17 the patient population.

18 When we get into the world of drug  
19 interactions, though, I think we're trying to bridge the  
20 gap between the target population, what's in the label, and  
21 what is the dosage regimen for an individual patient out  
22 there in the community when this product is eventually  
23 approved. I would characterize that as a situation where  
24 we need to be aware of what dose adjustments are necessary

1 for these high risk groups. High risk groups are defined  
2 in turn by covariates that might range from demographic  
3 issues like age or gender down to things like disease  
4 states or, as the focus of our discussion today, the drug-  
5 drug interaction area and how do we adjust the dose for an  
6 individual patient who is receiving two potentially drug  
7 interacting substances.

8           So, that's the context for today's discussion  
9 in terms of both drug development and in terms of  
10 regulatory decision making.

11           Now, I'd say today's goal is to talk about  
12 policy development and the topic of drug interactions is  
13 under the policy development arm of the Center, the Medical  
14 Policy Coordinating Committee, specifically the Clinical  
15 Pharmacology Section. I've indicated a series of working  
16 groups that are active under this coordinating committee  
17 and you can see the covariate nature of these working  
18 groups. We have the renal and hepatic disease working  
19 groups over here and we have the in vitro drug metabolism  
20 and in vivo drug metabolism working groups over here.

21           This working group, of course, produced the  
22 guidance which was issued in April of 1997, and this is the  
23 working group whose issues we'll bring before the committee  
24 today in the hopes of moving forward in the development of

1 a subsequent guidance.

2 Over here we have two working groups that we  
3 view as clinical pharmacology tools, population PK/PD, and  
4 also PK/PD dose response working groups. These tools are  
5 used in turn to bring some analysis power to the various  
6 studies that deal with the covariates.

7 These four working groups are relatively new  
8 ones. We'll hear from one of them this afternoon which is  
9 the IND, not to be mistaken for individual, BE. This is  
10 the Investigational New Drug Working Group that's dealing  
11 with bioequivalence studies within the new drug development  
12 process.

13 Today you'll be hearing three sets of remarks  
14 from members of the working group. Dr. Shiew-Mei Huang,  
15 who's in the Office of Clinical Pharmacology and  
16 Biopharmaceutics, will lead the discussion and provide a  
17 general overview of what the issues are and then come back  
18 and talk a little bit more specifically about an  
19 interesting area of data analysis and label language.

20 Next you'll hear from Dr. Peter Honig, who's in  
21 the Office of Review Management. He's a team leader in the  
22 Pulmonary Division. Peter is on the working group and his  
23 focus will be the issues of study design for drug  
24 interactions.

1           Then finally, Dr. Jerry Collins, who heads the  
2     Laboratory of Clinical Pharmacology in the Office of  
3     Testing and Research, will come on and talk about the links  
4     and relationships between the in vitro and in vivo area of  
5     drug interactions.

6           The other names on here give you an idea of who  
7     else is on the working group from OCPB. We have a group of  
8     statisticians working with us and we have a group of  
9     special government employees and contractors working with  
10    us as well and some of those individuals are here today.

11          One of the things that we're cognizant of is  
12    the relationship of guidances to things going on globally,  
13    as well as locally in the United States. I just want to  
14    point out there are some important links between what we're  
15    doing in the area of in vivo drug interactions with our  
16    guidance and other things that are going on simultaneously.

17          As I mentioned, we already have provided a  
18    guidance for the industry and our reviewers on the area of  
19    in vitro drug metabolism. However, there are some other  
20    initiatives that relate to our guidance. One of them is a  
21    CPMP guideline which is coming out of the European sector,  
22    and at this point in time they have a guideline for  
23    investigation of drug interactions that we've had some  
24    discussion with them on it. This guideline has been out

1 for public comment. That public comment period has just  
2 closed, and we're looking at that in terms of similarities  
3 and differences in terms of the regions.

4 In the ICH there's a guideline called E-4 that  
5 deals with dose-response information, and in different  
6 parts of the ICH E-4 document, there's some reference to  
7 the use of dose-response information to interpret the  
8 outcome of drug-drug interactions in terms of adjustment of  
9 doses.

10 Then finally, we're in the early stages of  
11 discussing with NICH the common technical document. At the  
12 current time, there's a clinical pharmacology section. The  
13 details of this section haven't been worked out but it's  
14 anticipated that one of them will be a drug-drug  
15 interaction section. And one of the means of beginning to  
16 discuss harmonization is to look at the guidances that are  
17 currently out there.

18 So, when we talk about our guidance, we also  
19 have to think of various connections I think and  
20 recognizing the connections between them.

21 I think everyone could imagine, with all the  
22 different drugs out there, the number of drug-drug  
23 interactions that are potentially possible are quite  
24 substantial. I think the importance in recognizing that is

1 that somehow we have to transfer information to knowledge,  
2 information that comes out drug development or out of drug  
3 interaction studies into knowledge for the practitioner for  
4 optimal prescribing.

5 I don't think there's any one solution to this  
6 potential complexity of drug-drug interactions, and as a  
7 result, we tend to integrate various strategies and tactics  
8 into providing optimal information to the practitioner.  
9 So, if we think of the practitioner and patient here in the  
10 center, we'll be touching on a number of the strategies  
11 that we use to provide drug interaction information.

12 We'll be emphasizing today the area of phase I  
13 clinical studies. These would be the confirmatory studies,  
14 the discrete studies that are typically part of early  
15 clinical trials in drug development. We might call them  
16 phase I/phase II studies. Many of our issues today will  
17 focus on that.

18 We'll also hear about population PK/PD. I  
19 would say it's an area that's pretty much under-utilized in  
20 the drug interaction area but I think has a lot of  
21 potential if we can identify the issues that are important  
22 in accepting the information from pop PK studies or what  
23 some people refer to as pharmacokinetic screens.

24 Then we'll look again at preclinical studies or

1 nonclinical studies where we try to focus primarily on drug  
2 metabolism and inhibition and induction interactions, and  
3 we'll talk about the issues that we have for the current  
4 guidance in terms of in vitro/in vivo links.

5           Finally, we won't touch upon it, but I put it  
6 up here for completion that post-marketing  
7 pharmacovigilance is important in uncovering interactions  
8 that either were not anticipated mechanistically here, not  
9 studied discretely here or not picked up in the general  
10 population in phase III pop PK studies. We recently found  
11 several interactions, as I think everyone is aware, in  
12 terms of post-marketing interactions.

13           So, what we're going to focus on today then are  
14 the issues related to drug interactions that I would say  
15 underpin the guidance that we have under development. We  
16 planned about an hour of formal remarks this morning and  
17 left almost two hours for the committee discussion. So,  
18 we're looking forward to a lot of good input.

19           These are questions that I think will come out  
20 of the individual discussions. They may be somewhat  
21 general, but I think the individual speakers will try to  
22 direct the committee's attention to some specific questions  
23 that we'd like your input on in terms of moving forward  
24 with this guidance development project.

1           For example, in the area of the phase I  
2 confirmatory studies, some questions would relate to what  
3 is the best study design for drug interactions, a difficult  
4 question, but it might be rephrased to say, what are the  
5 issues that need to be considered to get us to the best  
6 study design for drug interactions?

7           Once we have the data in hand, what are the  
8 most informative methods of analyses? We'll see what the  
9 current situation is our product labels, and I think we can  
10 do much better.

11           Another question is, should drug interactions  
12 be handled as an equivalence problem? That has two  
13 components to it. One is the method by which we determine  
14 equivalence and the second is the criteria that we bring to  
15 bear on the results of that method in terms of claims.

16           Label language is another question we'll get  
17 into in terms of expressing the data from drug interactions  
18 in terms of making clinicians and patients knowledgeable in  
19 this area.

20           The role of population PK/PD and drug  
21 interactions.

22           And finally, what added value do the in  
23 vitro/in vitro relationships bring to the in vivo story in  
24 terms of selecting what confirmatory studies could do and

1 in terms of what to look for in the population PK/PD area.

2 So, with that overview, I'd like to conclude by  
3 just pointing out that in the background for today's  
4 meeting in the book that we distribute, there is a section  
5 related to this morning's topic, and in there are two  
6 documents that are relevant to the discussion.

7 One is the results of a workshop that we had  
8 with the trade association PhRMA in which we presented some  
9 issues and discussions, and what the committee has received  
10 is basically the consensus report from that workshop. So,  
11 it's a point of reference.

12 And then the second thing in that section was a  
13 beginning concept for the guidance which represents an  
14 early draft of what we envision to be in the guidance, but  
15 as we'll see from the discussions this morning, there are  
16 some issues that we need to resolve first before we can  
17 move forward. So, that's another point of reference.

18 So, with that introduction, I'll turn it back  
19 to the Chair, Dr. Zimmerman.

20 DR. ZIMMERMAN: Well, in the first presentation  
21 on the drug-drug interaction guidance, Dr. Shiew-Mei Huang  
22 will frame the discussion for us under the title of General  
23 Issues.

24 DR. HUANG: Good morning.

1           As Dr. Lesko mentioned, our working group is  
2 currently drafting a guidance for industry on in vivo  
3 metabolism-based drug-drug interactions. The working group  
4 was formed in January this year and has been going through  
5 a lot of issues, what should we discuss in the guidance,  
6 and we have discussed the issues in a public setting on  
7 various occasions.

8           For example, in May of this year, we have  
9 presented in front of this committee preliminary thoughts  
10 on the guidance.

11           In September, as Dr. Lesko mentioned, we had a  
12 metabolism workshop with PhRMA where we discussed issues  
13 and the in vivo and in vitro drug interactions.

14           And in November, just last month, we had a  
15 discussion, an exchange of ideas with our European  
16 counterpart on our perspective in the drug interaction  
17 area.

18           Again today probably is the last time that  
19 we'll have public discussion before we finalize our draft  
20 guidance and publish it for public comment.

21           The working group has deliberated on what  
22 issues we want to include in the guidance, and we reviewed  
23 the requirements for drug interactions based on the Code of  
24 Federal Regulations.

1                   You can see here under Contraindications, it's  
2                   indicated that the use of drug in patients may be  
3                   contraindicated because of concomitant therapy which may  
4                   have a substantial risk of being harmed by it.

5                   Also in the labeling under Precautions, it says  
6                   that in the labeling we should have specific practical  
7                   guidance for the physician on preventing clinically  
8                   significant drug-drug interactions. Also it says that  
9                   specific drugs or classes of drugs, the drug which the  
10                  labeling applies to, may interact in vivo, shall be  
11                  identified and the mechanism of drug interaction shall be  
12                  described.

13                  So, we know even some investigators have  
14                  studied drug-drug interaction in order to assess beneficial  
15                  effects, for example, the use of 3A4 inhibitors to increase  
16                  the oral availability of some HIV inhibitors, protease  
17                  inhibitors, which are poorly orally bioavailable. But we  
18                  know the goals of the majority of drug interaction studies  
19                  are to identify whether there are clinically significant  
20                  drug-drug interactions and to provide guidance on whether  
21                  to contraindicate the coadministration or to provide dose  
22                  adjustment information.

23                  So, we want to know, based on this requirement,  
24                  what kind of submissions that we have received which will

1 provide the proper information to guide the effective and  
2 safe use of the drugs.

3           So, I'd like to share with you a survey we  
4 conducted recently. This is a survey based on briefings  
5 provided by the reviewers of our office, Office of Clinical  
6 Pharmacology and Biopharmaceutics, where the reviewers,  
7 when they completed the NDA review on the clinical  
8 pharmacology and biopharmaceutics section, they convened a  
9 meeting where the team leaders and the other part of the  
10 NDA team including medical officers,  
11 pharmacology/toxicology reviewers, and the senior members  
12 of our office, where we will discuss the issues and the  
13 submission.

14           So, based on those briefings conducted between  
15 September last year and May of this year, we looked at the  
16 35 NDA's that have been reviewed. In all of them, we saw  
17 there were 14 NME's that were intended for oral  
18 administration. We looked at the information. Out of  
19 those 14, 13 of them had in vivo drug interaction studies.  
20 So, essentially more than 90 percent of the submissions  
21 we're seeing some information. Out of the 13, we saw 87  
22 drug interaction studies. So, with a median number of 6  
23 studies per NME with a range of 2 to 16.

24           This is a substantial increase from another

1 number which is 60 percent. This is another survey  
2 conducted by Dr. Marroum of our office who looked at the  
3 previous five years and what kind of drug interaction  
4 studies are we seeing. So, this is a substantial increase  
5 from the previous five years.

6 So, we're receiving drug interaction  
7 information from almost all submissions. We'd like to see  
8 if they do provide information that we need for the  
9 labeling.

10 So, the working group looked at these  
11 submissions in the context of these three basic questions.  
12 What do we like to know? What assumptions are we willing  
13 to make? And how sure do we want to be?

14 I think we'd like to know whether the dose-  
15 response relationship changed because of coadministration  
16 so that we can make proper labeling language whether to  
17 contraindicate or dose adjustment.

18 I'd like to point out that with all the  
19 submissions, about two-thirds of the studies were conducted  
20 in normal subjects. So, we're under the assumption that  
21 the concentration-response relationships do not change  
22 between the normals and the target population so that we  
23 can extrapolate the data from the specific studies to the  
24 labeling.

1           Also, more than 90 percent of the studies used  
2 PK parameters as the major point to look at to decide  
3 whether there's an interaction and whether we make dosage  
4 adjustments and how to make a dosage adjustment. So,  
5 there's an assumption that there's a direct pharmacokinetic  
6 and clinical endpoints relationship there.

7           Also we're seeing about 80 percent of the  
8 submissions with some kind of in vitro metabolism or  
9 interaction information, and about half of them use that  
10 information for in vivo. So, there is another assumption  
11 that there is an in vitro/in vivo relationship there.

12           How sure do we want to be? Most of the studies  
13 employ about 12 subjects in either a crossover study or a  
14 parallel design study. They range from 6 to 30, but the  
15 norm, the median number, is 12. I'd like to share with you  
16 later on, maybe when Dr. Honig presents the study design,  
17 whether this is sufficient.

18           The working group looked at the submissions,  
19 and we think these are important issues that we'd like to  
20 address in the guidance.

21           First, as we mentioned, the in vitro/in vivo  
22 relationship, and we'd like to talk about when in vivo  
23 studies are not necessary. I mentioned that one of the  
24 submissions had 16 in vivo drug interaction studies

1 conducted. Are they all necessary? We'd like to elaborate  
2 on that later on. Dr. Collins will talk in his discussion  
3 of the in vitro/in vivo relationship.

4 Also, we'd like to address issues in the study  
5 design and data analysis both in conducting the specific  
6 studies or employing the population approach. Dr. Honig  
7 will talk in detail on the study design issue, and I'll  
8 come back and talk about data analysis.

9 But all of this information is geared to proper  
10 labeling. Are the studies designed in such a way or data  
11 analyses performed in such a way that would give us proper  
12 labeling? This is very important and we have a section on  
13 labeling to say what kind of in vitro/in vivo information  
14 can be placed in the labeling.

15 Just to review the current status and what we  
16 see in the submission as far as the selection of  
17 interacting drugs, based on the 14 oral NME's, there are 13  
18 new molecular entities that have drug interaction studies  
19 based on the 87 studies. We find that a third of the  
20 studies are meant to study the other compound's effect on  
21 the new molecular entity and about two-thirds are designed  
22 to see the on the new molecular entity on the other  
23 compounds.

24 I've listed here the interacting drugs that

1 have appeared more than two times. You can see cimetidine  
2 was top on the list for other compounds effect on new  
3 molecular entities. So, that's accounted for about half of  
4 the new molecular entities.

5 If you look at the new molecular entities  
6 effect on other compounds, you can see the normally  
7 considered narrow therapeutic index compounds. Digoxin and  
8 warfarin are top on the list. Almost half of the studies  
9 looked at the interaction with these two compounds.

10 And oral contraceptives which has been  
11 increasingly seen in the studies, nifedipine, theophylline,  
12 terfenadine, and atenolol.

13 What about the study design? I'll just briefly  
14 review what we have seen. Again, I said there are 80  
15 percent of the submissions with some in vitro information.  
16 So, half of the sponsors have used this information in  
17 designing and the choosing of interactants and also on  
18 their design of what is the best study design.

19 Here I just listed -- again, I said a third of  
20 studies were designed to look at other compounds effect on  
21 the new molecular entity and two-thirds to look at it the  
22 other way. About 10 percent look at both ways. We saw a  
23 combination of this design of the studies, single dose on  
24 this compound or a single dose of NME, or there may be a

1 multiple dose here or a multiple dose here or multiple dose  
2 on both sides.

3           We have seen about 20 percent of the  
4 submissions used this design, single dose, and about 30  
5 percent used a combination of single dose and multiple  
6 dose. Another 40 percent used the multiple dose.

7           The majority of the study designs used  
8 crossover. They either randomized crossover or one-way  
9 crossover. You called it add-on crossover. And about 10  
10 percent using a parallel design.

11           My point of discussion here is we've seen some  
12 sponsors use one design for all studies. I would like to  
13 hear Dr. Honig talk about whether you can have one size fit  
14 all or maybe we should look at all the other proper  
15 pharmacokinetic/pharmacodynamic parameters before you  
16 design what is the best study for determining whether  
17 there's drug interaction.

18           I'll just quickly review what we saw in the  
19 data analysis. In most of the studies, we've seen the  
20 point estimates and essentially 90 percent used the null  
21 hypothesis of no interaction and reported p values. I will  
22 come back to these points later when I present the data  
23 analysis section.

24           The majority reported mean and standard

1 deviation, some with a range.

2 And we're seeing increasing submissions using  
3 the confidence interval approach and some even used the  
4 equivalency approach to determine whether there's drug  
5 interaction.

6 Most of the sponsors, once they determine the  
7 study results, once they determine whether it's a  
8 statistically significant interaction, then they look at  
9 whether they are clinically significant.

10 About 10 percent of the submissions have  
11 additional pharmacodynamic endpoints to look at. Some  
12 sponsors did use again the confidence intervals approach to  
13 evaluate whether the pharmacodynamic parameter changes are  
14 significant or not.

15 My last survey results are the use of  
16 population PK in our submission in general. Our office  
17 looked at the submissions between 1995 and 1996. We looked  
18 at all the NDA's and supplemental NDA's. So, we looked at  
19 a total of about 206 submissions. Out of them we looked to  
20 see how many of them used the population approach and how  
21 many of them had a final approved labeling, and also  
22 whether our main author has a chance to interview the  
23 reviewer to see what's the impact of the population  
24 approach on the labeling.

1                   He found that 47 of them met those criteria.  
2           In other words, we have at least 23 percent of the  
3           submissions attempted to use the population approach and  
4           directly resulted in labeling language.

5                   If we look at the breakdown of that, the  
6           majority of the 47 submissions look at the covariates.  
7           They identify and try to quantitate the different  
8           covariates' contributions to the total variation or try to  
9           identify the subgroups.

10                   And also look at a PK/PD relationship either  
11           using efficacy as an endpoint or toxicity.

12                   You can see there's a small number of the  
13           submissions using this approach to look at drug-drug  
14           interactions. Later on I'll give you some examples of how  
15           this is used and impacted on the determination of whether  
16           there was drug interactions.

17                   So, with that, I'll summarize our working  
18           group's activities. Since January of this year when the  
19           working group was formed, we had monthly meetings and we  
20           identified issues and discussed among our members and also  
21           talked to experts in the field. For example, we have many  
22           discussion meetings in house with our own members in the  
23           agency, with experts from industry and academia. We have  
24           presented the case last May, as I said, and today again

1 we'd like to talk about the major issues that's not  
2 resolved and get input from the committee members and  
3 invited experts.

4 As Dr. Lesko mentioned, we had meetings with  
5 PhRMA and we had discussions extensively in the September  
6 workshop.

7 Last month we crosstalked with the EMEA,  
8 provided our comments to the current version of drug  
9 interaction guidance which is on the Internet and they are  
10 being revised right now.

11 Again, today we'd like to get the committee's  
12 input before we finalize our guidance.

13 Before I close, I'd like to expand on Dr.  
14 Lesko's questions for the committee for you to consider  
15 during our presentations.

16 What assumptions are we willing to make in  
17 extrapolating data obtained from specific studies conducted  
18 in normal subjects to patients? We're assuming that the  
19 concentration-response relationships remain unchanged  
20 between normals and target populations and also in special  
21 populations.

22 And our assumption that dosage adjustment data  
23 we derived from the studies in normals and that can be  
24 extrapolated to target populations, for example, the

1 percent change, the 200 percent change in normals we're  
2 assuming that 200 percent change in the target population.  
3 We'd like to see your comments on this.

4 Second question. We have seen the increasing  
5 use of population approach in determining whether there are  
6 drug-drug interactions. Can data derived from the  
7 population PK analysis be confirmatory for lack of drug  
8 interactions? What other information do we need in order  
9 to say this population PK analysis can be confirmatory?  
10 And can data derived from the population PK analysis be  
11 used for dosage adjustment, or do we need confirmatory  
12 studies?

13 Finally, how do we translate the data to  
14 informative labeling language? What statistical method and  
15 analysis results be included in the labeling? Later on  
16 I'll show some examples on the data analysis submitted by  
17 the sponsors. I'd like to know if they are most  
18 informative. I mean, do they really provide information  
19 for patients and practitioners in the safe and effective  
20 use of the compounds?

21 And to what extent do we extrapolate the  
22 information to other drugs? Our current in vitro guidance  
23 discussed the cross-labeling approach. What about in vivo?  
24 Do we extrapolate the dose adjustment information from one

1 compound to the other? That's what I'd like the committee  
2 to consider.

3 When should the same labeling language for the  
4 study drug appear on the labeling for the interacting  
5 drugs? If the compounds are contraindicated, I think they  
6 should appear on both sides. If there is just minor dosage  
7 adjustment, should they also appear -- how do we set the  
8 priority in revising of the labeling?

9 These are some of the questions I would like  
10 you to consider. Thank you.

11 DR. ZIMMERMAN: Thank you.

12 Our next speaker will talk about study design.  
13 It's Dr. Peter Honig.

14 DR. HONIG: Thanks, Shiew-Mei. I think you did  
15 a very nice job of setting the table for the discussions  
16 that will hopefully follow my presentation and the later  
17 presentations.

18 As I heard the advisory committee and the  
19 special members of the advisory committee introduce  
20 themselves, I was really impressed with the wealth of  
21 expertise assembled here, and I fully anticipate that we're  
22 going to get some valuable feedback on the ideas that we're  
23 going to set forth here.

24 As I went through the audience this morning, I

1 hope that we get substantive comments from the observers in  
2 the audience as well.

3           As Shiew-Mei said, I'm going to be talking  
4 about the design of clinical drug-drug interaction studies.  
5 As Dr. Lesko mentioned, there was in your briefing handout  
6 a narrative going over the fundamental principles I'll be  
7 highlighting in my talk here. I hope the advisory  
8 committee has had a chance to read that. Please feel free  
9 to offer comments on that narrative as well as the  
10 highlights that I put forward here.

11           One of the issues I'd like the advisory  
12 committee to address is the choice of subjects in clinical  
13 drug-drug interaction trials, the use of normals versus  
14 patients. I think we have to recognize that there are  
15 tradeoffs of convenience, the convenience of using normal  
16 healthy volunteers versus the scientific, ethical, and  
17 perhaps even statistical necessity of using patient  
18 populations in these type studies.

19           I think by and large we see these studies being  
20 conducted in normal volunteers, and I can appreciate why  
21 that is done from a practical and recruitment perspective.  
22 However, at times one sees the necessity to use patient  
23 populations. For example, the study of oncolytics in the  
24 normal population would not be an ethical study.

1                   But I think we have to also consider some of  
2     the scientific and statistical issues that are not  
3     necessarily well appreciated now, but I think we're  
4     beginning to understand that these may play a role in the  
5     interpretation of the results of these studies. For  
6     example, I think we're beginning to understand how disease  
7     may influence the body's ability to metabolize certain  
8     drugs, and there is literature coming out about the effect  
9     of HIV disease on acetylation and that may sort of dictate  
10    the choice of the study population you use when you enroll  
11    when you do these types of studies.

12                  Another issue that I think we should consider  
13    is perhaps the variability around the point estimates in  
14    patients versus normal volunteers. I don't think there's  
15    an abundance of literature on this, but I think it's  
16    something that we have to consider when one writes a  
17    guidance.

18                  In attempting to write such a document, an in  
19    vivo drug-drug interaction document, I think the take-away  
20    message is that there is no one right design for these  
21    studies. I think you have to have some general  
22    considerations of the drugs that are involved here that  
23    dictate the study design. Some of these general  
24    considerations that I've put on this slide are certainly

1 the mechanism of the interaction.

2           If it's an inhibition interaction, it certainly  
3 wouldn't make a lot of sense to do a single dose study of  
4 the -- I'm sorry. If it's an inhibition interaction, it  
5 depends on the mechanism of the inhibition. If it's a  
6 purely competitive inhibition, that may guide you to do one  
7 type of design. If it's a suicide inhibition, that may  
8 dictate another type of study design.

9           Certainly for induction, it wouldn't make a lot  
10 of sense to do a single-dose induction study in order to  
11 have a clinically interpretable result.

12           I think again we have to consider non-metabolic  
13 contributions of changes in absorption. I think this is  
14 becoming a big issue. I'm glad to see Dr. Watkins on the  
15 advisory committee here. This is a particular interest of  
16 his, and it's something that we have to consider in  
17 designing these types of studies.

18           Furthermore, one has to take into account the  
19 therapeutic index of the subject drugs in question and the  
20 likelihood of coadministration of these and the  
21 interpretation of those data.

22           Finally, the bidirectionality of the potential  
23 interactions. One has to take into account not only the  
24 effect of another drug on your particular drug of interest,

1 but the drug of interest on the other drug as well.

2           These are some of the other issues that I've  
3 chosen to highlight when one considers the design of drug-  
4 drug interaction studies.

5           The choice of interactants. I think this is  
6 something that we hopefully, in the case of metabolism-  
7 based interactions, would use the in vitro data to sort of  
8 guide us in the choice of interactants.

9           But that's not the only information that goes  
10 into that. I think we have to consider the likelihood of  
11 coadministration of the drugs. It wouldn't be reasonable  
12 to say every single particular likely interactant if it's  
13 not going to be administered with that drug. For example,  
14 if one is studying a drug that's going to be developed for  
15 an asthma population that has been shown to be an inhibitor  
16 of 3A4, it wouldn't necessarily be necessary to study its  
17 effect on benzodiazepine, which is a drug which would be  
18 unlikely to be administered to an asthmatic population.  
19 So, this is what I'm trying to say with this.

20           Similarly, the choice of interactants from a  
21 non-scientific but from a marketing perspective is  
22 something that we have to consider as well -- the study of  
23 drugs to sort of promote it as a niche in the marketing  
24 environment.

1           Again, the route of administration has to be  
2 considered in the design of these trials. If a drug is  
3 being developed and it has multiple routes of  
4 administration, both intravenous and oral routes, one has  
5 to consider which would be the most appropriate route to  
6 study. For example, if one had a drug that was a CYP1A2  
7 substrate, it might be reasonable to get away with an  
8 intravenous administration study alone. However, if one  
9 was developing a 3A4 substrate, I think that one would not  
10 get a lot of comfort out of doing an intravenous  
11 interaction study alone because of the other contributions  
12 of gut metabolism as well as some absorption modulation.  
13 So, these are other things we have to consider.

14           The dose and the dosing duration is an  
15 important consideration. Should we be studying the maximum  
16 approved dose at the maximum approved daily dose? Then one  
17 has to consider the potential safety implications of  
18 studying the maximum approved dose. If safety implications  
19 come into play, if one study is a lower dose, can the lower  
20 dose findings be extrapolated to the maximum dose, et  
21 cetera?

22           And also the mechanism of interaction comes  
23 into play as a general consideration here. If one is  
24 studying an induction reaction, one would really like to

1 stress the system with both the maximum dose as well as the  
2 time period over which one is dosing.

3 Shiew-Mei touched on this briefly, the  
4 crossover versus the parallel design, but it's the drug  
5 characteristics that can at times dictate the choice of  
6 these two designs. For example, a drug with a very long  
7 half-life. It would be very difficult to study that in a  
8 crossover fashion because to keep patients in a study for  
9 an extended period of time is difficult. A drug that comes  
10 to mind immediately is astemizole, a drug with an extremely  
11 long half-life. With days to weeks to achieve a steady  
12 state, it would be unreasonable I think to study this in a  
13 crossover fashion.

14 Similarly, patient stability issues come into  
15 play. If one has a drug that is a disease modifying agent  
16 and you can't assure that the patient is going to come back  
17 to a stable baseline, a crossover design really doesn't  
18 make a lot of sense for that type of drug.

19 Again, single versus multiple dosing. The  
20 reality of the situation is if you have a drug that is  
21 being developed for once-only dosing, it doesn't make a lot  
22 of sense to study as a drug-drug interaction in a multiple  
23 dose setting.

24 Single versus multiple dosing also comes into

1 play when one is looking at convenience and trial design  
2 issues. For example, if one wants to study the effect on a  
3 single dose, certain assumptions have to be met,  
4 assumptions such as that the multiple dose kinetics can be  
5 predicted reliably from a single-dose administration.

6 And the clinical relevance has to come into  
7 play as well. Can the differences that are seen in single-  
8 dose studies be interpretable? Can those pharmacokinetic  
9 differences be interpretable to a multiple-dose clinical  
10 situation?

11 This slide is a variation on Dr. Huang's slide  
12 and it basically outlines the four basic drug-drug  
13 interaction designs. Single dose on single dose. Let's  
14 for simplicity purposes assume that the test drug is the  
15 drug that's being developed, the new molecular entity being  
16 developed, and the interactant is either an inhibitor or an  
17 inducer that's already on the market. The four basic study  
18 designs are single dose on a single dose, single dose on a  
19 multiple dose, multiple dose on a single dose, and multiple  
20 dose on a multiple dose.

21 If one sort of takes the general considerations  
22 that I've outlined as a factor, one can see that perhaps if  
23 one is dealing with an inducer, if your in vitro data has  
24 indicated that your drug is likely to be affected by the

1 induction and you want to study that, a study design in  
2 which single doses of the inducer were designed, it  
3 wouldn't really make a lot of sense.

4           Similarly, if one wants to study the single-  
5 dose effects of an inhibitor on your single dose of a drug,  
6 one really has to make sure that the pharmacokinetic  
7 changes seen here are going to be interpretable. Secondly,  
8 you're going to have to make certain assumptions that this  
9 mechanism of inhibition is a purely competitive inhibition  
10 and not a mechanistic or a suicide type inhibition.

11           A very popular study design is a single dose of  
12 the test drug on a multiple dose on the inhibitor or  
13 inducer, and with the assumptions that the inhibitor or  
14 inducer are dosed to steady state, one has to take that  
15 into account.

16           One also has to take into account the activity  
17 of the metabolites of the inhibitor or inducer. A good  
18 example of that is fluoxetine. Fluoxetine in itself is  
19 quite a potent inhibitor of CYP2D6. However, one also has  
20 to take into account the metabolite of fluoxetine is also a  
21 potent inhibitor. So, a single dose of fluoxetine may not  
22 give the entire story, but assuming that the multiple dose  
23 is done to an appropriate steady state and an effect steady  
24 state, a single dose added on top of that, one has to make

1 the assumption that the single dose kinetics here predict  
2 multiple dose kinetics of your test drug and that changes  
3 in any pharmacokinetics you might see are clinically  
4 interpretable.

5 To that end, one may logically conclude that  
6 the most clinically relevant and interpretable study design  
7 would be a multiple dose on a multiple dose.

8 What would be the appropriate pharmacokinetic  
9 endpoints for a drug-drug interaction trial? I think the  
10 usual measures of  $C_{max}$ , AUC, and perhaps clearance. For  
11 when you're studying drugs to multiple dose, one wants to  
12 also determine  $C_{min}$  to sort of give some assurance that  
13 you've really reached steady state before and after the  
14 interaction.

15 The assay really dictates the study design and  
16 the dosing strategies at times. One has to be assured that  
17 the appropriate sensitivity is there so that you can study  
18 the parent, as well as the major active and/or toxic  
19 metabolites, as well as assaying both ways, assaying the  
20 effect on your test drug as well as perhaps the effect on  
21 the interactant.

22 The incorporation of pharmacodynamic endpoints  
23 is not a simple consideration as well. If one has a drug-  
24 drug interaction whose effect may not be solely dictated by

1 the pharmacokinetic changes, one would reasonably like to  
2 see pharmacodynamic endpoints incorporated into such a  
3 study, and that becomes difficult. Which pharmacodynamic  
4 endpoints do you choose to put in such a study? Do you use  
5 a surrogate? Do you use a biomarker? How interpretable  
6 are changes in those measures?

7 A reasonable example of that I think would be  
8 the effect of quinidine on the pharmacokinetics and  
9 pharmacodynamics of a tricyclic. Although you may have  
10 profound pharmacokinetic changes, that may not be the whole  
11 story. What you're really looking for is the  
12 repolarization effect, and that is an additive effect  
13 pharmacodynamically as well as just pharmacokinetically.

14 My final slide is dealing with the role of  
15 population pharmacokinetics in assessing drug-drug  
16 interactions. Shiew-Mei has sort of framed the questions  
17 we'd like you to address there. I'm operating under the  
18 assumption that everybody really knows what population  
19 pharmacokinetics is.

20 I would like to highlight there are certain  
21 limitations of population pharmacokinetics in phase III  
22 trials. Phase III trials are designed to limit the noise  
23 around the estimates of efficacy, and to that end, the  
24 inclusion/exclusion criteria are quite rigidly defined.

1 So, one typically sees that likely interactants are  
2 specifically excluded from these trials, so one comes into  
3 a power issue of do you really have enough data, when one  
4 analyzes it, to make an interpretation.

5 But the role of population pharmacokinetics, as  
6 I see it, includes the potential identification of  
7 unsuspected interactions, the confirmation of absence of  
8 clinically significant interactions that may have been  
9 predicted. I think they are less valuable in ruling out  
10 completely and certainly in quantifying likely  
11 interactions. I think that's where the role of the more  
12 rigidly controlled, smaller clinical drug-drug interactions  
13 lies.

14 That's all I had to say on the topic. I hope  
15 this engenders a reasonable amount of discussion. Dr.  
16 Huang is going to return now and talk about the analysis of  
17 these studies.

18 DR. ZIMMERMAN: Thank you.

19 DR. HUANG: What I'd like to do right now is  
20 talk about issues in not only data analysis, also data  
21 interpretation and the resulting labeling language.

22 As I had mentioned earlier, most of the  
23 submissions that we have seen have provided point  
24 estimates, and the majority used the null hypothesis of no

1 interaction. We're seeing all of them have mean standard  
2 deviation, and we're seeing increasing numbers of  
3 submissions using confidence intervals.

4           However, none of these values are really of  
5 significance unless they're related to the clinical  
6 relevance. While we're seeing the submissions usually  
7 would be the studies are statistically significant or not  
8 significant statistically and then say, well, this may not  
9 be clinically significant and left as such.

10           I would like to review with you some examples  
11 to show maybe these p values are not of that much use and  
12 the use of the two-step approach may not be as efficient as  
13 the one-step approach I'd like to propose in using the  
14 flexible goal posts.

15           Again, there is some information on  
16 pharmacodynamic measurement. We'd like to encourage to see  
17 more of this measurement in the submissions, although I  
18 won't be talking about the data analysis.

19           The first example I'd like to give you is one  
20 submission that we reviewed last May. This is compound  
21 drug A. The sponsor has studied cimetidine interaction on  
22 drug A. Again, these are point estimates that's presented  
23 in the submission, and the confidence interval that's  
24 presented, also p value, based on a null hypothesis.

1 Again, with Cmax, the same thing, point estimate,  
2 confidence interval, and p value.

3 The same thing with drug A's affect on  
4 warfarin. I'm here showing the S-warfarin data. Again,  
5 point estimate, confidence interval, and p value. You can  
6 see we're seeing a statistically significant difference  
7 here, but no difference in the warfarin case.

8 The labeling that's agreed upon both by the  
9 reviewer and the sponsor are that clinical interaction  
10 studies with cimetidine and warfarin indicated that the  
11 coadministration of A with these drugs does not result in  
12 clinically significant drug interactions. So, obviously p  
13 values does not provide any input into the final decision.  
14 Obviously, the confidence intervals were looked at and also  
15 the point estimate. So, is the p value really of any value  
16 in the submission?

17 Next I'd like to show an example on how  
18 significant is the point estimate, mean standard deviation  
19 have an effect on the labeling. This I used an example  
20 from the 1997 PDR on Indinavir. Currently the regimen is  
21 800 milligrams Q 8hour, although I understand the sponsor  
22 is working on a b.i.d. dosing regimen.

23 Here in the clinical pharmacology section of  
24 the labeling it says Indinavir increased rifabutin AUC by

1 200 percent. And in the dosage administration area, it  
2 says that dose reduction of rifabutin should be to half of  
3 the standard.

4 In another case, ketoconazole increased  
5 Indinavir AUC by 68 percent, and in the dosage  
6 administration it says dose reduction to three-quarters  
7 recommended.

8 In other cases, Indinavir increased zidovudine  
9 AUC by 36 percent. Here the standard deviation was not  
10 given, and it said no dosage adjustment is required.

11 Indinavir increased stavudine by 25 percent.  
12 Again, no dosage adjustment is required.

13 So, here if you look at the information  
14 provided both in the clinical pharmacology section and also  
15 in the dosage adjustment area, you can see that it looks  
16 like 50 percent was used as a range no matter what  
17 compounds you're looking at to determine whether dosage  
18 adjustment is necessary.

19 There is a lot more information in the  
20 Indinavir labeling. Some of them says the interaction  
21 caused a 6 percent change. Some of them said there's no  
22 change and without giving a number. So, are these  
23 information helpful for the practitioner? We can see this  
24 is not uncommon in most of the labeling. We would say,

1 well, there's a 22 percent change in drug interaction and  
2 then clinical significance not known.

3 I'd like to propose, well, maybe we should use  
4 a different language. If 6 percent is not significant, 22  
5 percent is not significant, do we need to provide this  
6 information or should we just say there is no clinically  
7 relevant drug interaction?

8 So, this is summarized in this slide. I think  
9 maybe we can use a one-step approach where we calculate the  
10 confidence interval of our observation, whether it's AUC or  
11 Cmax, provide 90 percent confidence interval of the  
12 comparison with interacting drug or without interacting  
13 drug, and compare this information with a pre-specified  
14 range or a goal post which is unique to each drug and which  
15 is flexible, and based on that comparison to determine  
16 whether there is a clinically relevant drug-drug  
17 interaction.

18 The goal post can be based on your  
19 pharmacokinetic/pharmacodynamic information. The high end  
20 will be depending on the clinical effect of the safety  
21 endpoint and the lower end will be on the effectiveness  
22 endpoint.

23 So, if we find the confidence intervals are  
24 within the preset goal post, again which is flexible and it

1 does not have to be symmetrical -- if they're within the  
2 goal posts, then we can claim no interaction. We don't  
3 have to give 22 percent, 30 percent, or certain information  
4 that may not be able to help the prescriber.

5           If we find the mean and confidence interval are  
6 outside the goal posts, then we can claim that there is  
7 drug interaction and then we ought to recommend dosage  
8 adjustment.

9           On the other hand, when we don't have enough  
10 information to determine the goal posts, maybe a fall-back  
11 position will be use a conservative approach. For example,  
12 you may want to use 80/125 percent, the usual  
13 bioequivalency approach, to declare that there is no drug  
14 interaction, and with this that can cover a big range of  
15 drug interaction results. We're seeing that sponsors have  
16 been using this approach, and I'd like to share with you  
17 some of the examples.

18           When we looked at the literature, we found  
19 there are several cases where the investigators have used  
20 the 80 to 125 percent and they treated drug interaction as  
21 an equivalence question. These are the examples in the  
22 literature and also in one of their submissions. They used  
23 the 90 percent confidence interval and compared to 80/125  
24 to declare there is no drug interaction.

1                   Actually in a couple cases where the  
2 pharmacodynamic endpoints were measured, they also used the  
3 80/125 percent to declare no change in the pharmacodynamic  
4 endpoint.

5                   I'd like to share with you in one of the cases  
6 on rifampin on nelfinavir where the sponsor actually used  
7 the flexible goal post approach to determine whether there  
8 is clinically significant drug interactions. This was in  
9 our submission and also was presented at the March ASCPT  
10 meeting where the sponsor looked at rifampin's effect on  
11 nelfinavir where they have predetermined that within 50 to  
12 200 percent change, the point estimate, then it's not  
13 clinically significant. So, they have a preset goal post  
14 between 50 and 200 percent.

15                   With this study, they found that rifampin has  
16 increased the clearance and decreased the AUC and Cmax of  
17 nelfinavir. You can see the 90 confidence intervals were  
18 outside the preset range.

19                   The current labeling says that they should not  
20 be given together. Part of the reason is we don't know how  
21 to dose them when the rifampin is coadministered.

22                   Similarly the sponsor did another study with  
23 ketoconazole, and they found with ketoconazole  
24 administration the AUC and Cmax were within the boundary.

1 The current labeling stated that there was no dosage  
2 adjustment necessary, but this is one approach that we have  
3 seen using the so-called flexible goal post.

4 So, with that, I'd just like to reiterate for  
5 the committee members to consider. What kind of  
6 information can we translate to informative labeling  
7 language? Again, what statistical method/analysis results  
8 should be included in the labeling? Should we have all the  
9 information, 10 percent, 20 percent, 30 percent statistical  
10 analysis results in the labeling, or should we tie that  
11 into clinical relevance and to declare whether there is  
12 interaction or there is no interaction? If there is no  
13 interaction, we don't have to say what is the percent  
14 change? If there is interaction, recommend dosage  
15 adjustment.

16 To what extent again we can extrapolate the in  
17 vivo information to the other drugs? And this I have  
18 discussed earlier.

19 Next, I'd just like to use two examples that we  
20 see in the submission using a population approach in the  
21 drug interaction studies. The first example involving  
22 again drug A which is believed to be not metabolized. The  
23 bioavailability is about 23 percent. It's a radiolabeled  
24 study. It showed that the majority of the radioactivity

1 was eliminated in feces as unchanged, and less than .6  
2 percent as unchanged in the urine. So, the sponsor did not  
3 expect a drug interaction with the average  
4 inhibitor/inducer.

5           However, when the sponsor did line extension  
6 studies with the new formulation, they measured plasma  
7 levels to see if they're within the so-called therapeutic  
8 range. They found that four patients appeared to be  
9 outliers. Now, these four patients all have very low  
10 concentrations. They all received rifampin. The clearance  
11 values increased by 110 percent.

12           So, they went back and did a specific study  
13 with rifampin and they confirmed that rifampin did increase  
14 the clearance of the compound. Now the labeling has  
15 changed to say that there is indirect evidence to show the  
16 compounds and metabolites.

17           So, the population approach has been shown to  
18 be hypothesis generating and to uncover unexpected drug  
19 interactions.

20           My next example, which has been presented in  
21 the fall PhRMA workshop, is viramune which is well absorbed  
22 with a percent bioavailability about 90 percent. The renal  
23 excretion, only about less than 3 percent, and 3A is the  
24 major isozyme for two of the three major metabolic pathways

1 for 2 and 12-hydroxylation. 2B6 appeared to be responsible  
2 for another third, another major pathway.

3 Based on the in vitro study, ketoconazole  
4 appeared to be inhibiting the metabolism of all three, even  
5 2B6, the major enzyme for 2, 3-hydroxy, and it appeared to  
6 inhibit all three pathways. So, the committee expected to  
7 see an inhibition of ketoconazole on the viramune.

8 However, in the population study, in the phase  
9 II clinical trial, well, the sponsor took steady state  
10 trough values. They had previously validated that the  
11 trough value would correlate well with the total AUC.

12 When they looked at 283 controls versus 14,  
13 they were given with ketoconazole. You can see here the  
14 group with ketoconazole actually do not have a higher  
15 value, which you would expect if ketoconazole has inhibited  
16 the metabolism of viramune.

17 So, the company went back and said, well, maybe  
18 the in vitro data is not predictive of in vivo. So, they  
19 prospectively designed a study to look at the  
20 coadministration of ketoconazole with viramune.

21 You look at the data here with coadministration  
22 of ketoconazole with viramune and with two other studies  
23 where viramune was given by itself. You can see there is  
24 only a slight increase in viramune when ketoconazole was

1 given. It's not significantly different. When the sponsor  
2 went back to look at the ketoconazole level itself, they  
3 found that the ketoconazole levels were decreased by the  
4 coadministration of viramune. The AUC was decreased 63  
5 percent. The Cmax was decreased by 40 percent. So, this  
6 may explain why we have not seen an expected interaction.

7 So, this again illustrates how population data  
8 can help us either uncover unexpected interaction or to  
9 show in real life whether the interaction would happen or  
10 not.

11 But again, I'll leave with the committee  
12 members, if the in vitro data suspected to have interaction  
13 and if the population study did not show interaction  
14 without a confirmatory study, are we assured that there is  
15 lack of interaction? Or another case, if the in vitro does  
16 not predict there will be an interaction, can the  
17 population analysis be confirmatory for lack of  
18 interaction?

19 And also can data derived from population  
20 analysis for dosage adjustment? Dr. Honig has addressed  
21 this on our current thinking, and we do have population  
22 guidance right now out on the Internet and we have received  
23 comments. We're in the process of revising it. So, we'd  
24 like to hear the committee members and your comments as far

1 as the using of this approach on drug interactions.

2 DR. ZIMMERMAN: Thank you, Dr. Huang.

3 Our next speaker will talk about in vitro/in  
4 vivo relationships and our speaker is Dr. Jerry Collins.

5 DR. COLLINS: Thank you.

6 From previous sessions of this committee, many  
7 of the members know that CDER has a small laboratory-based  
8 program in the area of drug-drug interactions and  
9 metabolism, and part of our role is to participate in the  
10 working groups and in the development process for guidances  
11 in the agency and not to just hang out entirely in our  
12 ivory tower even though that seems attractive some days.

13 The next overhead reminds you that when I was  
14 last visiting with you in May, we had just released a few  
15 weeks earlier our guidance on studies of drug metabolism  
16 and interaction in vitro, and now with the announcement of  
17 the development of a guidance in vivo, this is really a  
18 good time to say what are the connections between the  
19 guidance we already have out there on in vitro studies and  
20 the emerging or about-to-be-emergent guidance on in vivo  
21 interactions.

22 Just a reminder of our goal. We really are  
23 motivated to increase confidence in product safety by  
24 avoiding undesirable drug-drug interactions. There are

1 actually times when drug-drug interactions are beneficial  
2 to the patient, but our focus here is on avoiding those  
3 things that are unpleasant and, in particular, those things  
4 that in the past have been unanticipated. We'd like to  
5 manage this problem by bringing the best science that we  
6 can. There will always be some outliers, but how much of  
7 the problem can we avoid by bringing to bear the technology  
8 that already exists and that's emerging.

9           The reality of where we are in December of 1997  
10 is there is just no other word to describe what's happening  
11 than an explosion of data in vitro. Our agency routinely  
12 receives what I can only call an avalanche of data from in  
13 vitro data. Editors of journals are beginning to gripe and  
14 complain that there's just lots of data being submitted to  
15 their journals and they don't exactly know what to do with  
16 it. And finally, the Internet, that ever-pervasive source  
17 of information, has pages and pages of information on in  
18 vitro data. The Washington Post and the New York Times may  
19 not have these data, but it seems to be everywhere else.

20           I would say, though, for the purposes of our  
21 conversation this morning, merely collecting data isn't the  
22 whole job, and unless these data are predictive of results  
23 in vivo, I'd even suggest that we don't have any interest  
24 in these piles of data. So, our real focus has to be on

1     how predictive the results are, how helpful they are in  
2     reaching our goal of avoiding unpleasant drug-drug  
3     interactions.

4             Just as an example, this is obviously not a  
5     slide that everyone is supposed to read from either the  
6     front or the back of the room. This is from the well-known  
7     toxicology text, Casarett & Doull, the chapter by Professor  
8     Parkinson, summarizing, sort of collecting in a semi-  
9     encyclopedic way all of the substrates, inducers, and  
10    enzymes combination in tabular feat.

11            Anyone who tries to undertake this exercise  
12    realizes that you quickly run the risk of being out of  
13    date, but I can tell you for sure when we're reviewing a  
14    submission, it's really handy to have as many of these  
15    tools available as possible. No single tool may be enough  
16    to help us remember and collect these data, but as many  
17    different approaches that people can come up with to  
18    collate the data, the better off we are.

19            The next slide shows that if you're really  
20    concerned about being out-of-date, there's a number of web  
21    pages that exist that can be updated on a monthly or daily  
22    basis with these things. This particular one is from  
23    Professor Flockhart from Georgetown University and it  
24    handily has some hyperlinks so that if you can't remember

1     what P450 2E1 is, you just click on it and it will give you  
2     a bunch of references that you can read.  And, of course,  
3     it can be updated.  This is one of several that are out  
4     there and frequently used by people who are roaming the web  
5     -- excuse me -- crawling the web and want to get some  
6     information.

7                     (Laughter.)

8                     DR. COLLINS:  It wasn't very long ago that we  
9     had this enormous gap in evaluating drug-drug interactions  
10    between having absolutely no information other than  
11    idiosyncratic, anecdotal, and usually unpleasant clinical  
12    case reports on the one hand versus a newly expanding CRO  
13    industry which was doing a bunch of studies in vivo, which  
14    volunteers by the dozens were rounded up and drug-drug  
15    interactions were studied in vivo.  That's just an enormous  
16    gap between knowing nothing at all versus having to go into  
17    the clinic and doing a drug-drug interaction study.

18                    So, our focus over the last couple of years has  
19    been filling in the gap, and the next slide just puts  
20    something in between no information and only studies in  
21    vitro.  That's what I would call targeted or guided in  
22    vitro studies, not just collecting data for their own sake,  
23    but data that will make a difference in terms of our  
24    ability to interpret it.

1           The next slide talks about our central theme,  
2           and that's that for cases for which we agree that data in  
3           vitro are not just collection of numbers, but they really  
4           are information which predict the situation in vivo, then  
5           it's official FDA policy and generally accepted in the  
6           academic and industrial communities, that in those cases  
7           there's no need for clinical studies.

8           Now, this is the kind of statement that causes  
9           a certain amount of uneasiness. Every new policy does.  
10          Every new exploitation of technology, but I think the next  
11          slide will help us all have a little bit more comfort with  
12          this, and that's a policy but the implementation of the  
13          policy, the boundaries of the agreement on which cases we  
14          can have confidence on and which cases we don't is an area  
15          of constant debate, but it's also an area of constant  
16          improvement as we understand our tools better. Where are  
17          we specifically this morning in December of 1997?

18          The next slide lists a couple of ways we might  
19          address this question of what is the correlation between  
20          these piles of data in vitro and the clinical situation.  
21          What are some criteria for judging where we are today and  
22          what kind of progress we made.

23          To several audiences I've tried to sell them  
24          the concept that really we've had a revolutionary change in

1 our ability to interpret these data. I have to tell you it  
2 has gone over real flat. People have been doing these  
3 studies for so long that it's hard to convince them that  
4 there's anything but a real tiny, quiet revolution. So,  
5 I'm dropping that from my road show.

6 I also have not said to any audience that the  
7 correlation between in vitro data and in vivo is perfect.  
8 I think that's the wrong standard. I know that we've  
9 assembled a high-powered collection of academically based  
10 consultants who will be expert at finding exceptions to the  
11 rule. We do that at FDA on a routine basis and industry  
12 can do that as well. The standard is not whether it's  
13 perfect but perhaps whether it's generally reliable, and I  
14 would say most importantly is it an improvement over what  
15 our options have been in the past.

16 Specifically I think we often lose sight of the  
17 most common finding of drug-drug interactions, whether  
18 they're in vitro or in vivo, and that's that nothing  
19 happens. Although we're very concerned about obvious  
20 serious cases, high profile interactions, the reality is  
21 combining drug A and drug B most often has a result of  
22 absolutely no interaction. And that's a very comforting  
23 finding when you go through perhaps an overreaction to  
24 adverse reactions. If we can define the cases where there

1 aren't interactions, there's a great deal of therapeutic  
2 value in that.

3           The particular successes that we've had in  
4 defining areas where in vitro data are particularly good at  
5 predicting in vivo data I think are in the areas where our  
6 new drug X may or may not inhibit other drugs. I would say  
7 by far the preponderance of data that we've looked at from  
8 the agency says that if you have a well-designed study in  
9 vitro and your new molecular entity does not inhibit the  
10 metabolism of other drugs, we just don't see that in the  
11 clinic. So, I think that's a clear success in the area of  
12 use of in vitro data to predict what happens in vivo.

13           The other area that we're concerned about is  
14 there's lots of other drugs out there that our new drug X  
15 will be taken with simultaneously, and I think by the same  
16 kinds of technology, we can rule out drugs that inhibit the  
17 metabolism of drug X. Now, we'll talk about some details in  
18 that, but generally the overwhelming preponderance is that  
19 if you're concerned about concomitant administration  
20 inhibiting the metabolism of drug X, you can determine that  
21 in vitro and it is predictive of what happens in vivo.

22           There's variable interest from year to year in  
23 genetic polymorphisms and ethnic and pharmacogenetic  
24 differences in drug metabolism. The in vitro tools are

1     excellent at either ruling them out or telling you yes, you  
2     do have a problem.

3             Finally, in terms of sorting out, sifting  
4     through all the different techniques and technologies that  
5     are out there, I think without appointing a presidential  
6     commission or something of that order, somehow there's a  
7     consensus that has evolved on which drugs are good model  
8     compounds for specific pathways either in terms of  
9     substrates or inhibitors.

10            So, the amount of progress we've made in a  
11     relatively short period of time is really not only  
12     impressive, but it's helpful. It helps us make actual  
13     decisions in labeling and in therapeutic practice.

14            Now, when I came before this committee in  
15     August of last year, I identified some areas that I thought  
16     were loose ends that needed particular attention, and I'd  
17     like to comment on just a couple of them. As many of you  
18     know, I have a rule of never giving a talk at FDA without  
19     showing some data from our laboratory. These data were  
20     generated by Mike Fitzsimmons in our lab -- he's now at the  
21     University of Michigan -- looking at the HIV protease  
22     inhibitor saquinovir, looking at the metabolic profile in  
23     human intestine versus human liver.

24            One of the loose ends I'm a little bit

1 concerned about and we almost never see any data in NDA's,  
2 almost every drug that we evaluate is swallowed, goes first  
3 to the GI tract before it sees the liver. We know there  
4 are enzymes in the GI tract. We rarely think and evaluate  
5 the comparison between human intestine and human liver.

6 In this particular case, since the dominant  
7 pathway is P450 3A4, the metabolic profile is both  
8 qualitatively and quantitatively similar in human intestine  
9 and human liver, and again that's reassuring. If you're  
10 trying to get to sleep at night and thinking about all the  
11 things that can go wrong, it's somewhat comforting to know  
12 that some things are the same in the intestine and the  
13 liver and don't at least generate new problems.

14 Another area that I mentioned last year at this  
15 committee was the area of induction of drug metabolism, and  
16 that's certainly an area in which our tools and technology  
17 is the weakest. Our lab is collaborating with Al Li at In  
18 Vitro Technologies in this area. There are many other  
19 groups that are working in that. We presented a poster at  
20 the ISSX meeting a couple of months ago. It's not there  
21 yet. I can't say that, but it's very encouraging to see  
22 the numbers of groups that are standardizing their  
23 approaches and the kinds of results that we're getting.

24 Next the major arguments that we have behind

1 the closed doors at agency with the sponsors are the  
2 borderline cases. You can tell when there's absolutely no  
3 interaction. You can tell when there's a huge interaction.  
4 A lot of things are in the middle. Ken Thummel and others  
5 have begun focusing on parameters such as the ratio between  
6 the unbound concentration of drug and the  $K_i$  for the  
7 interaction. Don't be fooled by total drug concentration.  
8 Several folks have done that. Don't be fooled by  $IC_{50}$ 's  
9 instead of  $K_i$ 's. Beginning to sort that out, I see that as  
10 an area for continued improvement, but I'm encouraged by  
11 what's already happened.

12           The biggest problem that we see in submissions  
13 is inappropriate conditions for in vitro and therefore  
14 inappropriate predictions for what's going to happen in  
15 vivo.

16           The number one problem is astronomically high  
17 concentrations of drug that are incubated with systems in  
18 vitro and saturating enzymatic pathways, switching from  
19 high affinity to low affinity pathways, and really no  
20 confidence in our ability to predict.

21           I also continue to see a P450-centric approach  
22 to drug metabolism. There are lots of drugs in the  
23 pipeline that we're reviewing in which P450 is a minor  
24 pathway. Just because we can do it well doesn't mean that

1 that's the kinds of studies that we ought to be routinely  
2 doing.

3 My last plea for area of improvement. I am  
4 sensitive to the constraints in industry, even if I'm not  
5 as sophisticated as those who spent their careers there.  
6 But we have to see the data that are already generated and  
7 published. We don't actually have to do any more  
8 experiments to move the field ahead. If all experiments  
9 that are currently existing in industry files and locked up  
10 in our confidential files back in Rockville were published,  
11 we'd be able to leap ahead substantially by knowing where  
12 the outliers are and where the levels of confidence are.

13 So, there are still a few areas under  
14 construction. For those of you who are worried about this  
15 field winding down and coming down to an end, there's  
16 plenty more work to be done. I think we've got to at some  
17 point be grateful for the progress that has been made, but  
18 let's keep our focus on what else has to be done.

19 Next slide, winding down, my colleagues on the  
20 working group have asked me to remind the committee that  
21 not every drug-drug interaction is metabolism-based. We  
22 heard a previous speaker mention pharmacodynamic-based  
23 drug-drug interactions. There are transporters, excreters,  
24 absorbers, and things like that that can also be saturated,

1 and those are important areas that are not primarily  
2 addressed by this. We tried to pick something that we  
3 could focus on and not get lost on. And also our judgment  
4 was that most of the high profile ones were in this area.  
5 We'd at least start with this area.

6 For my last slide, again in addition to  
7 reminding people that we've come quite far by recognizing  
8 the opportunities that were there with mature technology  
9 already developed and taking advantage of it, we're at a  
10 crucial point, as several previous speakers have said this  
11 morning, in the development of this in vivo guidance, and  
12 this is the moment for brainstorming and suggestions. None  
13 of our guidances are the work of one person or one working  
14 group. They all reflect input from diverse constituencies  
15 and this is a chance to continue to build on the good work  
16 that has been done so far, not rest on it, but try to make  
17 this guidance launch as appropriate and helpful as  
18 possible.

19 Thank you.

20 DR. ZIMMERMAN: Thank you, Dr. Collins.

21 With that, we're going to take our morning  
22 break for about 20 minutes, and so we will reconvene here  
23 at 10:20. Then we will have a committee discussion on the  
24 morning's presentations.

1 (Recess.)

2 DR. ZIMMERMAN: Ladies and gentlemen, let's get  
3 started. Well, welcome back, everybody.

4 We have quite a number of questions that we've  
5 been asked to discuss, and we've kind of prioritized them  
6 over the break. We have five main issues I think that  
7 we've been asked to talk about. What I've done is made the  
8 executive decision to talk about each of them 20 minutes.  
9 If we don't use the 20 minutes, we'll go on to the next  
10 one, but at least we'll have a chance to talk about all  
11 five of these points.

12 Before I open the discussion, I would like to  
13 introduce two more of our experts who I neglected to ask  
14 them to introduce themselves. Dr. Lu and Dr. Venitz, would  
15 you mind introducing yourselves and telling us your current  
16 affiliations?

17 DR. VENITZ: I'm Jurgen Venitz. I'm Associate  
18 Professor at the School of Pharmacy at Virginia  
19 Commonwealth University.

20 DR. LU: I'm Anthony Lu, special government  
21 employee.

22 DR. ZIMMERMAN: Thank you.

23 All of our panel of experts, including Dr. Lu  
24 and Dr. Venitz, will be part of the discussion today, and

1 we'll ask to contribute and ask questions, et cetera.

2 I see that Dr. Branch has now joined us on the  
3 committee as well.

4 For those who weren't here yesterday, we rule  
5 this with an iron hand. So, we would ask that you raise  
6 your hand and ask to be allowed to speak so that we don't  
7 talk over each other. I'll try to be fair about this. So,  
8 thank you.

9 The first subject that we would like to spend  
10 some time on is the following question that was set up for  
11 us. What assumptions are we willing to make in  
12 extrapolating data obtained from specific studies conducted  
13 in normal subjects to patients?

14 So, I'll simply open the discussion. We can  
15 ask questions of the agency or simply bring forward  
16 comments and questions. So, I open the open discussion.  
17 Yes, Dr. Lamborn?

18 DR. LAMBORN: Could I ask a question that sort  
19 of goes back even to before this, but it is related to the  
20 issue of normal subjects to patients?

21 What about the issue of whether or not the  
22 availability of the agents in the blood necessarily relates  
23 to toxicity and efficacy when you have two active  
24 compounds? We seem to be making the assumption that just

1 because the blood distribution does not change, that that  
2 implies that you will not change the effect.

3           So, are we just sort of ignoring that part of  
4 it and saying that we're assuming in these circumstances  
5 that if you have equivalent blood levels, then you -- I'm  
6 thinking of an environment where you often are trying to  
7 combine agents where you hope you haven't increased the  
8 toxicity but where you think that they may together have  
9 some sort of synergistic effect on target organs.

10           So, could somebody just address that for me for  
11 a second?

12           DR. FLOCKHART: I think the take-home message I  
13 think that should be transmitted here is the importance of  
14 pharmacodynamics and that pharmacodynamic studies  
15 absolutely whenever possible in any conceivable way should  
16 be done.

17           Just to underline the point -- and Dr. Watkins  
18 can talk a lot more than I can about this particular point,  
19 but Dr. Honig referred earlier on to the interaction  
20 between quinidine and tricyclic antidepressants where what  
21 you're talking about would be non-useful. In other words,  
22 the simple change in concentration of tricyclics would not  
23 predict the total change in electrocardiac pharmacodynamics  
24 because quinidine has an effect not only on the

1 electrocardiogram itself, but it also probably affects  
2 P-glycoprotein and alters the distribution of the drug.

3           Now, the other example to me -- and this is  
4 from in vitro, but it stands out a mile is that if you look  
5 at the drug loperamide, which is Imodium, which is normally  
6 a non-narcotic -- there are not people walking around on  
7 the streets trying to make money out of selling Imodium.  
8 But if you take P-glycoprotein away in knock-out mice, many  
9 of us are aware, suddenly it becomes a potent narcotic, and  
10 the reason is that it suddenly is no longer being pumped  
11 out of the brain. There's an obvious example of where a  
12 drug suddenly becomes almost another drug at the same  
13 concentration in the blood.

14           So, I think that we could come at this from  
15 many angles. But there are obvious examples where the PK  
16 does not predict the PD, and I think it would be difficult  
17 to come up with parts in the guidance, lines in the  
18 guidance that say particular classes of drugs are to do  
19 this or particular drugs should not. But I think an  
20 overall thing that could be said is whenever possible a  
21 pharmacodynamic study should be done.

22           DR. ZIMMERMAN: And are you saying that would  
23 be in the patient population rather than in the normals?

24           DR. FLOCKHART: I do believe that. I spent a

1 fair amount of my life looking at antipsychotic drugs, and  
2 looking at antipsychotic drugs in normal volunteers is  
3 incredibly hard to do. So, I think there are many examples  
4 of situations where you have to do it in patients, but I  
5 fully recognize -- and everybody else does -- that there  
6 are many situations where we can't do that where you're  
7 limited.

8 DR. ZIMMERMAN: Dr. Williams?

9 DR. WILLIAMS: Well, I appreciate Dave's  
10 thought, but I have to admit I was actually trying to come  
11 to the reverse conclusion. I think it may relate to the  
12 sort of dichotomy between the desire to show something  
13 versus the desire perhaps from a regulatory public health  
14 standpoint it's nice to not show something.

15 I was also thinking that we have a very strong  
16 fundamental presumption, once you establish safety and  
17 efficacy, that PK of the active moiety can become a full  
18 surrogate for safety and efficacy. So, I was actually  
19 going to argue the converse, that maybe as a preliminary  
20 screen for these drug-drug interaction studies you could  
21 focus on PK -- and I think I'm coming back in a way to  
22 Kathleen's question -- in the sense that if you didn't see  
23 anything there, you could be reasonably assured that there  
24 wasn't a problem.

1                   Now, I think we all have to recognize that PK  
2 is a lot easier than PD when all is said and done.

3                   I guess I would come back to Dave and say I'm  
4 very interested in those examples where PK don't predict  
5 PD.

6                   DR. FLOCKHART: I share the overall concern  
7 that we're overburdening industry with a huge number of  
8 studies. I think, though, that when there is an obvious PD  
9 available, it absolutely ought to be used where the PD  
10 measure is available.

11                   Maybe a useful thing to talk about would be  
12 what would be situations where the PK does not predict well  
13 and where some time ought to be spent, and if they were  
14 outlined in the guideline, then that might help everybody  
15 and people wouldn't spend a lot of time.

16                   DR. ZIMMERMAN: Dr. Branch.

17                   DR. BRANCH: In terms of addressing the  
18 question there and this discussion, what are the  
19 assumptions that we're willing to make, it seems to me that  
20 the area that we're addressing is a very chaotic area at  
21 this point in time. One way to try and simplify this,  
22 instead of just saying there can be these alternative  
23 structures of study design, is, what is the question that  
24 we can try and address? What is the specific objective of

1 each interaction study?

2 By and large, we're using a surrogate approach  
3 and we're trying to target individual mechanisms with it.  
4 We're raising a hypothesis that one drug will interact with  
5 another drug on the basis of some a priori expectation, and  
6 it is that hypothesis that sets the assumptions that are  
7 reasonable to build into it. Is it reasonable to do it in  
8 normal people? Is it reasonable to do it in the target  
9 population? Do you need to link the dynamics or the  
10 kinetics? Is the kinetics a reasonable surrogate?

11 I think in trying to fit all questions into one  
12 box, it may be too constraining because I think what Jerry  
13 Collins was saying earlier on about the use of in vitro  
14 data and how applicable is that to in vivo data. Really  
15 what we're looking at is the weak links of the transitions,  
16 the transition between in vitro to in vivo, the transition  
17 from normal subjects to patients, the transition between PK  
18 to PD.

19 But within the areas that we can feasibly and  
20 reasonably do studies to say there is or there isn't a drug  
21 interaction taking place, I think those can be well worked  
22 out.

23 So, I would urge that we view this on the basis  
24 of hypothesis generation and the recognition that there is

1 a continuing process where the end result is a product  
2 label. The end result is a statement to the physician of  
3 how best to use the drug. But there are a number of  
4 intermediate steps going through it. There needs to be  
5 discussion about if you do an in vitro study, can that be  
6 valid in the labeling. If you do a study in normal  
7 subjects, can that be valid, and what are the parameters  
8 that relate to that.

9 But I think it's a mistake to try and get it  
10 all constrained into too tightly defined a box. This is  
11 too variable an area and there are too many alternative  
12 mechanisms that can be influenced by drug interactions.

13 DR. ZIMMERMAN: Dr. Brazeau?

14 DR. BRAZEAU: I would like to bring up  
15 something I think we discussed that's related to that first  
16 issue, and that's we heard a lot yesterday about the  
17 variability in patient response. Is it possible that  
18 normal individuals in their concentration-response  
19 relationship will vary widely? Likewise target populations  
20 may vary widely. So, will you get that much useful  
21 information out depending how variable the pharmacodynamic  
22 measurement is?

23 And if patients differ -- there's some evidence  
24 by I think some very distinguished scientists that have

1 looked at that the PH of the concentration-response  
2 relationships vary much more than the pharmacokinetic  
3 relationships, and that you might not be able to  
4 necessarily differences between normal and target  
5 populations. So, it goes back to this idea of individual  
6 variability.

7 DR. ZIMMERMAN: Dr. Cantilena.

8 DR. CANTILENA: I guess part of my concern  
9 would be that when you're formulating a guidance, sort of  
10 the motivation for doing that is, in essence, to come up  
11 with rules that sort of fit all or generalizable kinds of  
12 things. I guess I would sort of echo what Bob says that  
13 there are areas with individual drugs that you're not going  
14 to have the relationships. If you don't have them, it is  
15 probably unrealistic to try to come up with a one-size-  
16 fits-all sort of a guidance. I guess there are just really  
17 too many holes.

18 For the obvious cases that Roger mentioned, I  
19 think all of us are comfortable. If there is absolutely no  
20 effect, then there probably is not going to be any kind of  
21 an issue, and you can probably translate that comfortably  
22 into labeling. But for all of the borderline areas, as one  
23 of the speakers was describing, I think that's the point  
24 where you have to say is the science at a stage where you

1 can generalize. I think for the majority of drugs, it  
2 probably isn't at this point.

3 DR. ZIMMERMAN: Dr. Lamborn.

4 DR. LAMBORN: Would you be saying then perhaps  
5 that you would initially consider normal volunteers, but if  
6 you got a maybe there is/maybe there isn't, that you should  
7 be then looking at it in what you expect to be the primary  
8 patient population? Is that what you're referring to?

9 DR. CANTILENA: I guess I couldn't sort of  
10 answer that in a general way. I would say that if the  
11 pharmacodynamics were likely to be different in the patient  
12 population versus normal volunteers, then I would say, yes,  
13 you should actually look at it. But a lot depends on the  
14 slope of the dose-response and those kinds of things.

15 So, I think that in general you would say that  
16 if you thought that the pharmacodynamic response was  
17 different in a patient versus a normal volunteer, then you  
18 should probably look at it. But if the slope is extremely  
19 flat, if it's not a serious issue, then you might not have  
20 to.

21 So, again, coming up with a guidance, if you  
22 will, a generalization for all compounds, I think has some  
23 risk.

24 DR. LAMBORN: But would you be saying then

1 start with the normal, even in those instances where there  
2 may be some differences, still do the normal study first as  
3 being easier, or are you saying skip it if you think that  
4 there's a difference? I'm just trying to make sure I  
5 understand what you're saying.

6 DR. CANTILENA: I guess I was using that  
7 example in response to what Roger said. If you saw no  
8 difference.

9 DR. LAMBORN: But no difference in a normal --

10 DR. CANTILENA: In normal --

11 DR. LAMBORN: Thank you. That's what I needed  
12 clarified.

13 DR. ZIMMERMAN: Dr. Byrn?

14 DR. BYRN: I was just going to suggest some  
15 kind of extension of this idea to some of kind of decision  
16 tree in the guidance where you might do some kind of test  
17 to see, and then if it went on one branch, you could use  
18 the PK data. If it didn't, you'd have to use the PD data.

19 DR. ZIMMERMAN: Dr. Williams.

20 DR. WILLIAMS: Just to offer a thought to the  
21 committee that I think echoes a lot of what you've heard.  
22 My feet stand both in the product quality world and the  
23 safety and efficacy world. I think in both worlds we're  
24 always struggling with this issue of going from in vitro to

1 early PK/PD or to maybe pop PK/PD to late phase clinical to  
2 post-marketing, and each of them have tools associated with  
3 how you look at the data and what do you conclude from the  
4 data. And I could say the same is true for product quality  
5 topics, and I won't waste the committee's time to draw that  
6 parallel.

7           But what's interesting to me is there's kind of  
8 a declining precision and accuracy -- you know, you start  
9 with something that's very precise -- and rising clinical  
10 relevance. So, it's almost like you see something going  
11 down in terms of signal to noise and something going up in  
12 terms of clinical relevance. I think the challenge to us,  
13 which I think Steve was mentioning by the decision tree, is  
14 saying which tools to you pull out to address the question.  
15 What are their pros and cons? When do you feel like you've  
16 adequately addressed the question and can stop? And when  
17 do you keep monitoring? It's a great general discussion  
18 for the committee.

19           DR. ZIMMERMAN: Yes, Dr. Honig?

20           DR. HONIG: I'd just like to go back and  
21 perhaps revisit that issue in a little bit more detail  
22 about the choice of subjects in these studies, patients  
23 versus normal volunteers. I heard a little bit of  
24 crosstalk perhaps about is the concentration-response

1 relationship likely to be different.

2 Well, before we go there, maybe let's backtrack  
3 a little bit and just talk about not looking at PD, just  
4 looking at normal volunteers as a bioassay, as it is, to  
5 quantify the pharmacokinetic changes because we already  
6 know what the concentration-response relationship is in  
7 patients hopefully at this point if this is going to be an  
8 approvable product. So, therefore, we're able to make a  
9 judgment on what changes in concentration are likely to be  
10 clinically interpretable.

11 So, the question really is then, do normal  
12 volunteers present an unusual problem in the interpretation  
13 of changes as a result of inhibition or induction? Are  
14 they likely to have larger changes, smaller changes than  
15 patients? Are they likely to have more variability or less  
16 variability than patients? And maybe we could have the  
17 committee go there.

18 DR. ZIMMERMAN: Dr. Lamborn.

19 DR. LAMBORN: I guess I'd like to ask a  
20 question on your basic assumption that usually by this time  
21 you have a relationship between the concentration and the  
22 efficacy in patients because in most instances that I'm  
23 familiar with, you don't have anything like that kind of  
24 relationship. You may have multiple doses that have been

1 tested with general averages, but you certainly don't have  
2 anything that's like a concentration by efficacy  
3 relationship.

4 DR. HONIG: Yes, and there you have the dose-  
5 efficacy relationship hopefully. I know you deal with  
6 drugs that are particularly problematic where you don't  
7 necessarily have dose-response relationships, but then you  
8 have one further level of disconnect from PK/PD to dose/PD.  
9 Hopefully we'd know how dose relates to pharmacokinetics,  
10 though, so we can make that sort of evaluation.

11 DR. ZIMMERMAN: Dr. Lesko.

12 DR. LESKO: I guess one of the thoughts I had  
13 on this normal volunteer versus patients is that it would  
14 seem that if you start out with the default position that  
15 normal volunteers are appropriate, there would be some  
16 instances where you might have a mechanistic understanding  
17 of combinations of drugs where you might create the  
18 argument that there's a need to look at patients in a  
19 particular subset of drug combinations. I don't know if  
20 our knowledge base is at that point to define many of the  
21 drugs in that subset, but conceivably if you've identified  
22 mechanistically combinations where PK/PD would change in  
23 patient populations in a way that would be meaningful, you  
24 could then step back and consider the possibility of

1 examining that in an in vitro system, not too much unlike,  
2 say, the in vitro drug metabolism, recognizing that dynamic  
3 interactions in vitro has not involved to the point where  
4 drug metabolism has. But I think there are some systems,  
5 based on receptors, for example, that could be used to  
6 perhaps test the hypothesis that concentration effects may  
7 be different under certain circumstances.

8 DR. ZIMMERMAN: Dr. Mayersohn?

9 DR. MAYERSOHN: This is a very confusing issue.  
10 There are so many parameters involved.

11 It seems to me that this area or the question  
12 that we're addressing is a work in progress. It goes  
13 through phase III and post-marketing surveillance as well  
14 where you start really learning about the problems you  
15 have.

16 I agree very strongly with Steven's comment  
17 that you need a paradigm. You need some kind of logistic  
18 approach to if not this, then this, some kind of a decision  
19 tree early on, and I think that will help define the  
20 problem.

21 These other issues that we're dealing with we  
22 may never solve. The issue of variability in dynamics  
23 within and between people. How you determine what clinical  
24 significance is in terms of an interaction, that's beyond

1 me. I don't know how one does that other than in the  
2 setting where you measure the response.

3 So, this is going to be an evolving issue. I'm  
4 convinced you can't work it out precisely for all  
5 situations because you can't predict them all, and you do  
6 the best you can. I don't know what else you could do.

7 What makes it even more complicated is Jerry's  
8 comment, which I agree with, that it's not just metabolism.  
9 It's absorption. It's renal excretion. Binding may not be  
10 important, but that opens it up to even more complexity.

11 DR. ZIMMERMAN: I guess I would say that in  
12 terms of being able to predict pharmacodynamics, the  
13 concentration-effect relationship in patients as opposed to  
14 normals would also depend on the disease state because it  
15 would seem to me that in some diseases the concentration-  
16 effect relationship would be much more variable than in  
17 other diseases. So, it would also depend on the disease I  
18 would think. In some cases, there might be less  
19 variability in how patients respond to the drug than in  
20 others. So, that part of it is complex as well.

21 Dr. Williams.

22 DR. WILLIAMS: I don't want to interrupt the  
23 flow of the committee as it moves through its questions,  
24 but I actually would like to have about three minutes to

1     argue to the committee that there is a paradigm at your  
2     fingertips that would help straighten out some of these  
3     issues, and it's the equivalence concepts that we talked  
4     about yesterday.

5             DR. ZIMMERMAN: We were going to talk about  
6     equivalence actually in our next section.

7             DR. WILLIAMS: Okay.

8             DR. ZIMMERMAN: Will you allow us to do that?

9             Dr. Flockhart.

10            DR. FLOCKHART: I think actually what Roger is  
11     referring to is the concept of individual bioequivalence  
12     being applied to this study --

13            (Laughter.)

14            DR. FLOCKHART: -- which is slightly different  
15     from talking about bioequivalence itself. It's using the  
16     variability as a marker. Is that right, Roger?

17            DR. WILLIAMS: That's the case I would like to  
18     make when you're ready.

19            (Laughter.)

20            DR. FLOCKHART: He's not actually wanting to  
21     talk about bioequivalence itself. So, I for one would like  
22     to hear him talk about it.

23            DR. WILLIAMS: Well, the only thing I would  
24     drop is "bio" and I would say everything else can be

1 translated conceptually and talk about individual  
2 equivalence.

3 DR. ZIMMERMAN: The next topic that we were  
4 just about to go into is how to translate the data to  
5 informative labeling language which has to do with the  
6 equivalence issue as it has been set forth to me. So, if  
7 you don't mind, we'll move on to our next topic unless  
8 there's a final -- oh, I'm sorry. Shiew-Mei?

9 DR. HUANG: I just want to mention that when we  
10 put the question up, it also included special population  
11 groups. In other words, most of the interaction studies  
12 that we've seen done in the submissions are using normal,  
13 healthy, young volunteers. They're a mix of male and  
14 female. And I do want to say, what about the extrapolation  
15 from this group to elderly or when the drug is indicated  
16 for that group of patients? So, I'd also like the  
17 committee to consider that, whether there's enough  
18 information to see if we can extrapolate the information.  
19 I just didn't hear any comments in that area.

20 DR. ZIMMERMAN: Well, I think everybody is  
21 agreed that we'd spend 20 minutes per topic and then if we  
22 have time, we'll go back to it.

23 The second question that we've been asked to  
24 deal with is this one, how do we translate the data to

1     informative labeling language, which also Dr. Lesko has  
2     said the following parts should also be added to this.  
3     Should drug interactions be handled as an equivalence  
4     problem? So, that is something that relates to this as  
5     well.

6                     So, how do we translate the data to informative  
7     labeling language? What do we need to include in the  
8     labeling in terms of statistical method/analysis? How do  
9     we extrapolate the results to other drugs? Should the same  
10    labeling language for the study drug appear on the labeling  
11    for the interacting drugs? And should these issues be  
12    dealt with as an equivalence problem?

13                    Dr. Lamborn, do you want to start off?

14                    DR. LAMBORN: Could I ask a question relative  
15    to the presentation? You mentioned a specific instance  
16    where they had determined goal posts that were considered  
17    to be clinically significant. Could you tell us how they  
18    defined those as being the clinically significant goal  
19    posts?

20                    DR. HUANG: Well, Anthony, would you like to  
21    comment on that?

22                    One of the examples that I used is for Merck's  
23    crixivan, and the other one is the nelfinavir. Actually  
24    they used 50 to 200 percent, but Merck appeared to use 50

1 percent. I'll defer to Anthony for that.

2 DR. LU: I think the 50 to 200 percent criteria  
3 is somewhat arbitrary and also I think considered by the  
4 conditions in terms of the safety and therapeutic index of  
5 the compound.

6 I'm more in favor of the flexible goal post  
7 approach. I think the sponsor needs to justify based on  
8 both the safety and all the other information available to  
9 set up their flexible goal posts.

10 DR. LAMBORN: Well, I think in this case it was  
11 being presented as an example of a flexible goal post, and  
12 I'm really asking in that particular instance what  
13 justification was given.

14 DR. HUANG: As far as nelfinavir?

15 DR. LAMBORN: Yes.

16 DR. HUANG: Well, I can say that based on our  
17 experience, as Peter has mentioned, we don't have a lot of  
18 PK/PD information to really justify whether 200 percent or  
19 50 percent is appropriate. However, a lot of times it's  
20 based on convenience of dosage form. Whenever you can make  
21 half of the dose or when you can make dose adjustment  
22 easily and that's the way the dose recommendation is going,  
23 and that's part of the reason that 50 to 200 percent comes  
24 into play when you can halve the dose or increase the dose

1 or change your dosing interval.

2 Most of the time what we heard -- maybe we can  
3 hear more discussion this afternoon -- is based on some  
4 safety dose-response data where you're seeing higher doses  
5 given and there are no clinically significant serious  
6 adverse events found. Most of this was being discussed  
7 with the medical officer with our office, and they felt  
8 that it's comfortable and I think this was the case.

9 DR. ZIMMERMAN: Other comments? Dr. Lesko?

10 DR. LESKO: Cheryl, I think the question about  
11 goal posts actually precedes the question that I would hope  
12 the committee would address and that is how the data is  
13 initially analyzed and expressed from the drug interaction  
14 study. Dr. Huang presented what we currently see which is  
15 really heterogeneity in presentation of drug interaction  
16 data, ranging from a point estimate only, which I don't  
17 think has much value, to perhaps a p value which has  
18 limited value.

19 So, I think if we can maybe discuss the pros  
20 and cons or the advantages, if you will, of a different  
21 statistical presentation of the drug interaction data, I  
22 think that follows and leads into then a subsequent  
23 discussion of the interpretation of that once it's  
24 analyzed.

1 DR. VENITZ: I would encourage the committee to  
2 discuss the issue about equivalence, whether the problem of  
3 drug-drug interactions can be reduced to an equivalence  
4 problem. I would argue personally that it depends. It  
5 depends on what your a priori expectations are. If your  
6 intent is to show that two drugs don't interact, your  
7 expectation is the null hypothesis and you're trying to  
8 prove it or at least use the current bioequivalence or  
9 individual bioequivalence logistics to come up with an  
10 answer to that question.

11 A different question is if you have some  
12 mechanistic data to suggest there is a drug interaction,  
13 your question is not is there one in a clinical study, but  
14 how much of a drug interaction do you have, how clinically  
15 significant is it and what are you going to do as a result  
16 of it?

17 I think that might determine whether you  
18 consider the drug-drug interaction in the equivalence issue  
19 or not. I think once you've decided that, then the  
20 statistics become I think secondary both in terms of what  
21 you actually want to do statistically as well as how you  
22 interpret it.

23 DR. ZIMMERMAN: Dr. Lamborn?

24 DR. LAMBORN: I guess I would argue that

1 whether you wanted to demonstrate the size of the  
2 inequivalence or whether you wanted to demonstrate  
3 equivalence, the same methodology would work because what  
4 you're ultimately coming out with is a confidence interval  
5 saying how are the two related. I think you can very  
6 easily fold this in.

7           So, I guess I would specifically like to go  
8 back to addressing do we think we can address this in the  
9 same way we've been addressing bioequivalence. From  
10 everything I hear, it is a question of bioequivalence and  
11 the analysis could very effectively be done in the same  
12 way, giving an interval which gives you a picture of how  
13 accurate your information is. I would propose that that is  
14 a very good way of approaching the problem.

15           DR. ZIMMERMAN: Well, I will let Dr. Williams  
16 speak in just a minute. Dr. Flockhart has his hand up.

17           DR. FLOCKHART: Just one small point about  
18 this. I don't think this is actually rocket science. I  
19 think that the comparisons between groups have been very  
20 well outlined by Dr. Honig.

21           There's one small thing that I think is  
22 important, and that is that the possibility of nonrandom  
23 distribution always be addressed. I'm looking at papers  
24 about drug interactions. The mean, the confidence

1 intervals, and so on does not -- hides the possibility  
2 behind it of outliers.

3           Whenever we're looking at that kind of data,  
4 we're all aware of the possibility of genetic polymorphisms  
5 in our field doing that kind of thing. But there may be  
6 unusual surprises in there. The statistical  
7 appropriateness of the testing therefore starts to fall  
8 apart if the results aren't randomly distributed.

9           Obviously that's just a small point. You  
10 shouldn't statistically apply these tests if there's not a  
11 random distribution in the first place.

12           DR. ZIMMERMAN: Dr. Williams?

13           DR. WILLIAMS: You know, I think one of the  
14 exciting things about this committee is it's a chance to  
15 talk about exciting concepts without necessarily leading to  
16 any regulatory conclusion. When I was talking to Larry  
17 this morning, he said, Roger, don't talk about this.  
18 You've already got half the industry trying to kill you.

19           (Laughter.)

20           DR. WILLIAMS: So, I will not talk about this  
21 in the sense of forming any regulatory policy, but I will  
22 talk about it in the sense that it might be a very  
23 constructive paradigm to lead to research.

24           We got some good suggestions for research

1 yesterday and I always want to keep in mind that we have  
2 these two collaborations emerging as a focus for further  
3 research.

4 I have to tell you the other thing I thought as  
5 I drove in on the Indiana 500 beltway speedway this  
6 morning, that I might not be around tomorrow. So, I think  
7 that this might be my last chance to tell you this story.

8 I will make the argument, turning to Walter as  
9 the true expert in this and the person who has really got  
10 us thinking about this with some other people -- and I  
11 would hope Walter would feel free to comment.

12 Now, I would argue that you can make the case  
13 that it is a prescribability and switchability question.  
14 As I talk about this now, I will no longer talk about  
15 population and individual bioequivalence. I will talk  
16 about population and individual equivalence. I will drop  
17 the "bio" term, although it may creep back in because it's  
18 part of the aging brain memory cells. Let me see if I can  
19 articulate how I think it might be a prescribability issue.

20 The prescribability issue, the way I think  
21 about it, is sort of the physician is sitting there,  
22 confronted with the patient for the first time, and he's  
23 trying to pick the right dose. He or she is trying to pick  
24 the right dose. You base that on a population average from

1 the clinical trials.

2 Now, imagine now the physician, the health care  
3 professional, is sitting with the patient in from of him  
4 who is not just sitting there naive to the drug that the  
5 physician is trying to prescribe, but is also taking a  
6 potentially interacting drug. So, in other words, our  
7 understanding of that population mean with which the  
8 physician uses to choose the right starting dose is somehow  
9 adjusted by his understanding that the patient is also  
10 taking another drug.

11 Now, I would argue that if we can agree on that  
12 kind of concept, then you immediately fall into the world  
13 of population equivalence with all its ramifications. I  
14 would come back to what Shiew-Mei was saying. It relates  
15 to what's your question. This is sort of the question.  
16 The physician is saying how do I adjust this dose in the  
17 presence of a potentially interacting drug.

18 I would also come back to what Peter Honig very  
19 nicely summarized, some clinical trial designs, that if you  
20 can agree on this is the question, it is a prescribability  
21 question, I also think that that needs to start driving  
22 your clinical study designs in very interesting ways that I  
23 think we need to think more about.

24 Let's leave that world and now move into the

1 other part of the world which is you have a patient who is  
2 stabilized on a drug. Everybody is happy. The patient is  
3 well-titrated, tolerating the drug well, maybe taking it  
4 for many, many years, all of a sudden takes an interacting  
5 drug. I would argue that's an individual equivalence  
6 question. It's very analogous to the generic question.  
7 You're switching them from one dose form to another. Here  
8 you're adding an interacting drug. And the question is now  
9 you're going to change these levels in some way.

10 So, I would argue again it's kind of a paradigm  
11 for population and individual equivalence that I think  
12 could be very useful as we further consider these things.

13 I would argue, coming back now to Dave, when  
14 Dave talks about the dose-response relationships, I think  
15 this is a population dose-response and an individual dose-  
16 response relationship, and we talked about that yesterday.

17 Now, let me focus a little bit on this world  
18 and I'll make this case now, focusing on the equation of  
19 the moment, and say let's now translate this equation into  
20 our understanding from the discussion yesterday. I won't  
21 say test and reference anymore. I might say reference is  
22 drug and test is interacting drug. Well, that was easy. I  
23 just have to change it in the word processor.

24 I will argue that you could imagine

1 interactions that would change the within-subject variance  
2 relative to the within-subject variance before the  
3 interacting drug was added. I don't know what that would  
4 be. I think we would have to think about it  
5 mechanistically, but I think we could understand it in that  
6 way.

7 Of course, it gets tricky when we talk about  
8  $\sigma_D$  and  $\sigma$  within reference. So, let me talk about  
9 those for just a second.

10 I've been looking at Walter and I say we've got  
11 terminologies for a subject-by-formulation interaction.  
12 What is the corresponding interaction for an equivalence  
13 question with the drug interaction? I think it's something  
14 like a subject-by-interacting-drug interaction. This gets  
15 very difficult, but let me see if I can elaborate  
16 mechanistically by how that might be.

17 Let's say you had two polymorphic populations.  
18 One were slow metabolizers and one were fast metabolizers.  
19 Could we imagine an interacting drug that would affect the  
20 slow metabolizers but not the fast metabolizers? I'm going  
21 to ask Walter sometime, but let me finish. But can we  
22 imagine that being a subject-by-interacting-drug  
23 interaction? Ponder that one and you can debate that one.

24 Now, what about scaling to the reference? And

1 this comes now to Tony's comments about flexible goal  
2 posts. We start with that 80 to 125 as kind of the base  
3 point, and then we sort of look to the clinicians to say,  
4 well, what do you think the goal posts should be based on  
5 your understanding of the PK/PD dose-response relationship?  
6 Frequently the clinicians can't really answer us because  
7 they don't have the population or individual dose-response  
8 relationships to give us the correct answer. Remember, we  
9 talked about that yesterday. The drug development process  
10 sometimes doesn't give this to us.

11 I would draw the committee's recollection back  
12 to our decision on metered dose inhalers where a priori the  
13 pulmonary community agreed, in a public standard-setting  
14 sort of way, to set the goal posts for albuterol metered  
15 dose inhalers to 75 to 150. Does some of the committee  
16 remember that discussion?

17 Now, the reality of that, that was a very ad  
18 hoc decision. I wouldn't argue that it was based on an  
19 individual dose-response curve understanding.

20 So, we're frequently caught when we talk about  
21 being flexible with the goal posts the way Tony would like  
22 us to be.

23 But getting back to scaling to the reference  
24 drug product, one of the appealing things about scaling to

1 the reference drug product is it lets that variability  
2 drive the goal post. So, you could make the argument, just  
3 like we do for comparisons of formulations, that whatever  
4 the goal post is, it should be related in some way to the  
5 variability of the drug before the interaction. I'm not  
6 going to call it the reference drug now. I will call it  
7 the drug prior to the interacting drug.

8 Now, I would argue again this is a very rich  
9 concept, and I think it's going to apply in other settings  
10 to us as well. But it really raises all the questions that  
11 in some way or another we've been talking about. Healthies  
12 versus patients. It goes back to this. If you think there  
13 might be a subject-by-interacting-drug interaction, then it  
14 really doesn't make much sense to study this in healthy  
15 volunteers, just like studying a subject-by-formulation  
16 interaction doesn't make much sense to study in healthy  
17 volunteers.

18 Now, if we as a society don't think subject-by-  
19 interacting-drug interactions are likely, then we can  
20 forget about that term, just like we might forget about  
21 that term as a society if we think subject-by-formulation  
22 interactions don't occur very often.

23 Now, I don't know that I have anything more to  
24 say, but I'm sure the committee sees it exactly. It's a

1 complete translation from the discussion yesterday.

2 What I would like to close by arguing is I  
3 would, first of all, like to assure the innovator  
4 pharmaceutical industry that I am not asking for replicate  
5 drug-drug interaction studies.

6 (Laughter.)

7 DR. WILLIAMS: I would like to be able to go  
8 home tonight in perfect safety.

9 (Laughter.)

10 DR. WILLIAMS: And I will try to drive safely  
11 on the beltway.

12 But I would like to argue that it is a very  
13 rich concept that might lead to some research in CDDI. I  
14 could imagine maybe working with the committee perhaps to  
15 design some studies that would stress some of these  
16 concepts and either prove or disprove the general  
17 applicability.

18 Okay, I appreciate the time. Thanks very much.

19 DR. ZIMMERMAN: Thank you.

20 Let's talk about this. Dr. Brazeau?

21 DR. BRAZEAU: I want to go back and propose  
22 some ideas for the statistical method or analysis results  
23 to be included in the labeling. I think what's important,  
24 at least when I look at the PDR or when I look at the

1 labeling, I look at the package inserts, is that what you  
2 tend to look at I think is how many patients were studied  
3 in this and how many of these patients actually had this  
4 interaction. This goes back to some of the variability  
5 that we talked about. I think those are important  
6 components that should be somewhere in the labeling.

7 Are we looking at 24 patients and 23 exhibited  
8 this interaction? Are we looking at 100 patients and 20  
9 exhibited this interaction? I think that's some component  
10 that might want to be considered on the labeling. So, I'm  
11 trying to, I guess, address one of the specific issues that  
12 you asked about.

13 About the analyses, I'd have to defer that to  
14 my statistical colleagues, but from a practical point of  
15 view in trying to think about, let's say, a pharmacy  
16 clinician who would want to be reading this, I think those  
17 are the kind of things I'd like to see.

18 DR. ZIMMERMAN: Other comments? Yes, Dr.  
19 Lamborn.

20 DR. LAMBORN: A question of clarification.  
21 When you say you'd like to know how many had the  
22 interaction, you're thinking of a clinically observed  
23 interaction, or are you still thinking about blood level  
24 differences?

1 DR. BRAZEAU: I guess I'm thinking about a  
2 clinically significant reaction.

3 DR. LAMBORN: Yes. So, you're really talking  
4 about how many patients who had the two agents together  
5 were observed to have some sort of toxicity or something?

6 DR. BRAZEAU: I don't know if we're talking  
7 patients or normals, but if a study was run, you probably  
8 won't see it in normals.

9 DR. ZIMMERMAN: Would somebody like to speak to  
10 the concept that Dr. Williams just presented to us of  
11 bringing the equivalence concept into this drug interaction  
12 realm?

13 DR. LAMBORN: I think I've already said that I  
14 think that it would apply very well, and to the extent that  
15 you move from whatever choice you make about how you use  
16 equivalence, I think that's really what we're looking at.

17 DR. ZIMMERMAN: Yes. I think it's a very  
18 attractive concept.

19 DR. WILLIAMS: I might ask Walter to comment,  
20 but before I do, I would say -- and it comes back to what  
21 Gayle was talking about. Sometimes I think it's nice from  
22 a public health standpoint and very valuable to say an  
23 interaction is not occurring. That's why I like these goal  
24 posts concepts and I sort of like the flexible goal post

1 concepts that I think you can see by scaling to the  
2 reference variability, I'm trying to get to that  
3 flexibility that I think Tony was arguing for.

4 But you can only really say with some  
5 assurance, based on confidence interval approaches, that an  
6 interaction isn't important, isn't likely. I think that's  
7 a very valuable thing to be able to say in the labeling.

8 DR. ZIMMERMAN: Dr. Lesko.

9 DR. LESKO: Just to clarify because sometimes  
10 there's confusion about no interaction versus no  
11 difference. I think there's going to be a difference in  
12 the metric, an area under the curve or a Cmax, which may  
13 lead one to conclude no interaction. I think that's kind  
14 of the idea of setting a goal post, not only the goal post.  
15 When we say no interaction, it conveys no difference or no  
16 interaction of the two medications.

17 DR. ZIMMERMAN: Dr. Flockhart?

18 DR. FLOCKHART: I'm going to try and bring  
19 Roger's and my earlier disagreement together on this. I  
20 think if we try and focus on how best to protect the public  
21 in a way that does not overburden industry, and I think the  
22 idea of flexible goal posts, individual drug variability-  
23 determined goal posts, is very, very useful in the sense  
24 that it does reduce the regulatory burden, if you like, for

1 drugs that intuitively might have relatively large changes  
2 with little pharmacodynamic consequence.

3 My own perspective on this, as a person who  
4 practices medicine, is that there's far too much  
5 pharmacokinetics in the PDR. There's a huge amount of  
6 irrelevant information to the practicing physician and  
7 again coming back to my point about pharmacodynamics.

8 But there should be a number of drugs for which  
9 -- and this feeds into the narrow therapeutic range  
10 discussion yesterday -- for which one finds that the  
11 pharmacodynamic variability, if you like, Dr. Williams,  
12 would be such that you would require relatively replicate  
13 -- you know, the regulatory burden would be greater because  
14 the pharmacodynamic variability was greater were it to be  
15 in your equation.

16 Therefore, inevitably, were we using the  
17 flexible goal posts as so defined, you would get around the  
18 problem. Where you needed a regulatory burden, you would  
19 have it. Where you do not need a regulatory burden, where  
20 the PD variability was relatively low even though the PK  
21 might be high, you wouldn't have it.

22 DR. ZIMMERMAN: Dr. Brazeau?

23 DR. BRAZEAU: I think we need to clarify  
24 something that's important, as I listen to this

1 conversation. I think it's the idea of drug variability,  
2 which could be more a product quality issue, versus patient  
3 variability with the drug. I think there are two different  
4 issues here that need to be resolved. We're talking about  
5 how this drug acts in a patient, not necessarily about the  
6 drug. I think some confusion might be because I think one  
7 is a product quality issue and one is a care issue, and I  
8 think we have to be careful in how we talk about that  
9 terminology.

10 DR. ZIMMERMAN: Other comments? Dr. Mayersohn?

11 DR. MAYERSOHN: Roger, in your paradigm you're  
12 assuming a narrow therapeutic range? Does that underlie  
13 the whole concept?

14 DR. WILLIAMS: I'm glad you brought that up,  
15 Mike, because I was actually thinking, as I sat down, there  
16 was one correspondence that I didn't draw and that was the  
17 correspondence that I think also is applicable, that you  
18 might want to always scale for narrow therapeutic index  
19 drugs. Now, I'm going to say narrow therapeutic index  
20 drugs and not drug product.

21 DR. MAYERSOHN: So, that does underlie your --

22 DR. WILLIAMS: I think it's a complete  
23 correspondence is what I'm saying.

24 DR. MAYERSOHN: So, it's fair to say that if

1 there's a huge therapeutic range, penicillin for example,  
2 and there's an interaction, you're not particularly  
3 concerned.

4 DR. WILLIAMS: Exactly.

5 DR. MAYERSOHN: Okay. And therefore you  
6 wouldn't want to be so precise as to characterize the  
7 parameters in that equation.

8 DR. WILLIAMS: Well, I think what we're coming  
9 to is two ways to achieve flexibility in the goal posts.  
10 One is your understanding of the dose-response  
11 relationship, either population or individual. Now, you've  
12 just mentioned penicillin. The efficacy versus toxicity  
13 relationship that John Balian talked about yesterday is  
14 incredibly wide, so your goal posts might be infinite  
15 there.

16 The other way to come to flexible goal posts is  
17 to let the variability of the drug prior to the interaction  
18 drive the goal posts.

19 I think both are fair and can be used by  
20 industry.

21 DR. ZIMMERMAN: Other comments, or we'll move  
22 on to our next topic.

23 DR. BRAZEAU: What about these last two  
24 questions?

1 DR. ZIMMERMAN: Which?

2 DR. BRAZEAU: Well, I guess I have a question  
3 about the labeling language for the study drug to appear on  
4 the labeling for the interactant drug. I certainly think  
5 that's a valid thing to do, but I'm not sure it's a  
6 practical thing, the idea of cross-labeling.

7 Where I think it's absolutely essential and we  
8 need to talk about it is in the area of OTC products. I  
9 think about cimetidine, a number of these drugs that are  
10 over-the-counter. We have patients taking these. I think  
11 if it's possible without being too burdensome, I think we  
12 have to be very aware of this cross-labeling because we  
13 have patients all the time taking many of these drugs that  
14 might potentially, like cimetidine, have a problem.

15 DR. GOLDBERG: I would agree with Gayle. With  
16 cross-labeling, I'm not so sure that whatever difficulty it  
17 is, that it's worth doing it in the name of public safety.

18 DR. ZIMMERMAN: I think we'll move on to the  
19 question of study design. What it says on the very top  
20 that I put off the screen is simply Study Design Issues.  
21 We come back to the issue of patients versus normals. If  
22 two routes of administration are to be available, do we  
23 have to study the effects of an inhibitor or inducer on  
24 both routes? Can this decision be guided by in vitro data?

1 And do we have to study drugs which are unlikely to be  
2 coadministered but between which a clinically significant  
3 interaction is likely?

4 I'll open this for discussion. Dr. Branch.

5 DR. BRANCH: I'd like to go back to the  
6 statement I made earlier which is I think it depends on the  
7 question you're asking. I think that the study design  
8 flexibility should be there to allow you to address is the  
9 hypothesis that this is a clinically significant  
10 interaction -- is the hypothesis that because this drug is  
11 handled by a specific route of metabolism, is it going to  
12 be subject to all the known interactions that are involved  
13 in that route of metabolism? If it's a question of route  
14 of administration, how will the drug get to the site of  
15 administration?

16 So, there's so much complexity that is  
17 potentially available in the drug interaction arena that it  
18 really comes down to precisely defining the question. I  
19 guess the query I would have is what is the extent of  
20 interaction between a sponsor and the agency in having an  
21 agreement up front when you design the study before it's  
22 executed, that if we do the study this way, will the agency  
23 accept this particular hypothesis? Is there an ability to  
24 have that interaction so that by the time you actually

1 generate your data, that the interpretation of it, when  
2 you've got the statistics -- it's not a question of  
3 statistical significance. It's what's the relevance of the  
4 information. Is there an agreement that if you're going to  
5 get this sort of information that that's the way that the  
6 agency would interpret it. I think that's part of the  
7 value of creating a guidance because you're actually  
8 putting down on paper what is an acceptable format. But  
9 that's the key element that would seem to me that you're  
10 wanting to get out of your guidance.

11 DR. ZIMMERMAN: Dr. Lamborn.

12 DR. LAMBORN: I'd like to say something about  
13 item 3 first and then go back. It seems to me that the  
14 obvious answer to number 3 is that at some point you have  
15 to stop. We cannot test for all potentially idiosyncratic  
16 situations. So, where that cutoff is I'd have to defer to  
17 others, but clearly you cannot test all drugs might  
18 theoretically have an interaction no matter how unlikely it  
19 is that they would be given together.

20 With regard to the two routes of  
21 administration, I think I would tend to go back to the  
22 earlier suggestion that a decision tree makes a lot of  
23 sense and that a lot of this would depend on knowledge of  
24 where in the process of the drug's action through the body

1 the interaction is likely to occur and whether that would  
2 be affected by which route of administration. That goes to  
3 the previous comments that this really has to be  
4 individualized, but I think that the tree structure gives a  
5 basis for that discussion with the agency I would hope.

6 DR. ZIMMERMAN: Dr. Flockhart.

7 DR. FLOCKHART: I think in echoing Dr. Branch,  
8 really my answer to all three questions would be it  
9 depends, it depends, it depends.

10 But I also agree with Dr. Lamborn. I think you  
11 can say it depends, we ought to have a decision tree for  
12 patients versus normals which would include the risk-  
13 benefit ratio and include the obvious consideration of  
14 oncolytics that Dr. Honig referred to.

15 If two routes of administration are to be  
16 available, it depends. I think Dr. Watkins could speak to  
17 many examples of where that would be instructive in the  
18 construction of that decision tree. In other words, if  
19 something is a 3A substrate or a 1A2 substrate, it's likely  
20 that GI things might have an effect on it. If it doesn't  
21 seem to be, then it might not matter.

22 Thirdly, I think if there's a potential  
23 interaction at all with something that could be lethal,  
24 even though it's unlikely to be co-prescribed, that ought

1 to be in the decision tree for that.

2 So, you could devise decision trees for all  
3 three.

4 DR. ZIMMERMAN: Any other comments? Dr.  
5 Goldberg.

6 DR. GOLDBERG: I was wondering whether it would  
7 be feasible for the agency to design a decision tree and  
8 then retrospectively look at the data that we do have in  
9 the archives to see what would be picked up when and where.

10 DR. ZIMMERMAN: I think you're going to have to  
11 speak right into --

12 DR. GOLDBERG: I'm sorry. I asked whether it  
13 would be possible for the agency to design a decision tree  
14 and then retrospectively look at all the interactive data  
15 that we do have in files and see what would be picked up  
16 where. It's difficult to decide what we want to do without  
17 enough data to look at.

18 DR. ZIMMERMAN: I like that idea.

19 Dr. Branch?

20 DR. BRANCH: I'd like to raise the question of  
21 taking maybe an adaptation of number 2 there. They're  
22 saying two routes of administration to be available. How  
23 acceptable is it to use known co-substrates for one  
24 mechanism to generalize to others? For example, do a drug

1 interaction with cimetidine or preferably, say,  
2 ketoconazole. You show an interaction that it actually  
3 occurs in man for your new drug with that agent. How  
4 acceptable is it to extrapolate from that?

5           Because I think this really relates to how can  
6 there be a rational approach that is not going to  
7 completely consume a sponsor's budget to come up with a  
8 reasonable set of recommendations to the practicing  
9 physician. From the point of view of the people who are  
10 trying to develop which interaction to look at, which ones  
11 are sort of acceptable? What criteria would the agency  
12 like to see for validation of the system, going to Roger's  
13 idea of what research is needed for the future? How far  
14 can we take, say, the phenotypic approach of probe drugs  
15 for individual mechanisms and use that as an example?

16           We're clearly in a work in progress, but at  
17 what stage will some of these principles be able to be  
18 incorporated into drug ruling? We're seeing this happening  
19 in product labeling of using in vitro data to say we expect  
20 on the basis of in vitro studies that this may occur. What  
21 sort of validation do we need in the in vivo area and can  
22 we actually further this discipline by an organized series  
23 of studies which will lay a clearer framework than is  
24 present right now?

1 DR. LESKO: I think there were a couple of  
2 questions in there, but I don't know if I heard them  
3 correctly.

4 I think the last part, the validation part, is  
5 getting back to two comments, one that Dr. Goldberg made  
6 about looking at data that exists. That's harder than one  
7 thinks it is, but nevertheless I think there is some  
8 validation that could go on by looking at that information.

9 I think Dr. Collins in his presentation also  
10 talked about the large volume of data that we see on the in  
11 vitro side and don't see that isn't published that could be  
12 used to validate what we perceive to be the need for in  
13 vivo studies.

14 The early comments that you made seem to at  
15 least trigger in my mind the notion that there is a worst  
16 case scenario approach to confirmatory in vivo studies.  
17 That is to say, if I took the worst case inhibitor and  
18 found a negative outcome in a clinical study, I might  
19 extrapolate and say for anything that's not quite as  
20 inhibiting, it would be safe to assume there would be no  
21 interaction.

22 Conversely, if you take a worst case inhibitor  
23 and see a positive outcome, then I think you're into  
24 looking at other studies if you want to make some sort of

1 claim about extrapolating the results.

2 So, I don't know if that's where you were  
3 heading with sort of trying to narrow down the number of  
4 interaction studies that one would do in a phase I study,  
5 for example.

6 DR. BRANCH: But, say, taking the idea that Dr.  
7 Collins was suggesting earlier, if only industry would  
8 present all its data, then there would be a richer  
9 framework. It would seem to me that the FDA is a very rich  
10 repository. If the data could be taken like you're doing  
11 in your studies right now, rather than limiting your  
12 analysis to how was it presented to you, can you take the  
13 data and start to re-evaluate which particular approaches  
14 appear to have the greatest validity, using that  
15 information and then maybe using it even to develop  
16 hypotheses that can be specifically tested to further test  
17 that and be able to use this information to constructively  
18 simplify the procedures for the future.

19 DR. ZIMMERMAN: Dr. Lu?

20 DR. LU: Yes. I think not only should we look  
21 into all the data we have, but I think in the next couple  
22 years there will be more systematic studies from academia  
23 and also from the industry to look into the whole process  
24 from the in vitro extrapolation to the in vivo, also the

1 use of probe compounds to do the studies, also look into  
2 various new mechanisms, for example, the role of P-  
3 glycoprotein. I think in the next couple years we're going  
4 to do much more and be a little more confident about the  
5 whole process.

6 So, for that reason, I think we should leave  
7 the flexibility in the guidance so that when we have new  
8 information, we know to adjust the new approach  
9 accordingly.

10 DR. ZIMMERMAN: Dr. Watkins.

11 DR. WATKINS: I'd like to just amplify a little  
12 bit on the probe drug approach of phenotyping that both Bob  
13 and Anthony brought up.

14 I have a potential conflict here in that I've  
15 devoted a considerable part of my research to looking at  
16 the use of probe drugs, but also have patented a test, the  
17 erythromycin breath test, given it to a small company,  
18 Metabolic Solutions in which I own equity.

19 Having said that, though, I see enormous  
20 potential in the use of well-characterized probe drugs to  
21 ferret out the contribution in vivo specific pathways to  
22 the metabolism of drugs and also then to allow  
23 extrapolation of in vitro to in vivo data in terms of drug  
24 interactions. Now, of course, I'm only talking here about

1 pharmacokinetic issues exclusively.

2           But initially I think we all thought it would  
3 be a relatively straightforward exercise to extrapolate  
4 data obtained in vitro, particularly drug metabolism data  
5 generated either in microsomes, certain in vitro systems or  
6 cultured hepatocytes, directly into predicting what the  
7 effects of drugs would be in vivo. That has turned out to  
8 often be disappointing right now simply because of the  
9 holes that we have in knowledge in certain areas.

10           For instance, in the question, does your new  
11 molecular entity affect the metabolism and kinetics of  
12 other drugs, narrow therapeutic indices drugs, the critical  
13 issue there is often what is the relevant concentration of  
14 the drug in vivo at the site of the enzyme or transporter  
15 or receptor if you're talking about induction. That turns  
16 out not to be a straightforward issue, and that's a big  
17 hole in our area.

18           The other side of the coin is what will other  
19 drugs that are inducers or inhibitors of enzymes or  
20 transporter or other relevant processes -- what affect they  
21 will have on the kinetics of your molecular entity. In  
22 that case the relevant question is what is the contribution  
23 of the particular process in the body, be it a particular  
24 enzyme or transporter, to the kinetics of your drug and how

1 much does that vary if it's given orally versus  
2 intravenously?

3           In most areas, we don't have a good handle on  
4 this, but I think the approach of using well-characterized  
5 probe drugs has enormous potential. For instance, we would  
6 all agree that, all things being equal, it would be  
7 desirable to do all your studies, whether they're drug  
8 interaction studies or initial phase I studies, in the  
9 relevant patient population matched for age and disease.  
10 That's rarely ethical, practical, doable to do that.

11           But it is possible, taking for instance the  
12 Pittsburgh cocktail approach as an example of giving  
13 multiple probe drugs simultaneously in very low  
14 concentrations to patients in the relevant population  
15 because the doses are too low to have a pharmacodynamic  
16 effect, and then study in the population how these drugs  
17 are metabolized, extrapolate to how much variability  
18 naturally exists in the population in these pathways, and  
19 then by using forward multiple regression, take a PK  
20 parameter like the oral clearance or other PK parameters  
21 and actually then assess the contribution of individual  
22 pathways to the kinetics of a given drug, whether it's your  
23 new molecular entity or another drug. Then at least you  
24 know what the relevant variables are in vivo, and then you

1 can begin to extrapolate what affect your drug might have  
2 on those relevant pathways or another drug might have on  
3 those relevant pathways.

4 In fact, it's now possible, using some  
5 technology with some probes, to actually estimate the in  
6 vivo  $K_i$  based on the plasma concentration or free  
7 concentration and the relationship it has to inhibiting a  
8 particular metabolic pathway.

9 Now, all this is still largely theoretical, but  
10 in the future it should be possible, if we pursue this  
11 path, get appropriate databases, to say my new molecular  
12 entity causes a 50 percent increase in P450 3A4 and a 30  
13 percent decrease in P-glycoprotein mediated transport in  
14 vivo in the relevant population and then extrapolate to  
15 another table to know exactly what that will mean in terms  
16 of the kinetics of other drugs and possibly make  
17 predictions that will turn out to be valid even without  
18 ever doing a single drug interaction study in people.

19 Now, that's a dream but I would hope that the  
20 guidelines from the FDA would encourage this sort of work  
21 and also encourage the pharmaceutical industry, where most  
22 of this work will be done, to share data and create a  
23 database that would be useful in the future.

24 DR. BRAZEAU: I'd like to make a comment

1 relating to what Dr. Watkins and Dr. Lamborn said.

2 I think this goes back to what we talked about  
3 yesterday. I don't think it's going to be as easy, but I  
4 think where there has been a lot of very positive work is  
5 when we started classifying drugs like the  
6 Biopharmaceutical Classification System.

7 I wonder if the same type of approach could be  
8 done to this type of area, talking about some of the things  
9 that -- we talked about scaling things and having  
10 parameters that might be able to evaluate whether you need  
11 to do more in vivo studies. Can you classify based on some  
12 metabolic parameters whether the reactant is likely to be  
13 impossible? And that type of classification system might  
14 be useful and trying to go back to the idea of making a  
15 decision tree.

16 DR. ZIMMERMAN: Other comments?

17 DR. WILLIAMS: I think that's a very intriguing  
18 thought. I'm not sure it would be based on its  
19 physicochemical characteristics like BCS. It might be  
20 based more somehow on its safety/efficacy or something like  
21 that. r.m.s., no, it doesn't play a role. So, in general you  
22 could say in this case it doesn't really play a role.

23 Now here is a case where a compound has been  
24 targeted to the follicle. It has been designed on purpose

1 to enter into the follicle. In fact, you see high  
2 concentrations. This compound is fluorescent. It is a  
3 synthetic retinoid. It is fluorescent and in fact it  
4 enters into the follicle and the distribution is different.  
5 Here is a case where I wouldn't dare to say the stripping  
6 technique predicts this. Certainly not.

7 So, it's only when a drug is targeted to the  
8 lower lumen of the follicle that one cannot expect the  
9 liberation/distribution process of the skin surface to be  
10 representative.

11 Let's go on. These cases we can again verify  
12 them and by a relatively simple technique which is call the  
13 follicular cast technique. In essence, what is it? It  
14 means that you put magic glue on a glass slide. You press  
15 it to the skin, leave it on the skin, and tear it off. The  
16 upper part of the follicle comes with it. So, in fact what  
17 we do in this case, we cut this part off and quantify what  
18 is in this part relative to the normal stripping technique.  
19 Then we can tell, yes, there is a follicular targeting or,  
20 no, there is no follicular targeting.

21 But keep in mind this depends on the substance.  
22 It depends not really on the compound. Once you are  
23 dealing with a compound, a given compound, you know whether  
24 it enters into the follicle or not. In most cases it

1 won't.

2                   Now, since we have been talking about  
3 corticosteroids and retinoids, I only wanted to show you an  
4 example of an antifungal which is a cortisol, as far as I  
5 recall. Again, you see here the stripping, that is, the  
6 horny layer. These are the concentrations in the horny  
7 layer. It's not the other way around, but you see clearly  
8 here's the skin surface, the horny layer, the  
9 concentrations, again this typical logarithmic gradient,  
10 and here the subsequent distribution in the epidermis and  
11 the dermis, kinetics which are absolutely normal and you  
12 see the correlation between the two of them. They are  
13 clearly linked by logarithmic functions.

14                   Here is another extreme case which shows you  
15 that, yes, you can distinguish. This is hydrocortisone  
16 formulated in a liposome formulation. Here is the normal  
17 formulation of hydrocortisone, the normal distribution,  
18 high concentrations in the upper layers of the horny layer,  
19 low concentrations in the lower layer, the typical  
20 logarithmic distribution epidermis and dermis.

21                   And here is the liposome formulation. Quite  
22 obviously the liposomes have completely changed the  
23 distribution kinetics in the horny layer. It's distinctly  
24 different from this kinetic, and quite obviously this has

1 changed the distribution in the epidermis and the dermis,  
2 that is, at the target site too.

3 So, in other words, this shows that, yes, in  
4 certain cases you can tell the difference between two  
5 different formulations, and it tells too that change in  
6 characteristics in type of formulation, of course, does not  
7 allow with this technique to prove bioequivalence. It  
8 cannot be equivalent. Here we show that it is not.

9 So, to come to the conclusion in normal cases  
10 of corticosteroids, retinoic acid, of undefinables, we have  
11 shown that there is parallelism between the distribution  
12 process, as measured by the stripping technique, and the  
13 subsequent concentrations at the target site in the skin.

14 As soon as there is a change in phase, that is,  
15 as soon as you're dealing with solid material, you cannot  
16 compare the two anymore because solid material -- let's  
17 say, part of hydrocortisone -- would be not dissolved, but  
18 in crystalline form in the formulation, then you have to  
19 deal with different dissolution kinetics, with  
20 polymorphism, similar problems, and you cannot compare  
21 them. New studies would be needed. So, we are only  
22 dealing with dissolved compounds when we are talking about  
23 the stripping technique.

24 The other exception is that whenever compounds

1 are specifically targeted -- but this is in most cases  
2 solid material -- to the deep follicle, then of course one  
3 should not compare them. But you can distinguish them by  
4 the second technique, which I have shown, that is, the  
5 follicular cast technique.

6           Coming from there, the obvious question: Is  
7 there a distinct difference between hydrophilic and  
8 lipophilic compounds? No, there isn't.

9           There is no class of compounds in which you can  
10 use the technique relative to the other class where you  
11 cannot use it. That's not the case.

12           It is the physical characteristics of the  
13 formulation and it's the targeting which makes the  
14 difference. It's not the form in itself; it's not the  
15 compound in itself because once you have established the  
16 kinetics for a given compound in a given formulation, under  
17 the given condition in human volunteers, then yes, to my  
18 experience you can compare them.

19           Thank you for your attention.

20           DR. SHAH: After hearing the different ways of  
21 measuring the bioequivalency for a topical dosage form, I'd  
22 like now slightly to consider how many bioequivalency  
23 studies are needed if a firm is interested in manufacturing  
24 more than one strength of the product, meaning two or three

1 lower strengths.

2 But before we go into that, as in the morning  
3 we made some comparisons between the orally administered  
4 drugs and the topicals, I'd like to bring to the attention  
5 of the committee members that as far as the oral drugs are  
6 concerned, oral immediate release drug products, the  
7 bioequivalency studies are conducted at the highest  
8 strength level, and all the lower strength products are  
9 approved based on the composition similarities and the  
10 dissolution profiles.

11 So, I'm trying to take a similar approach, even  
12 though there are drastic differences between the topicals  
13 and the dermatological drug products, that can we use the  
14 same approach, like have the bioequivalence studies for the  
15 highest strength and then approval of the lower strengths  
16 made from the composition similarity and in vitro drug  
17 release? That is the question that we have.

18 In order to do that, we have to make some  
19 assumptions and certain requirements, the assumptions being  
20 that the formulations, the two strengths, differ only in  
21 the concentration of the active ingredient and there is no  
22 difference in manufacturing process and type of equipment  
23 used between the two strengths. As you recall, for the  
24 topical drug products, the active ingredients, the amount

1 is somewhere between .05 percent or .001 percent, very,  
2 very low concentrations.

3 So, here what we are indicating is only  
4 differences in the small amount of the active ingredient  
5 and no other difference, and the requirements being that  
6 the reference listed drug, which is the innovator product,  
7 is marketed at both the strengths, the higher strength as  
8 well as the lower strength, and the generic product, the  
9 test product, is determined to be bioequivalent to the  
10 innovator product using the appropriate bioequivalency test  
11 criteria.

12 It can be any method, either the  
13 pharmacodynamic method, if the DPK method is acceptable, or  
14 the clinical method, but it is found to be equivalent and  
15 therefore the only difference would be like a small amount  
16 of the drug.

17 Now, in order to apply the in vitro release  
18 methodology, which is similar to the drug release  
19 methodology, all the release rates should be measured under  
20 the same test conditions, and the in vitro release rate  
21 should be compared between the reference product at the  
22 higher and the lower strengths and the test product at the  
23 higher and the lower strengths.

24 Then you need to calculate the ratio, the

1 release rate of the higher strength over the lower strength  
2 of the reference product, and the same thing for the lower  
3 strengths. Based on this comparison, if this ratio is  
4 similar to this ratio, then the proposal is, yes, they  
5 could be given the biowaiver.

6 To show you some examples, like in this  
7 particular case, it was concentrations of the two steroids,  
8 the release rate of the higher strength was 45 units and  
9 that of the lower strength in this particular manufacturer  
10 was 16 right here. Whereas, in the case of a second  
11 manufacturer, the two release rates were 21 and 7, but if  
12 you compared the release rate ratios of higher strength  
13 over the lower strength in both the cases, it turns out to  
14 be nearly the same.

15 And that's what we are suggesting, that if the  
16 release rates are nearly the same in both the cases, then  
17 maybe we can give the waiver of the lower strength of the  
18 test product, that is, this particular one.

19 To show you one more example, this is the  
20 example of the hydrocortisone. The higher strength and the  
21 lower strength here has the ratio of 1.63 from one  
22 manufacturer. The second manufacturer, where they used  
23 completely different formulations, which was manufactured  
24 at the University of Michigan by Professor Flynn and others

1 -- even there also for the same strengths, the ratios of  
2 the two strengths was about 1.63. So, what we are  
3 suggesting again is that if this ratio is nearly the same  
4 as this, if we consider this as a reference product, this  
5 being the test product, then we can give the waiver for  
6 this lower strength.

7 Now, some scientists say that, well, we cannot  
8 just go by only two different strength measurements and say  
9 that they're okay. We need to make sure that the release  
10 rate between the two strengths is linear.

11 Well, we had done that. At least for one  
12 particular drug, hydrocortisone, we manufactured several  
13 different strengths and we found that both the strengths in  
14 which we were interested, the one I showed you earlier,  
15 they are all linear when we make an appropriate plot. So,  
16 again, the suggestion is probably we can waive the lower  
17 strength.

18 So, I come back to the two initial discussions  
19 or the points that I would like to discuss now with the  
20 committee and have their opinions as to whether the DPK  
21 methodology can be used for the bioequivalency  
22 determinations of all these different types of topical drug  
23 products, and the second point being, can the in vitro  
24 release test be used to grant the biowaivers?

1 Thank you.

2 DR. ZIMMERMAN: Thank you, Dr. Shah, and thanks  
3 to all the presenters this morning.

4 We're actually running behind, but we need to  
5 have the committee have the opportunity to discuss the  
6 dermatological issues. So, we will shoot for a 17-minute  
7 discussion period and try to adjourn by 12:15.

8 So, with that, I'm going to open the floor to  
9 questions to our panel here. Dr. Brazeau?

10 DR. BRAZEAU: I guess I might need a little  
11 education. I guess I'm bothered to some extent by the skin  
12 stripping technique. When I think about assaying drugs,  
13 the key assumption is that the sampling technique isn't  
14 going to affect the values. In the material that you sent  
15 us to read, you propose to do a skin stripping over a 3-  
16 hour period, and I'm wondering about the impact of the  
17 inflammatory process on this as you might be stimulating  
18 cytokines over that period of time and is that going to  
19 impact upon those values. I don't understand that the  
20 sampling strategy is going to affect the values you get  
21 because it seems to me it will.

22 DR. SHAH: I guess since that's an important  
23 question, I'll give the opportunity for everybody to give a  
24 response.

1                   But let me just say initially I know it's scary  
2 when everyone hears the skin stripping, but the skin  
3 stripping is nothing but if you take scotch tape, you put  
4 it on your arm and remove it. That's the skin stripping.  
5 When you put it at the same spot and remove it about 10  
6 times, 15 times, each time you remove the scotch tape, you  
7 get a layer of the stratum corneum. Along with the stratum  
8 corneum, you also get the drug which is embedded inside  
9 that. So, all those samples are removed and then analyzed.  
10 So, that particular scenario is not traumatic that one gets  
11 worried when they actually see what's happening, but  
12 without knowing that, it is really scary.

13                   Hans?

14                   DR. SCHAEFER: The stripping itself takes no  
15 more than 10 to 15 minutes. It's after 3 hours or after 6  
16 hours or after 24 hours, most normally after 30 minutes  
17 that you strip the horny layer away. We take normally 10  
18 strippings in order to quantify. We don't need more  
19 stripping films in order to do a quantitative analysis. It  
20 takes at least 50 strips to provoke an inflammatory  
21 reaction. So, in this sense too, I would say it's a  
22 noninvasive method. There wouldn't be any immediate  
23 influence of an inflammatory process on the technique  
24 itself.

1 DR. ZIMMERMAN: I have a question about  
2 analytical methods. Presumably one is developing this  
3 technique so that we don't have to use radiolabeled  
4 compounds. But it seems to me that you're going to be  
5 dealing with very low levels and low amounts, and trying to  
6 quantitate these amounts in these skin strips might be  
7 difficult.

8 Secondly, you have to have an extraction  
9 procedure. I assume you dissolve the tape or whatever and  
10 you need an appropriate extraction procedure.

11 So, are the analytical issues sort of rate  
12 limiting?

13 DR. SHAH: To start with, yes. But right now  
14 it is very simple. We have done at least about 10 to 12  
15 different drugs, 6 different glucocorticoids, antivirals,  
16 antifungals, and retinoids. You take about 10 strips. You  
17 extract it in an organic solvent that extracts the drug and  
18 maybe some of the junk also along with the glue and all.  
19 But then you do the further extraction and you inject it  
20 straight into the HPLC.

21 Yes, I would agree with your comment earlier  
22 that, no, we don't want any radioactivity because what we  
23 are comparing is the two formulations, the test  
24 formulation, the reference formulation, and there is no

1       radioactivity or nothing. It's the direct comparison of  
2       the two marketed or to-be-marketed dosage forms.

3                 DR. ZIMMERMAN: Dr. Byrn?

4                 DR. BYRN: Two questions. They're really a  
5       little bit questions about your questions. Okay?

6                 Number 2, can in vitro drug release be used for  
7       granting a biowaiver for lower strength? What the issue  
8       there is -- well, maybe you could say, but my understanding  
9       of what the proposal is is that you would compare the rate  
10      of release of two drug products that were the same, if I  
11      could use one of Roger's words, except for concentration in  
12      some in vitro test, and then if they both passed and were  
13      correlated, then you would not need to do a BE study of the  
14      lower dose product. Is that the proposal?

15                DR. SHAH: Right, exactly, because again some  
16      of the requirements, as I identified, if there is  
17      absolutely no difference between the two strengths except  
18      the smaller amount, .1 percent or .05 percent of the active  
19      ingredient. Otherwise there is no difference.

20                DR. BYRN: Now, would the active be in solution  
21      in both of those or could it be partially in solution and  
22      partially in solid? Is that an area of variability? Do  
23      you see what I'm saying?

24                DR. SHAH: Yes, I do see that. It could be

1 either. It could be completely in solution or it could be  
2 the other way around because again here what we are doing  
3 is we are making a similar comparison between the reference  
4 product. The reference product also has a similar ratio.  
5 The R is the reference product. The T is the test product.  
6 So, whatever was happening with the reference product which  
7 went into the clinical studies and which is now approved,  
8 now we have the anchor between the two higher strengths,  
9 the reference higher strength and the test higher strength,  
10 and we think that we do not need to be more concerned about  
11 that.

12 DR. BYRN: Now, what I'm a little worried about  
13 is solubility, let's say, of a corticosteroid in the  
14 formulation. If you have a lower amount of corticosteroid  
15 in the same amount of formulation and the proportion in  
16 solution I think would be higher, right, in the low dose  
17 formulation? That might be more bioavailable in that --  
18 the amount in solution. So, there may be -- you see what  
19 I'm saying? There may have to be a calculation done. I'm  
20 not really that concerned with the idea, but you may have  
21 to do some correcting.

22 DR. SHAH: The chemical calculations from the  
23 equations and all have been done along with Professor  
24 Flynn.

1 DR. BYRN: Okay. So, that's all corrected for.

2 DR. SHAH: Right.

3 DR. BYRN: Okay.

4 The second question is about number 1, and I'm  
5 new to this so I'm very naive in this area. We know that  
6 if the infection is in the follicle, that it may not --  
7 let's say that if there is an infection in the follicle,  
8 that the way the drug gets to that infection would be  
9 different from the way it gets to an infection in other  
10 parts of the skin. Is that a factor related to question  
11 number 1? Do you see what I'm saying?

12 DR. SHAH: Yes, that's a factor and that's what  
13 I would really like to discuss. Maybe I can request  
14 Professor Schaefer to really give some more comments on  
15 that. Hans?

16 DR. SCHAEFER: When there is an infection,  
17 including an inflammation, then normally the follicle is  
18 closed. The drug has to bypass the normal horny layer  
19 sideways in order to enter into the infected area. The  
20 likelihood that a drug then enters directly into the  
21 follicle through the roof of a pimple is very low because  
22 you have to deal with a lot of material in the infected  
23 area, in the inflamed area relative to the non-inflamed  
24 area.

1           When we are dealing with another scenario, that  
2 is, I would say almost prevention of hyperkeratinization in  
3 acne in order to prevent over a long period the process,  
4 the pathological process, in acne, things are different.  
5 Then we would have to look into it, but as I said, we can  
6 look into this in specific cases.

7           However, up to now to my experience, the cases  
8 where you see accumulation in the follicles in the lower  
9 part are very rare. In fact, we have seen it once, and in  
10 the other case it was aimed to reach the hair follicles.  
11 So, it's not impossible. It's not excluded.

12           But still to my experience, the distribution  
13 process in the horny layer takes place anyway and in my  
14 book it's indicative for what happens in the follicle too  
15 because there you have a release process in situ of a given  
16 compound from the formulation to horny material anyway.  
17 So, to my mind there shouldn't be much difference. That's  
18 what can be said about this knowing that this has not been  
19 investigated in that.

20           DR. BYRN: Just one last question, Chairman,  
21 and I'll let other people.

22           One idea. First I thought maybe we should have  
23 some kind of decision tree like is the follicle open or  
24 closed -- you see what I'm saying -- and then make

1 decisions. But then I heard at the end I think you were  
2 saying most of the time this isn't an issue anyway. So, I  
3 don't know whether we need a decision tree.

4 But one approach to some of these questions  
5 might be to try to have some kind of decision tree to rule  
6 out certain cases and then apply it.

7 DR. SCHAEFER: May I add one aspect? If either  
8 the innovator or the generic claims targeting to the  
9 follicle and has shown it and specific activity that is a  
10 split between inflammatory action on the epidermis and  
11 activity in the follicle, which would be typical for  
12 retinoids, then yes, you better ask the question of whether  
13 this is suitable. But apart from that, for most  
14 dermatological indications, no, I would say it makes no  
15 difference.

16 DR. ZIMMERMAN: Dr. McGuire?

17 DR. MCGUIRE: I was thinking about some studies  
18 that were done a few years ago showing retention of benzoyl  
19 peroxide in the follicle and the benzoyl peroxide did not  
20 arrive in the follicle through the stratum corneum. It  
21 went directly in the follicle. What I'm saying is that we  
22 have a lot of targets in the epidermis and some of those  
23 targets are going to be reached through stratum corneum and  
24 some are probably going to be reached directly through the

1 pilosebaceous apparatus.

2 DR. SCHAEFER: That's the typical case, Joe.  
3 This is benzoyl peroxide in a non-dissolved form in a  
4 suspension and as a wash which is applied short-term to the  
5 skin, and then in fact you find, surprisingly enough,  
6 entrance of particles deep into the follicle and  
7 distribution from there. This is one of the exceptions,  
8 yes, clearly.

9 So, that's why I said at the end of my  
10 presentation whenever it comes up to solid material, half  
11 dissolved or dissolved to a certain extent, then we have to  
12 take care. There is no clear-cut proof that then this  
13 method can be applied.

14 DR. ZIMMERMAN: Dr. Branch?

15 DR. BRANCH: One of the statements you were  
16 making earlier on was the nature of the vehicle was not  
17 really important. It was just the amount of drug that you  
18 were comparing.

19 But the data you showed with the liposomal  
20 preparation I thought was fascinating in that it looked as  
21 though the kinetics, once you have got that initial  
22 absorption, was different in the deep part. It implies  
23 that the drug and the liposome actually travels right  
24 through the skin. So, it sort of questions your primary

1 assumption that your vehicle is not an important component  
2 in terms of looking at bioequivalence.

3 How confident are you that the vehicle and  
4 whatever you're trying to dissolve it in -- it's a point  
5 that was raised a little earlier -- the matrix that your  
6 drug is presented could be a key factor in addition to the  
7 concentration. That's one question.

8 The second --

9 DR. SCHAEFER: May I answer it immediately? I  
10 obviously made myself misunderstood. The vehicle is of  
11 utmost importance. There must have something gone wrong.  
12 I didn't want to say that the vehicle is of no importance.  
13 Quite the contrary. You have to stay in the same class and  
14 same properties of the vehicle in order to be able to  
15 compare bioequivalence.

16 Whenever you change the nature of the vehicle  
17 -- I'll give you an example. You add salicylic acid -- you  
18 increase the amount of propylene glycol by a factor of 2 or  
19 similar changes. Not comparable, clearly not. So, the  
20 vehicle is of utmost importance. You have to stay in the  
21 same class in order to compare.

22 If ever you have an influence on the properties  
23 of the horny layer itself, on its barrier and reservoir  
24 function, it doesn't hold anymore. Let's be absolutely

1 clear about that.

2 DR. LAMBORN: You're saying that this  
3 substitute assay would not pick up whether or not it's  
4 bioequivalent if in fact the vehicles were different?

5 DR. SCHAEFER: Yes. I would say you would find  
6 a difference anyway.

7 DR. LAMBORN: That's what I would think. What  
8 you're talking about you would, in fact, be able to see by  
9 that assay, but that would still make that assay valid  
10 then.

11 DR. SHAH: Yes. With the difference in the  
12 vehicles, you will find that there is a difference in the  
13 DPK measurements, and that would be reflected upon and it  
14 will make the product not bioequivalent.

15 DR. LAMBORN: Right. So, that's the whole  
16 point I thought, that if there is a difference, such as  
17 vehicle which impacts, then you would hope you would be  
18 able to see that.

19 DR. SHAH: I think maybe the point Dr. Schaefer  
20 was making at that time of the slide was the vehicle does  
21 play a role as to how the drug is released and it comes to  
22 the surface of the skin, but then the stratum corneum takes  
23 over and that's why you do not measure the vehicle into the  
24 stratum corneum but you measure actually only the drug,

1 otherwise there may be a thousand-fold difference in terms  
2 of the different vehicles. I think that was the point Dr.  
3 Schaefer was trying to get across.

4 DR. BRANCH: But the kinetics of the drug going  
5 through the skin in the liposomal preparation, once you got  
6 deeper to the horny layer, was very different. It was as  
7 though the changes are not confined just to the outside,  
8 but the changes are going right through.

9 DR. ZIMMERMAN: Dr. Mayersohn?

10 DR. MAYERSOHN: Vinod, how do you assess the  
11 reliability of the methods currently used to measure  
12 release rate from an ointment?

13 DR. SHAH: Right now only the clinical study  
14 was done for the products. There are not many generic  
15 products except for the glucocorticoids, and for  
16 glucocorticoids we have the pharmacodynamic measurements.

17 DR. MAYERSOHN: The question was in vitro  
18 release.

19 DR. SHAH: Oh.

20 DR. MAYERSOHN: You have an in vitro release  
21 procedure. How do you assess its reliability or  
22 predictability?

23 DR. SHAH: The in vitro procedure is not a  
24 standard requirement. It has become a tool to assert the

1 sameness of the product between the pre-change and the  
2 post-change product under the SUPAC-SS guidance. So, only  
3 when the SUPAC-SS guidance got finalized in last May we  
4 have now the in vitro release in place.

5 DR. MAYERSOHN: So, you wouldn't even look at a  
6 comparison between formulations.

7 DR. SHAH: No. But I have some data. If  
8 people have some time, either now or later, to show you how  
9 the formulation factors would be affecting the in vitro  
10 release rate.

11 DR. MAYERSOHN: So, you're not at a point where  
12 you would even propose an in vitro release rate procedure  
13 to help determine whether or not there was a potential  
14 difference in formulations.

15 DR. ZIMMERMAN: They're proposing it for number  
16 2, for lower strengths.

17 DR. SHAH: I'm proposing it only for comparison  
18 of the lower strength for approval of the lower strength.

19 DR. MAYERSOHN: Within products.

20 DR. SHAH: Within the product.

21 DR. MAYERSOHN: No. I'm asking can it be  
22 applied more globally. Can it reach the point where we're  
23 trying to use dissolution data for all the products?

24 DR. SHAH: Yes. The answer is yes.

1                   May I have permission to go on the floor, or  
2                   should I come back?

3                   DR. ZIMMERMAN: You may have 30 seconds. The  
4                   committee is hungry.

5                   DR. MAYERSOHN: Vinod, while you're searching,  
6                   I'll also make the same comment I made this morning about  
7                   animal models. This seems to be an ideal situation for  
8                   developing potentially useful animal models.

9                   DR. SHAH: This slide shows the in vitro  
10                  release of about nine different manufacturers. As you can  
11                  see it -- and this is the compositions of all the nine  
12                  different manufacturers, what all the different ingredients  
13                  are. It is all taken out from either the labels or the  
14                  PDR, so I'm not disclosing any trade secrets.

15                  But if we take a look at it, most of the  
16                  products fall into two categories, either this group or  
17                  this group, and that depends whether they have this  
18                  particular ingredient or these ingredients. You can see  
19                  that it can differentiate if there is a difference in the  
20                  formulation with the results in the release rate profiles.

21                  DR. MAYERSOHN: Do you have any idea if this  
22                  correlates with in vivo dynamics?

23                  DR. SHAH: We have some idea on at least two of  
24                  the drug products that we had studied. One was the

1 hydrocortisone, which Dr. Schaefer talked about it. He  
2 showed the pharmacokinetic profile and the pharmacodynamic  
3 profile. If we add the third leg of that, which is the in  
4 vitro release or the liberation, they all are parallel with  
5 one another. Faster release, higher concentration in the  
6 stratum corneum, higher pharmacodynamic response. There is  
7 a rank order relationship.

8 Similarly, we have done two other studies with  
9 Dr. Stoughton and at Duke University where we had products  
10 which differed significantly in their in vitro release  
11 profile and they were different in terms of the  
12 pharmacodynamic measurements of betamethasone valerate.

13 DR. MAYERSOHN: So, you're hopeful that you  
14 could develop a reasonably rigorous in vitro procedure that  
15 will correlate with in vivo data.

16 DR. SHAH: I would not go to that extent. It  
17 will be the same way as you can say for the in vitro  
18 dissolution aspects, and that's the reason I said that if  
19 the in vitro is significantly different, then it's going to  
20 give you a signal that there may be a difference in terms  
21 of the bioavailability or the bioequivalency product. But  
22 yes, given more time, more effort, we can develop the  
23 method that would be in vitro/in vivo correlation.

24 DR. MAYERSOHN: I encourage you to do that.

1 DR. SHAH: Yes. Thank you.

2 DR. ZIMMERMAN: Dr. Williams has, I'm sure, a  
3 short comment that he would like to make.

4 DR. WILLIAMS: Well, I'll be very brief. I  
5 think Dr. Mayersohn is getting to a very critical point for  
6 us, and it depends on how you look at the question. I  
7 would say our view now of in vitro release is it's a signal  
8 of inequivalence, but we feel uncomfortable using it as a  
9 test of equivalence. Now, I think with some further  
10 studies, some further research, we could move in the  
11 direction you're talking about. Again, I like to think of  
12 the test in vitro as sort of a canary in the mine so that  
13 if you don't see any problem, you can be assured of  
14 clinical comparability.

15 So again, I think, Mike, you're bringing to our  
16 attention a good area of future research that we can talk  
17 about.

18 DR. MAYERSOHN: Roger, I think with the  
19 enormous amounts of money you're going to be saving the  
20 United States citizenship with your procedures, some of  
21 that money through the benevolence of Congress will find  
22 its way back in your pockets to support some of this  
23 research.

24 DR. WILLIAMS: That was not a setup comment.

1 (Laughter.)

2 DR. MAYERSOHN: Absolutely not.

3 DR. ZIMMERMAN: On that very optimistic note, I  
4 think we will break.

5 In terms of consensus on this section, I think  
6 we've talked a bit about Dr. Shah's number 1 question,  
7 whether the DPK methods can be used for determination of  
8 bioequivalence for all types of products. I think that we  
9 agree that perhaps, if there's specific targeting to the  
10 lower follicle, perhaps DPK may not be appropriate and we  
11 may need to do more work in these areas.

12 I think there may be still a few questions  
13 about the in vitro release being used for granting  
14 biowaivers for lower strengths based on some of Dr. Byrn's  
15 comments in the sense of if the compound of interest, if  
16 the drug is not in solution in the higher doses, that in  
17 fact you may have greater free drug, if you will, as a  
18 percentage in the lower doses. That may be something that  
19 needs to be looked at.

20 Are there other consensus? Dr. Lamborn?

21 DR. LAMBORN: I just want to clarify. So, what  
22 you're saying is these are the things we have consensus on.  
23 It does not imply consensus in the other direction. I'm  
24 looking at number 1. Can we use these? And we're not

1 saying, yes, you can except for this.

2 DR. ZIMMERMAN: Right.

3 DR. LAMBORN: We're simply saying do not use  
4 it.

5 DR. ZIMMERMAN: We're saying that there may be  
6 a -- from what I'm hearing, there may be a question as to  
7 whether that is appropriate for that --

8 DR. LAMBORN: But isn't there still also a  
9 question with regard to the others? I didn't hear enough  
10 discussion that we had all said we agreed that in all other  
11 cases there was not a problem.

12 DR. ZIMMERMAN: That's what I'm asking. This  
13 is the only one I've heard that there may be a problem  
14 with.

15 DR. MAYERSOHN: Cheryl, what is handout from  
16 Metzler, Sources of Variation? Did we talk about that?

17 DR. ZIMMERMAN: No, we did not. Oh, apparently  
18 not yet. We may be talking about it later.

19 DR. MAYERSOHN: Okay.

20 DR. ZIMMERMAN: With that, we will stop for  
21 lunch, and we will reconvene at 1:15. Thank you.

22 (Whereupon, at 12:25 p.m., the committee was  
23 recessed, to reconvene at 1:15 p.m., this same day.)

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AFTERNOON SESSION

(1:31: p.m.)

DR. ZIMMERMAN: Ladies and gentlemen, I think we'll get started for the afternoon.

We will now begin an open hearing with speakers who have registered ahead of time. They will each be given 15 minutes to speak. Our first speaker is Dr. Carl Metzler with Nutwood Associates. Dr. Metzler?

DR. METZLER: As you try to help the agency answer the two questions that Dr. Shah addressed to you, sooner or later you're going to have to look at the variability in these metrics, and it may even be that by looking at variability in the metrics, it will help you to answer the questions.

1           I want to talk this afternoon about the sources  
2 of variation in the tape stripping assay only.

3           Now, it's my opinion -- and I recognize there  
4 are some differences out there -- in the last 20 years  
5 we've done very good, very well, done a good job, with oral  
6 bioequivalence testing. I would be hopeful that as we move  
7 into the bioequivalence of other dosage forms, such as  
8 topical and inhalation, some of what we have learned in the  
9 last 20 years can be carried forward to help us with that.  
10 Dr. Shah sort of alluded to this this morning when he  
11 talked about the lower strength problem.

12           The data I'm going to talk about was generated  
13 in the Dermatopharmacology Laboratory at Little Rock, and  
14 both they and I are paid by ALPHARMA. So, it lays out my  
15 biases that you can evaluate accordingly.

16           I went to my database and drew out not at  
17 random but haphazardly the data for two individuals, one of  
18 which was the classic oral dosing form and one of which was  
19 tape stripping. On this overhead, the blue is tape  
20 stripping and topical. The red is oral where you have  
21 samples of plasma. You have two scales of course because  
22 in the classical oral we looked at concentrations in those  
23 plasma samples, and in the tape stripping you look at the  
24 amount of drug recovered.

1           I fudged the time scale to make it come out the  
2 same. The tape stripping in this case was over 3 days, or  
3 72 hours, and the oral was over 12 hours.

4           But you see you sort of suggest there that  
5 those measures we looked at with the oral dosage forms,  
6 area under the curve and Cmax, can also be useful metrics  
7 with the tape stripping.

8           Now, this is one possible layout for a tape  
9 stripping study. An individual has two arms, right and  
10 left. On the arms you have the sides which I call the  
11 thumb side and the little digit, but the professionals call  
12 lateral and medial. Then on each side, you have assignment  
13 of sites for stripping from the elbow down to the wrist,  
14 and it's possible to get as many as 16 on one individual.  
15 If you can get that many on that, it seems possible you  
16 could divide it into two sets of 8 and put one formulation  
17 on 8, another formulation on the other 8.

18           If you can do this, then of course, unlike the  
19 oral dosing where the 1992 guidelines talk about using the  
20 same individual on separate occasions, we use the same  
21 individual on one occasion and therefore we avoid those  
22 difficult issues of sequence effect and period effect,  
23 those things that we don't quite know what to do with when  
24 we do see them.

1           To build a statistical model of this, divide  
2 the sources of variation into two classes, the fixed and  
3 the random. An arm is fixed because we only have two arms,  
4 right and left. We're not sampling from a big population  
5 of arms. Likewise, side and site are fixed effects. The  
6 random effects are subject and then certain interactions  
7 with the subject, arm of subject, side of subject, and site  
8 of subject.

9           Interpretation of this would be, subject arm,  
10 for example, that in different subjects the difference  
11 between arms will have some kind of random component in  
12 addition to the right versus left. So, this is one way to  
13 assign the sources of variability as fixed and random.

14           The two studies I'm going to talk about and  
15 show the data from had this kind of layout. Each of them  
16 had 6 subjects. We used both the right and left arms, of  
17 course, both the lateral and medial sides. Four sites were  
18 numbered from elbow to wrist. 22 tape strips were taken 4  
19 hours after applying the drug, and only strips 17 to 22  
20 were assayed. So, the first 16 were thrown away and 17 to  
21 22 assayed.

22           Now, as you probably gathered from the  
23 presentation this morning, there are a lot of issues in  
24 this question about using the tape stripping assay to

1 measure drug and its disappearance and bioavailability and  
2 bioequivalence. I'm not either qualified or have time to  
3 talk about them. So, we're going to assume this is a  
4 reasonable kind of experimental layout and look at the  
5 data.

6 Taking that data, you get these estimates of  
7 variance components from the two studies. Unfortunately  
8 the major source of variation here is an error term, which  
9 we cannot identify the sources of error. The next biggest  
10 is subject. Subject and arm is considerable, and then  
11 subject by site.

12 Now, rather than spending much time looking at  
13 those numbers, if you look at the next slide, I have  
14 graphed the sources of variability as a percent of the  
15 total variability. So, you see error is the largest.  
16 Between 40 and 50 percent of the variability in this tape  
17 stripping study was an error term we couldn't identify  
18 because of variability. More than 30 percent was due to  
19 subjects. Now as I implied, if we measure two formulations  
20 in the same subject, just as with the oral dosing  
21 bioequivalence studies, we can remove that source of  
22 variability so we get a more precise estimation.

23 The next largest is the subject by arm, and  
24 these other two are minor. Subject by side, that is the

1 difference between the lateral and medial, from subject to  
2 subject, is probably zero. There may be some site, but in  
3 one study it was zero; in the other, small.

4 So, just in these studies, this graph shows the  
5 relative size of the sources of variation.

6 Although the subject by site had a very small  
7 variability, there was some evidence in both studies that  
8 there was a trend. That is, if you look at the sites  
9 numbered from the elbow to the wrist, there was trend  
10 there.

11 This is the data from subject 1, and these  
12 straight lines are drawn by the trend option in Excel, so  
13 don't give them too much credibility. But what the  
14 statistics showed, when done with the very reliable  
15 statistical procedure, was there was a very small, perhaps  
16 non-significant upward trend as you go down from the elbow  
17 to the wrist.

18 So, what can we conclude just from these two  
19 little studies in this one particular setup? Well,  
20 subjects are a major source of variation and the design  
21 should permit removing subject effects. One way to do that  
22 would be to use them twice as we do in oral, but if you can  
23 actually do 16 sites in a subject, you can probably remove  
24 subject effect by studying both formulations in one

1 subject.

2           The subject by arm interaction is the second  
3 major effect, although the arms aren't random.

4           Subject by site is the third largest effect,  
5 but the sites may have a nonrandom effect.

6           So, what are the implications for this for  
7 designing tape stripping studies which test bioequivalence?  
8 Well, the first is the one I mentioned several times. You  
9 want to test both formulations simultaneously in each  
10 subject. Thus you remove that source of variation. You  
11 also have no period effect, no sequence effect.

12           You probably ought to randomize formulations to  
13 arms because that was a very large source.

14           And perhaps you should assign the sampling  
15 times to sites in a nonrandom manner.

16           Contrary to the impression you may get from  
17 many statisticians, randomization is not the Eleventh  
18 Commandment. Randomization is very useful for removing  
19 bias and other things, but there may be times when you  
20 don't want to randomize. What I'm suggesting is what you  
21 may lose by not randomizing down these sites you will gain  
22 in a much decreased logistical problem. You may understand  
23 that if you're going to apply drug to these 16 sites and  
24 then do the stripping that you probably don't want to go

1 jumping around from site to site over time. It's just  
2 asking for errors of mistesting.

3 That's all I had to say. Are there any  
4 questions from the committee? I know I should use animals,  
5 but what's your question, Michael?

6 (Laughter.)

7 DR. MAYERSOHN: Well, no. This gives a whole  
8 new meaning to the arm of a study I think, Carl.

9 (Laughter.)

10 DR. MAYERSOHN: Carl, it seemed to me you were  
11 nonrandomly assigning one formulation to one arm and then  
12 to the other arm. Is that correct? Or did you divide each  
13 arm in half?

14 DR. METZLER: You put one formulation only on  
15 an arm.

16 DR. MAYERSOHN: Why not divide that? You have  
17 two columns.

18 DR. METZLER: Well, you could. Just I think it  
19 gives you a chance for making errors. You could do that.

20 DR. MAYERSOHN: But doesn't that get rid of the  
21 arm effect, the arm form effect?

22 DR. METZLER: It could, right. I'd really  
23 defer to someone who does this as to how logistically  
24 difficult it is to do this and keep those sites absolutely

1 straight and separate and all that. But it's a  
2 possibility, right. That would be another way to do it.

3 DR. ZIMMERMAN: Other questions from the  
4 committee?

5 (No response.)

6 DR. ZIMMERMAN: Thank you.

7 DR. METZLER: Sure.

8 DR. ZIMMERMAN: Our next speaker will be  
9 Christopher Rhodes, speaking on behalf of Barr  
10 Laboratories, Incorporated.

11 DR. RHODES: Thank you very much, indeed. I  
12 greatly appreciate the privilege of being able to speak to  
13 you this afternoon. I am speaking to you on behalf of Barr  
14 Labs.

15 The general topic that I want to talk about is  
16 narrow therapeutic index drugs, and I am going to focus my  
17 remarks specifically onto warfarin sodium because this is a  
18 drug which has been the subject of much lively debate. A  
19 great deal of heat has been generated on it. I'm not sure  
20 if we've had much light.

21 But in your handout, I have given you the full  
22 text of a paper on bioequivalency that I published earlier  
23 this year. I hope it will be of some use, and I think that  
24 in particular the references at the end of the paper you

1 may find to be of some help.

2 Now, the topic I want to address specifically  
3 is, are the quality attributes of the generic product  
4 presently approved such that we can reasonably say that the  
5 FDA and the USP standards do give us a reliable assurance  
6 of safety and efficacy? I want to very strongly endorse  
7 the thesis that they are, indeed, quite satisfactory.

8 However, having said that, as you can see on my  
9 next slide, I do realize that indeed, although the present  
10 FDA standards have not only been remarkably successful in  
11 this country, but have also proved to be a very useful  
12 model in other jurisdictions, certainly we should not rule  
13 out the possibility of refining these standards. We know  
14 that the science is changing, and certainly we should be  
15 prepared to consider all sorts of possibilities to how we  
16 could refine these tests.

17 I'm going to suggest to you that any change in  
18 the bioequivalency standard should only be made when there  
19 is a proven scientific case for such a change. I think  
20 that it would be very imprudent of us to be swayed by mere  
21 fear tactics or unsubstantiated clinical anecdotes.  
22 Certainly unless there are well-substantiated major  
23 problems with generic products which are presently approved  
24 for marketing, there should be no retrospective or

1 retroactive changes.

2 I do believe it is highly important that any  
3 changes to bioequivalency standards should be made at the  
4 national level by FDA, when appropriate, working in concert  
5 with the United States Pharmacopeia on such matters of  
6 potency and content uniformity.

7 I speak as an EU registered pharmacist, and I  
8 find it very sad to see that while the EU is gradually  
9 centralizing its drug approval process quite properly in  
10 London --

11 (Laughter.)

12 DR. RHODES: -- while that is occurring, to see  
13 some what I would almost call as pharmaceutical Johnny Rebs  
14 trying to take the drug approval process away from the  
15 national level.

16 Any decision about the change in bioequivalency  
17 standards should be made on an individual drug basis. Each  
18 drug stands or falls on the basis of its own  
19 pharmacokinetic and pharmacodynamic properties. It is  
20 inappropriate to think about moving a whole group of drugs  
21 en masse into some new category.

22 Certainly if we are going to change  
23 bioequivalency standards for a particular drug, we must be  
24 assured that we have equal control over the innovator's

1 product as we do over the generic product. Therefore, such  
2 factors as batch-to-batch variability, potency, stability,  
3 and so on must be considered for both the generic and the  
4 innovator's product.

5 Finally, I think that the physicochemical  
6 classification system that we were talking about this  
7 morning provides an excellent starting point for any  
8 consideration as to what extent, if any, a bioequivalency  
9 standard for any given drug should be tightened or  
10 loosened.

11 Following from that, I would suggest to you  
12 that the golden rule for bioequivalency standard changes  
13 should be that if variation in the clinical response of  
14 patients to different versions of the same drug product is  
15 due to the inherent nature of the drug molecule per se,  
16 rather than the drug product quality -- in other words,  
17 rather than differences in formulation and processing  
18 factors -- then it is counterproductive to reduce or  
19 attempt to reduce intra or inter-subject variability by  
20 tightening bioequivalency standards.

21 Turning specifically to warfarin sodium,  
22 warfarin sodium has a high water solubility. It dissolves  
23 very rapidly, and therefore dissolution is not a problem.

24 It has good membrane flux. Therefore,

1 absorption is not a problem.

2 It is basically a very stable molecule.

3 Stability is not a problem.

4 The way the tablets are made is by dry mixing  
5 of ingredients, followed by simple, direct compression.

6 Ladies and gentlemen, this is a formulation exercise for  
7 PHC-101. It is very simple, very basic. The formulation  
8 and processing is robust and it yields products with  
9 excellent quality attributes.

10 What about the clinical response to this  
11 particular drug? Indeed, there is a lot of variability.

12 Now, I've chosen to take, as the standard  
13 reference I used here among the number I looked at, the USP  
14 DI, and the first thing we note is that the half-life of  
15 warfarin is about 2 days. This means that if a patient is  
16 receiving one dose a day and the dose is the same -- it's  
17 not always the same, by the way, but if it is, then on  
18 average, when a patient takes their daily dose in the  
19 morning, they already have in their bloodstream about two  
20 to two and a half doses.

21 Now, I want to tell you that when you look at  
22 the content uniformity data for the Barr product, it is  
23 excellent, but I also want to warn you that content  
24 uniformity is not especially critical for this drug because

1 the fact that each dose only contributes about a third of  
2 the total amount of drug in the body on any given day means  
3 that content uniformity is going to be less critical than  
4 for other drugs.

5 Now, warfarin, according to USP DI, quote, is  
6 an indirect acting coagulant that prevents the formation of  
7 active procoagulation factors. It's an indirect acting. I  
8 have underlined that. It is not underlined in USP DI. But  
9 there is a time lag, a significant time lag, from when we  
10 get the drug to when we see the effect.

11 What is unusual about this drug, as I'm sure  
12 most of you know, is that it is very, very susceptible --  
13 or the effect of this drug, I should say, is very  
14 susceptible to all sorts of changes. Changes in diet can  
15 push the prothrombin times up or down. Therefore, it is  
16 recommended that prothrombin times should be monitored on  
17 1- to 4-week intervals for the duration of treatment.

18 But most important, ladies and gentlemen, is  
19 this. When you look at data taken from anticoagulation  
20 clinics where they are only using the DuPont-Merck product,  
21 they find that many of the patients drift out of control.  
22 Now, I'm in no way suggesting that the DuPont-Merck product  
23 is not a good product. What I am saying is that it is an  
24 inherent property of this drug molecule, its complicated

1 mode of action, the fact that it is so very dependent upon  
2 diet and all sorts of other factors, that it is very  
3 difficult to keep your patients in control.

4           Now, I'm not going to bore you with going  
5 through lots and lots of graphs. I have in my time I think  
6 seen over 600 biostudies, and after a while they all merge  
7 into one gray mass. But when I looked at the Barr  
8 biostudy, I was particularly impressed to see how very good  
9 the comparison was between the test and the reference  
10 product. There are other graphs. They've got more than  
11 one strength. I just show this as an example to you.

12           In addition, I must tell you that recently I  
13 had the privilege of discussing with Dr. Joe Latelle who  
14 has recently completed a clinical study in which he  
15 compared the Barr product with the DuPont-Merck product.  
16 I've looked at the data. It is excellent. It's a very,  
17 very well-designed study with very clear conclusions, and  
18 indeed the Barr product is equally safe and effective. I  
19 understand that that clinical study will be published in a  
20 peer-reviewed journal early next year.

21           Thus, in conclusion, ladies and gentlemen, I  
22 think it is very clear that for this drug, warfarin sodium,  
23 the variation in clinical response is a function of the  
24 inherent nature of the drug molecule and does not reflect

1 upon the product quality. The product quality, as is  
2 determined by USP and FDA tests, shows that our present  
3 standards are perfectly satisfactory.

4 Thank you, ladies and gentlemen.

5 DR. ZIMMERMAN: Thank you.

6 Are there questions from the committee? Dr.  
7 Byrn?

8 DR. BYRN: I don't really have a question. I  
9 just want to make a comment that I think in narrow  
10 therapeutic index drugs we can do a lot of analytical  
11 studies to verify that there is a minimal batch-to-batch  
12 variability in these drugs with respect to all of the  
13 attributes such as dissolution, potency, stability, content  
14 uniformity, and so on. This might be a good place to start  
15 for investigating some of these questions about sameness  
16 because although I'm not an expert in bioequivalence, I'd  
17 hate to see product variations hidden under inter-patient  
18 variability in a bioequivalence study.

19 So, I think speaking as a person that's  
20 interested in pharmaceutical processing, this is a good  
21 area for us to work on to try to ensure excellent drug  
22 quality.

23 And that's really all I had to say.

24 DR. RHODES: I agree very strongly indeed that

1 when you have a drug of this type, it is very important  
2 that we do have extensive in vitro testing so, indeed, we  
3 can find what the cause of the variability is, yes.

4 DR. ZIMMERMAN: Dr. Branch.

5 DR. BRANCH: I think in terms of determining  
6 sameness of drugs, there's a fairly standard approach. The  
7 issue you're raising is that of biological variation. It  
8 would seem to me that if the major issue in hand is that  
9 variation, then an adaptation of the design of your study  
10 could show variance in the established product or variation  
11 in response to the established product and to the generic  
12 or the therapeutic alternative that's being introduced.

13 You didn't mention the design of the study of  
14 the Barr product, but it would seem to me that it's not  
15 beyond the realm of ingenuity to actually directly address  
16 your hypothesis, to demonstrate the extent of variation,  
17 maybe even the frequency of loss of control over time with  
18 alternative products, and provide a hard data set which an  
19 agency would be able to review on its own merits for that  
20 particular entity.

21 DR. RHODES: Yes. Let me respond to that.  
22 Firstly, the protocol used by Barr was that approved by FDA  
23 and FDA gave approval when they saw the results of that  
24 study.

1           One of the issues you raised is something that  
2 I have addressed in one of the papers that I reference in  
3 the handout, and that is this, that perhaps in the future  
4 when we're looking at possible changes to bioequivalency  
5 tests, we might want to consider including samples from two  
6 different batches of both the innovator and the test  
7 product. It's just another idea that we might want to  
8 think about.

9           DR. ZIMMERMAN: Other questions?

10           (No response.)

11           DR. ZIMMERMAN: Thank you.

12           DR. RHODES: Thank you.

13           DR. ZIMMERMAN: We next have two speakers  
14 speaking on behalf of the National Pharmaceutical Alliance,  
15 Marvin Meyer and Lane Brunner. Even though we have two  
16 speakers, they still only have 15 minutes.

17           DR. MEYER: Indeed, my sponsorship here is from  
18 the National Pharmaceutical Alliance. It's also of  
19 interest, however, and one of the reasons I'm interested in  
20 this topic is because, as some of you know, there has been  
21 a lot of initiatives at a variety of states. I come from a  
22 state that I'm told in January of this year there will be  
23 legislation introduced that is centered in part around the  
24 NTI list. So, if I could have the first transparency.

1           I think many of you know, but perhaps not all  
2 of you know, what the origin of this NTI list is. Back in  
3 the mid-1980's, there was a generic scandal, which I think  
4 most of you are aware of, and the FDA compiled a list of  
5 drugs and drug products that they wanted to be certain were  
6 examined in terms of their reliability from generic  
7 companies. So, I believe it was from the Commissioner's  
8 office there was this mandate to develop this list of,  
9 quote, important drugs that shouldn't be overlooked.

10           Subsequently in the SUPAC-IR Guidance, Appendix  
11 A, this list has been appended as drug products that should  
12 be looked at carefully before or even if bioequivalence  
13 studies should be waived in response to substantial changes  
14 in formulation.

15           The bottom line to that is this list was never  
16 intended as a negative formulary to be used by states to  
17 preclude generic substitution.

18           If you haven't seen the list -- in fact, it's  
19 in the handout that the committee has been provided with --  
20 there are 24 drugs on it. What I'd like to do is talk  
21 about six of those drugs that are on the narrow therapeutic  
22 list that we've actually been involved with testing and/or  
23 reviewing of data. I'll go alphabetically except I now  
24 shifted -- any slide will do. That's fine.

1 (Laughter.)

2 DR. MEYER: The first one I want to talk about  
3 is carbamazepine. That's one that's up there high.  
4 Everyone talks about it's a critical drug. With  
5 sponsorship by the Food and Drug Administration, we did a  
6 study on carbamazepine, 24 subjects, looked at the  
7 innovator product and importantly three generics that are  
8 available in the American marketplace.

9 You can see from the data that the Cmax values  
10 were very close. All the generics were virtually on top of  
11 each other, slightly higher than the innovator product.  
12 The Tmax's. The innovator was slower than the generics.  
13 They were all very close and somewhat more rapid. And in  
14 terms of AUC, all of the values were virtually on top of  
15 each other again.

16 Using the 90 percent confidence limits, they  
17 all ranged between 80 and 125 except for one Cmax  
18 comparison. That was 126. Indeed, that would have failed  
19 the upper limit of 125, but if you consider multiple dose  
20 use of this drug, a Cmax value that's a little bit high  
21 isn't going to have any effect on the therapy of this drug.

22 This is kind of an old drug but it is on the  
23 narrow therapeutic list. We did this study a number of  
24 years ago, looked at three products. These three had no

1     guaifenesin in them. We did three others. The even  
2     numbered products with guaifenesin. You can see the Cmax  
3     across the marketed products of this narrow therapeutic  
4     index drug, 5 percent difference; AUC, 2 percent  
5     difference. So, again, there didn't appear to be any real  
6     problem associated with these marketed products.

7                     This is not a generic versus brand comparison  
8     because there is no generic version of dilantin, but it's  
9     an interesting exercise to see just how variable phenytoin  
10    is in a panel of volunteers. The interesting part about  
11    this study is product 1 and 4 that are listed there are the  
12    same lot of dilantin, and 2 and 3 are also different lots.  
13    So, we have three lots with one replicate administration.

14                    It looks to us as though this drug product is  
15    pretty reproducible. Phenytoin itself apparently is pretty  
16    reproducible. All of the Cmax values range from 1.71 to  
17    1.79, AUC's from 53 to 54, very, very tight data. I would  
18    submit that if a firm comes up with a bioequivalent version  
19    of the innovator phenytoin, that it passes the FDA, there  
20    shouldn't be a problem with this narrow therapeutic index  
21    drug.

22                    Primidone is another narrow therapeutic index  
23    drug we looked at. We looked at three lots of the  
24    innovator, two old formulations, one new formulation, and a

1 generic version that's in the marketplace. All of the  
2 confidence limits for Cmax and AUC, making all comparisons,  
3 were within 80 to 125, and I think graphically you can see  
4 these products are all superimposable.

5           Theophylline, another product that was on the  
6 NTI list. We did this study a number of years ago of three  
7 marketed products, marketed dosage forms. A 4 percent  
8 difference in Cmax, a 4 percent difference in AUC, 0 to  
9 infinity. Again, I don't really see a reason for this  
10 product being on the NTI list, in terms of bioavailability  
11 anyway.

12           Then Dr. Rhodes showed you one slide. I have  
13 some supplementary data for the four strengths of the Barr  
14 warfarin product. I think Dr. Rhodes made a good point in  
15 terms of the physicochemical characteristics of warfarin.

16           Look at how tight the data actually are. What  
17 I've plotted here or given in the table, test over  
18 reference ratio as a percent, along with the confidence  
19 limits, Cmax for the 2 milligrams strength, 98 percent;  
20 2.5, 103 percent; 5 milligrams, 103; 10 milligrams, 102.  
21 The AUC's range from 98 to 102 for the Barr over the  
22 innovator firm. Confidence limits, worst case there was an  
23 89 and a 110. So, the limits are very tight. This is a  
24 very, very tightly controlled study, a well-designed study,

1 and clearly in my mind suggests that warfarin sodium  
2 tablets of this particular generic brand should be  
3 interchangeable with the innovator company.

4 Finally, some conclusions. I think that we  
5 need to communicate and it's unfortunate that people of  
6 Roger's status have to go around the country correcting  
7 state boards of pharmacy and state associations and  
8 legislative bodies, but unfortunately he has been forced to  
9 do that. People don't understand that when FDA published  
10 this NTI list, it was not a negative formulary. It was to  
11 trigger particular forms of information that would be  
12 required perhaps post-approval not preclude approving  
13 products at the state level once they've been approved by  
14 FDA.

15 There are numerous reasons to monitor patients  
16 and titrate the dosage regimen that might trigger an NTI  
17 classification. Included are changes in patient response,  
18 drug-drug interactions, changes in clearance, patient  
19 compliance, and bioinequivalent products. I think there  
20 are lots of examples in the literature of A through D. To  
21 my knowledge, there are no examples of E, bioinequivalent  
22 products that should be titrated because of  
23 bioinequivalence. In my judgment there are no well-  
24 documented examples of an inequivalent product that caused

1 the difficulty for an FDA rated AA or AB product that was  
2 manufactured in accordance with good manufacturing  
3 practices.

4 Finally, I believe that the available data does  
5 not support a need for FDA to modify the present standards  
6 for approval of drug products on the basis of  
7 bioequivalence studies whether or not they are NTI drugs.

8 Thank you.

9 DR. ZIMMERMAN: Are there questions for Dr.  
10 Meyer?

11 (No response.)

12 DR. ZIMMERMAN: I guess not.

13 DR. MEYER: I used an animal model.

14 (Laughter.)

15 DR. ZIMMERMAN: Thank you.

16 Dr. Brunner?

17 DR. BRUNNER: Dr. Zimmerman, members of the  
18 committee, thank you for the opportunity to come and speak  
19 before you.

20 My name is Lane Brunner. I'm an assistant  
21 professor of pharmaceuticals at the University of Texas at  
22 Austin. My responsibilities include teaching  
23 biopharmaceuticals and pharmacokinetics to graduate and  
24 undergraduate students, as well as being a clinical

1 pharmacology consultant to physicians and pharmacists.

2 I'm here on behalf of the National  
3 Pharmaceutical Alliance, and I've been asked to speak about  
4 my experiences on the national campaign against the  
5 substitution of generically equivalent NTI drugs. And I  
6 will be brief.

7 I became involved in the NTI issue last  
8 February when rulings were before the Texas Medical Board  
9 of Examiners to restrict the substitution of NTI drugs.  
10 That action was defeated, but that was only the beginning.

11 Since that initial involvement, I've traveled  
12 to various states to speak with state legislators and  
13 boards of pharmacy about issues of bioequivalence and  
14 substitutability of NTI drugs. So far I've been active in  
15 Texas, Colorado, California, Wisconsin, and North Carolina.  
16 Before you is an overhead of 22 of the states that have  
17 either pending legislation, pending talks, or legislation  
18 has been passed.

19 I've also been involved at three of the  
20 regional meetings of the American Association of Colleges  
21 of Pharmacy, as well as the National Association of Boards  
22 of Pharmacy.

23 At each hearing or meeting, the issue is the  
24 same: What is the science behind the substitutability of

1 NTI drugs?

2 To many of us the science is simple,  
3 straightforward, and nearly intuitive. However, this might  
4 not be the case to those who do not have a scientific  
5 background. Unfortunately, these are the individuals who  
6 are often responsible for creating our state laws.

7 Despite the apparent simplicity behind FDA's  
8 guidelines for bioequivalence studies, sometimes politics  
9 clouds the issue.

10 Not surprisingly, attempts to make the issue of  
11 NTI drug substitution controversial have been made by brand  
12 companies with a vested interest in preventing NTI drug  
13 substitution. Most notably, this has been perpetuated by  
14 DuPont-Merck, whether representing themselves or as their  
15 front organization, the Health Alliance for NTI Patient  
16 Safety.

17 DuPont-Merck originally began their attack on  
18 NTI drug substitution by petitioning the FDA to stop the  
19 approval of a generically equivalent product to their  
20 warfarin sodium product, Coumadin. The FDA reviewed the  
21 petition and flatly denied DuPont-Merck. The FDA's  
22 decision was based on the lack of scientific evidence of a  
23 potential national health risk.

24 After this denial, DuPont-Merck began a

1 nationwide state-by-state campaign to prevent NTI generic  
2 substitution. Since there was no clinical scientific basis  
3 for their claims, they decided to take the issue before a  
4 non-scientific organization or body, that is, the state  
5 legislators. This is where scare tactics and fear might  
6 gain support. Currently the issue has been brought before  
7 you to those 22 different states. This week alone the  
8 issue is being discussed in New Jersey, Washington, and  
9 Virginia.

10 I'm not sure if any of you have ever tried to  
11 explain pharmacokinetic principles or statistical methods  
12 to a senator, but at times it can be a bit of a challenge.  
13 So often, arguments turn political rather than remaining  
14 scientific.

15 DuPont-Merck has been lobbying the state  
16 legislators, physicians, pharmacists, and boards of  
17 pharmacy to severely limit or prevent the substitution of  
18 generically equivalent NTI drugs, specifically the warfarin  
19 sodium product. They continue to do this even though the  
20 FDA has approved an AB rated, therapeutically equivalent  
21 warfarin sodium product.

22 DuPont-Merck, in their lobbying effort, has  
23 mounted an advertising campaign which also calls into  
24 question the FDA's ability to approve generically

1 equivalent NTI drugs. When the issue of NTI drug  
2 substitution is brought before the state legislative  
3 bodies, the lawmakers are told by DuPont-Merck and the NTI  
4 Alliance that there is a national crisis in drug therapy.  
5 However, no scientific or clinical evidence is ever  
6 presented. What is presented are anecdotal stories.

7           Fortunately, DuPont-Merck has only had limited  
8 success and has been largely rejected based on their lack  
9 of scientific or clinical evidence of a problem, but they  
10 have been successful at eroding the public's confidence in  
11 the generic approval process by the FDA and have achieved  
12 special restrictions in certain states.

13           The opponents of NTI drug substitution appear  
14 to have a lack of understanding regarding the methods used  
15 by the FDA for approval of generic drugs. What is not  
16 understood is that the FDA guidelines evaluates the rate  
17 and extent of absorption. It is also not understood that  
18 the range of 80 to 125 percent represents the range for  
19 which the mean and the 90 percent confidence interval must  
20 fall. What is often quoted to lawmakers is that the two  
21 generic NTI drugs can vary in blood concentrations by up to  
22 45 percent, in addition that the amount of drug in a  
23 generic can range from between 80 to 125 percent that of  
24 the brand. Obviously, these are simply not true.

1                   Unfortunately, DuPont-Merck, the NTI Alliance,  
2                   and the respective experts continue to confuse and startle  
3                   state legislators. At present there is no scientific or  
4                   clinical evidence for changing the current FDA guidelines  
5                   for the approval of generic versions of NTI drugs. Instead  
6                   what would be prudent is to increase the education and  
7                   understanding of those clinicians, scientists, and even  
8                   lawmakers who may not be aware of the current FDA  
9                   guidelines.

10                   As a scientist and a pharmacist, I find the  
11                   tactics used by DuPont-Merck and the NTI Alliance  
12                   reprehensible. I strongly encourage the committee to  
13                   reaffirm the FDA's approval process and to condemn efforts  
14                   to oppose the substitutability of therapeutically  
15                   equivalent NTI generic products. We need to stop the  
16                   erosion of confidence in the FDA that is being perpetuated  
17                   now at the state level.

18                   Thank you for your time.

19                   DR. ZIMMERMAN: Thank you, Dr. Brunner.

20                   Are there questions, comments from the  
21                   committee? Dr. Branch?

22                   DR. BRANCH: Could you provide some sort of  
23                   sense or perspective of the power of the local state  
24                   legislature to actually be in competition with the FDA?

1 DR. BRUNNER: Well, to give you a little bit of  
2 background, what was initially brought about -- I'll use  
3 Texas as an example, since that's my home state -- is when  
4 the FDA rejected DuPont-Merck's petition and when DuPont-  
5 Merck started going state to state, they went to the State  
6 of Texas with the attempt to establish a mini-state FDA to  
7 oversee the bioequivalence or bioavailability of this small  
8 group of drugs. Of course, that was immediately rejected  
9 because Texas doesn't need any more legislation in that  
10 sense.

11 But what happened is they convinced one of the  
12 state legislators that in order to increase or be aware of  
13 patient safety, they needed to treat this group of NTI  
14 drugs very specially. So, what happened is, because of the  
15 lobbying effort, it got passed through one of the  
16 committees and was postponed but at the last minute was put  
17 onto a different bill and it was passed in Texas.

18 Now, what's currently happening is it is before  
19 the Board of Pharmacy, as well as the Texas Medical  
20 Examiners Board, to create a list that the law should  
21 pertain to. So, I believe in January they'll be meeting to  
22 determine which of the NTI drugs of those 24 will be part  
23 of the new laws that are restricting the substitution of  
24 their products.

1 DR. ZIMMERMAN: Other questions?

2 (No response.)

3 DR. ZIMMERMAN: If not, thank you.

4 DR. BRUNNER: Thank you.

5 DR. ZIMMERMAN: Now we have an opportunity to  
6 hear some comments from the general audience. DuPont-Merck  
7 would like to clarify its position on Coumadin and generic  
8 warfarin in response to statements that have been made just  
9 now. Dr. Richard Levy, the Vice President of Regulatory  
10 Affairs, has asked to speak, and we will give him two  
11 minutes to comment.

12 DR. LEVY: Yes, thank you very much.

13 Our position is not that generic products  
14 should not be approved. We asked and submitted a citizens  
15 petition prior to the approval of the Barr product that  
16 individual bioequivalence be used because we think it's a  
17 better approach. We've accepted the product has been  
18 approved and that other products may be approved based on  
19 average bioequivalence.

20 What we've done at the state level is to simply  
21 say that things are not quite certain on an individual  
22 patient basis, despite average bioequivalence or  
23 potentially even based on individual bioequivalence, and  
24 because there's a simple blood test that can be done, which

1 is a prothrombin time, to determine whether the patient's  
2 therapeutic response to a substituted formulation is the  
3 same as their response to the innovator formulation, that  
4 physician should be aware at the time of switch. We have  
5 not specifically ever asked that a product not be approved,  
6 only that physician notification should be required.

7 We have not been making much of anecdotal  
8 reports. We are collecting information. There are some  
9 patients in whom the only identifiable change has been a  
10 change in formulation. There is one patient who was on  
11 Coumadin, then to the Barr product and back to Coumadin,  
12 back to Barr, and back to Coumadin. Each time the Barr  
13 product was the one that was associated with a higher INR  
14 level which is the measure of the therapeutic effect of  
15 warfarin, and in each case on Coumadin it was lower. There  
16 are several other cases where patients were not tried twice  
17 on Barr but only once and we saw the same thing.

18 So, we're not saying that there is a known  
19 danger, that there is scientific evidence to prove that the  
20 products are not interchangeable. All we're saying is that  
21 given the limitations of our ability to predict on an  
22 individual patient basis and the simplicity of allowing  
23 physicians to know and check the prothrombin time, that  
24 physician should be made aware.

1 Thank you.

2 DR. ZIMMERMAN: Are there questions for Dr.  
3 Levy from the committee?

4 (No response.)

5 DR. ZIMMERMAN: Thank you.

6 Are there any other comments from the general  
7 audience that you'd like to make to the committee? If so,  
8 please come to the mike, identify yourself and your  
9 affiliation, and you'll have two minutes. Dr. Yacobi?

10 DR. YACOBI: I'm Avi Yacobi from Taro. I have  
11 two comments.

12 First of all, about warfarin, I believe I  
13 simply would like to reiterate what Dr. Meyer said and also  
14 what Dr. Chris Rhodes said about warfarin. I know this  
15 product very well, and I think the pharmacokinetic data is  
16 so robust that individual bioequivalence wouldn't make any  
17 difference in the final conclusion.

18 The other comment that I have is about  
19 dermatopharmacokinetics. I think I'm aware of this  
20 methodology. I'm familiar with it and I've seen a lot in  
21 the literature. The methodology is sensitive, is  
22 validatable, is specific, and I believe it's time to use it  
23 for bioequivalence evaluation.

24 Thank you.

1 DR. ZIMMERMAN: Any comments?

2 DR. MAYERSOHN: Avi, in your last comment, you  
3 were speaking specifically about the stripping method?

4 DR. YACOBI: Correct.

5 DR. ZIMMERMAN: Are there other comments that  
6 you would like to make to the committee? Anybody?

7 (No response.)

8 DR. ZIMMERMAN: Okay. If not, then we will be  
9 closing the open public hearing and moving on to our next  
10 topic.

11 For the remainder of the afternoon, we will be  
12 hearing about narrow therapeutic index drugs, and the  
13 moderator for this session will be Roger Williams and he  
14 will at first give us an overview of the issue. Dr.  
15 Williams.

16 DR. WILLIAMS: Well, thank you, Dr. Zimmerman.  
17 I would say we are moving on to another topic, but I would  
18 also say that the prior presentations in the open public  
19 hearing were directly related to what I'll be talking about  
20 and what we will be talking about before the committee in  
21 the next several hours. I hope the committee will indulge  
22 me because I'm going to be touching on a number of topics  
23 that perhaps at first might seem not entirely connected,  
24 but I do think there's a deep connection to them.

1           I might say to the committee that I think in  
2 some ways this committee is at a central focal point for  
3 some of the topics that I'll be touching on, and I think  
4 it's a very exciting set of topics.

5           I think if I started out by saying I were going  
6 to adjust the efficacy standard in the United States, that  
7 would cause a vigorous debate, and actually it has caused a  
8 vigorous debate if you look at congressional legislation  
9 over the last few months.

10           I think today we have talked about changing our  
11 equivalence standards, first this morning for drugs that  
12 are highly soluble/highly permeable. Now we're also  
13 talking about them in the context of population and  
14 individual bioequivalence.

15           I might also start out my remarks by pointing  
16 out to you that the draft guidance I think is in your  
17 information package. I might say to the audience it's also  
18 on the Internet now, so if you don't have a copy, please  
19 look on the CDER web page and you will see a draft,  
20 tentative, preliminary guidance that focuses on the topic  
21 that we have discussed before this committee on many  
22 occasions.

23           I emphasize that the document is draft, and the  
24 agency is encouraging explicitly firms that they not apply

1 the guidance now. It's explicitly stated in the preamble,  
2 and I'll try to explain why that's the case.

3 Nonetheless, I am delighted that the guidance  
4 is available and I think it reflects some very deep,  
5 powerful science thought about issues and bioavailability  
6 and bioequivalence. Of course, you know I would always  
7 congratulate the working group for their efforts in getting  
8 the guidance as far as it has.

9 Now, I will move through some of my overheads  
10 quickly, but I will use slides that I have shown the  
11 committee on several occasions perhaps.

12 I think the United States overall has a  
13 wonderful process for assuring product quality, and many  
14 things work to make that happen. Pioneer manufacturers,  
15 generic manufacturers, and the agency itself have worked  
16 together to create products in the marketplace that have I  
17 think an extraordinary high standard of quality.

18 It all begins in the IND phase for the pioneer  
19 product. There are changes post-approval for the pioneer  
20 after manufacture that we pay attention to. There's the  
21 period of multi-source manufacturers, and of course we pay  
22 close attention to that. And then for both pioneer and  
23 generic manufacturers, there is the post-approval change  
24 that we watch over very carefully collectively to make sure

1 that all these products still stay the same in some way  
2 relative to the clinical trial material on which safety and  
3 efficacy data were based. That brings the sameness issue  
4 that we talk about that the agency and the industry have  
5 sort of a communal commitment to assuring sameness barring  
6 intentional change.

7 I do say the time here is a long time, 75 or  
8 more years, and it also extends over the shelf-life of the  
9 product. And I always say it's a daunting science and  
10 technical challenge that I would say has been a principal  
11 topic for this committee on several occasions.

12 Now, I'm going to talk about the change  
13 concept, and I would hope that always the committee would  
14 understand me when I say that change affects both pioneers  
15 and generics. The whole concept behind SUPAC was to  
16 develop a consistent set of recommendations that would  
17 apply both to pioneers and generics.

18 It's certainly true that switching occurs here  
19 for the pioneer product even when multi-source products are  
20 not available. You will see in the SUPAC that at times  
21 SUPAC recommends a bioequivalence study in a post-approval  
22 change setting.

23 But I would like to focus some of my next few  
24 comments on the issue of generic substitution.

1           As you know, the agency has worked very hard  
2 with this committee and many other people to assure the  
3 quality of multi-source products, and on this particular  
4 overhead, you'll see what I would call the basic tenets,  
5 the conceptual principles, of Hatch-Waxman which is that a  
6 generic should generally follow the same quality controls  
7 as the pioneer product with the exception that  
8 bioequivalence studies, which we talk about frequently  
9 before this committee, are substituted for the very  
10 expensive preclinical and clinical safety and efficacy  
11 studies of the pioneer product.

12           Now, there have been at times over the last  
13 several years where I would say that the agency has had to  
14 confront the possibility of a two-tiered quality system for  
15 generics versus pioneer. I might say that I personally  
16 have always tried to resist that. I do not want to have a  
17 different set of quality approaches between pioneer and  
18 generic products.

19           I would also say that this committee at various  
20 times has struggled with the issue of both pharmaceutical  
21 and bioequivalence and we've talked about these on many  
22 occasions. These are the two hurdles that must be gotten  
23 over to achieve therapeutic equivalence.

24           I might argue that the science and technical

1 issues with regard to the documentation of pharmaceutical  
2 equivalence are exciting, are challenging, and I'm  
3 delighted to see that we have very sophisticated chemists  
4 on the committee who can help us with some of these  
5 deliberations in the coming months and years.

6 Of course, we also focus on bioequivalence, and  
7 you've heard in vitro studies, pharmacodynamic studies.  
8 Dermatopharmacokinetics now is a new approach which was  
9 discussed earlier today. And it's all very exciting. I  
10 might argue that the science of comparability is certainly  
11 not dull for those people who think it might be.

12 Now, as you also know, the United States has  
13 determined as a society that we will publish the approved  
14 products in the Orange Book. I think this is a very  
15 remarkable document. I keep encouraging people to read it,  
16 and they say, Roger, are you crazy? It's so boring. But  
17 actually to me it's exciting because it reflects a lot of  
18 science thought and certainly a lot of hard work on the  
19 part of both innovators and generics.

20 These are the criteria that you see expressed  
21 in the first four bullets in terms of pharmaceutical  
22 equivalence and bioequivalence, but we also must remember,  
23 as one of the earlier speakers emphasized, that we insist  
24 on manufacturing according to good manufacturing practices

1 and we insist on comparable labeling. If all those  
2 criteria are met, then an oral solid dosage form in the  
3 United States can be given an AB rating and substituted in  
4 all 50 states according to the agency for all aspects of  
5 safety and efficacy.

6 Now, with that little brief introduction, I  
7 would now like to turn a little bit to the issue of narrow  
8 therapeutic index drugs because in some ways life is  
9 getting complicated, and as many of my staff remind me, I'm  
10 the one who has been complicating it.

11 (Laughter.)

12 DR. WILLIAMS: First of all, I would like to  
13 say to the committee that -- and it gets back to something  
14 that I said this morning, that there are safety and  
15 efficacy considerations as well as product quality  
16 considerations.

17 For the most part, I would say this discussion  
18 focuses on product quality, and it is also certainly true  
19 that the agency speaks to the health care community and the  
20 patient in labeling to speak to drugs that are defined as  
21 narrow therapeutic index drugs.

22 Now, I support this. I think it's entirely  
23 appropriate. There are drugs for which the practitioner  
24 needs to take a special care in terms of dosing and

1 monitoring. I think we would all agree that warfarin is  
2 one of those drugs. Notice I said drugs now and not drug  
3 product. I think I'm talking about the active moiety that  
4 creates the clinical safety and efficacy.

5 We actually have a CFR definition of what a  
6 narrow therapeutic range or index drug is, and you will see  
7 occasionally in product labeling that a drug is defined as  
8 a narrow therapeutic index drug.

9 I might say that definition and the criteria  
10 for those definitions are not the business of OPS. You'll  
11 recall this morning that I said the new drug review process  
12 is conducted out of the Office of Review Management, and  
13 those judgments about the active moiety and its safety and  
14 efficacy, in terms of being narrow therapeutic index, would  
15 be the responsibility of the Office of Review Management  
16 under the direction of Dr. Lumpkin.

17 However, turning now to OPS and its  
18 responsibilities, OPS does and has concluded that under  
19 certain circumstances narrow therapeutic index drugs  
20 require increased product quality, recommendations, or  
21 requirements.

22 Now, I might argue that that's a good question  
23 for the committee. Is this appropriate? Do we want to  
24 single out a category of drugs for which we would like to

1 say additional product quality tests are required? I don't  
2 know if the committee wants to discuss it today, but I  
3 certainly think it's an excellent topic for the committee  
4 to discuss sometime and I would certainly facilitate that  
5 discussion in any way possible.

6 But for whatever reason, the agency has already  
7 taken that decision and you will hear discussion about that  
8 decision in the context of our SUPAC approach from Mr.  
9 Sporn, who's head of the Office of Generic Drugs. We did  
10 single out drugs to be defined as narrow therapeutic index  
11 drugs for which we wished additional quality controls.

12 There is also a compliance policy guide that  
13 you see on here with that strange set of numbers where that  
14 is also the case.

15 Now, I might also mention that in the  
16 individual bioequivalence document, you will see that it's  
17 an intent of the agency also to request that narrow  
18 therapeutic index drugs be singled out for an additional  
19 level of quality control that I will try to explain in just  
20 a few minutes in the context of individual bioequivalence.  
21 I would refer the committee to page 15 of the document  
22 where there's a very brief statement that we will always  
23 scale, if we adopt individual bioequivalence, for narrow  
24 therapeutic index drugs.

1           So, I hope it's very clear that in our product  
2     quality approaches we are not speaking to the health care  
3     community or to the patient. We are speaking to the  
4     pharmaceutical manufacturer and asking them under certain  
5     circumstances to exert additional tests to assure product  
6     quality for this category of drugs. I think that's a very  
7     important distinction, and if anything, I would say we are  
8     doing this so that we can assure the health care community  
9     and the patient that when substitution occurs, no  
10    additional precautions are necessary.

11           Now, I would emphasize that the agency does not  
12    agree with the statement of a prior speaker that you need  
13    to test the prothrombin time again when you switch from one  
14    formulation of warfarin to another. We would not recommend  
15    that either for the pioneer or the generic. So, if  
16    somebody is started on the generic product and switches to  
17    the pioneer, we do not recommend that they get an  
18    additional prothrombin test.

19           We feel, as some of the prior speakers said,  
20    that the natural variability in the way the patients take  
21    this drug, as well as its pharmacodynamics and the effect  
22    of diet and many other factors, far outweigh in terms of  
23    variability any of the variability you might see that  
24    arises from switching from one formulation to another.

1                   This is also a general position of the agency,  
2                   that we do not recommend additional tests when any generic  
3                   or any formulation is switched from one manufacturer to  
4                   another or during the period of exclusivity or patent  
5                   protection for a pioneer when switching occurs there. It's  
6                   a very broad principle that I think the agency stands  
7                   behind solidly and for good reason: based on our  
8                   experience and based on the level of testing that we  
9                   require.

10                   Now, I will point out that in the labeling of  
11                   warfarin -- and this is the labeling for the pioneer  
12                   product Coumadin -- it does refer to the fact that it is a  
13                   narrow therapeutic index drug. I'm delighted that the  
14                   labeling emphasizes that it's the drug that's narrow  
15                   therapeutic index and not the drug product.

16                   I will point out now -- and you'll hear more  
17                   about this from Mr. Sporn -- that we do have these PAC's  
18                   that are being developed, the post-approval change  
19                   documents. Those are defined to control the quality of  
20                   products in the marketplace in the presence of post-  
21                   approval change. Switching occurs there for all products,  
22                   both pioneer and generic.

23                   Now, I'd like to turn now to the fact that we  
24                   are in the process of discussing a possible change in the

1 way we look at bioequivalence both from a metric and  
2 statistical standpoint. I won't belabor this because I'm  
3 sure the committee understands this quite well. This is  
4 our current approach where we have the goal posts of .8 to  
5 1.25. We log-transform the data, and I might remind this  
6 committee that they made that recommendation to us, that  
7 log transformation occur. That decision was based on the  
8 fact that we were primarily interested in the ratio of the  
9 comparison as opposed to the difference.

10           There's a slight levity here. You remember I  
11 said barring intentional change. Well, intentional change  
12 in my mind is the world of new drugs, the 505(b) world. We  
13 live sometimes in the world of 505(j) when we talk about  
14 sameness. I always encourage people who say that they've  
15 got a better generic product to not talk to me, to take  
16 their product to the world of the 505(b) and have it  
17 approved as a pioneer new drug.

18           Now, as the committee well knows, we are  
19 engaged in a discussion about moving to a different  
20 approach, and the different approach is exemplified in this  
21 side of the equation which is a new criterion that is based  
22 on a series of articles and conceptual understandings that  
23 appeared over the last several years and that have been  
24 quite exciting to us inside the agency, and I think also

1 quite exciting outside the agency, in terms of possibly  
2 changing the way we do business.

3           The entire approach is based on the concept of  
4 prescribability and switchability, and I use this  
5 particular overhead to exemplify that. When a patient  
6 first visits the doctor, there may be a period of  
7 prescribability where the dose is adjusted and titrated to  
8 an optimal dose, and then at steady state, there is a  
9 persistent fluctuation which should be maintained in the  
10 presence of change relative to different drug products.

11           I think you can see down here there is the  
12 concept now in the current U.S. marketplace of perhaps  
13 starting on the pioneer product, moving to one generic,  
14 moving to another generic, and even moving back to the  
15 pioneer product.

16           There is also the concept of change in the  
17 presence of post-approval change for both the pioneer  
18 product and either of the generics.

19           So, you can see that I think as a society and  
20 in terms of the science and technical challenges, we have a  
21 lot of work to do to assure the patient and the health care  
22 community that all of these formulations can provide the  
23 same therapeutic benefit one to another compared.

24           And you'll see that I do not single this out

1 particularly as a generic problem but also a problem both  
2 for the pioneer product and the generic product.

3 Now, you will see -- and I will not belabor  
4 this in terms of my presentation now -- that we have  
5 concepts of individual and population bioequivalence. I  
6 certainly know that the committee will read this guidance  
7 very carefully. I hope they will resonate to many elements  
8 of it because those elements have been discussed before the  
9 committee on several occasions.

10 What we are talking about in considering going  
11 to this new criterion is the concept of perhaps looking  
12 more closely at variance than we have in the past. You'll  
13 see over there on the right that if I just look at this  
14 part of the equation, it looks very similar to what we do  
15 now.

16 But individual bioequivalence also includes a  
17 subject-by-formulation interaction variance term, which is  
18  $\sigma_{D}$ , and also a comparison of the within-individual  
19 variances of the test and reference product. On top of it  
20 all, it relates those variances and mean difference to the  
21 within-subject variance of the pioneer product.

22 Now, again, I won't go into all of this, but I  
23 think the science of this approach is quite compelling.  
24 What I think needs to bear further discussion is the public

1 health justification for the need for this equation. I  
2 don't need to perhaps remind the committee, but that was  
3 one of their main discussion points when it came up before.  
4 What is our justification for moving to this new approach  
5 which is more burdensome from the standpoint of requiring  
6 replicate study designs? You cannot get this equational  
7 information without doing replicate study designs for the  
8 test and reference product.

9 I think the burden of the justification does  
10 fall on the agency, and we certainly willingly take up that  
11 burden and hope to continue to make the argument and the  
12 justification publicly, as well as before this committee,  
13 at the appropriate times.

14 Now, I will say -- and perhaps I'm speaking now  
15 more to the audience -- that there was a meeting in Boston  
16 in November. All I can say is I must have developed a very  
17 thick skin after being in Washington over seven years  
18 because it was a vigorous debate, and I wouldn't say that I  
19 came out of it in a strong position. Some people have  
20 described the meeting as a train wreck, and I suppose  
21 that's a pretty accurate description.

22 But I will say this. I think it was a good  
23 meeting and I think it clarified for me something that was  
24 quite important which is you can have a very abstract

1 scientific discussion, but it's also an important part of  
2 the public process in the United States to gain the  
3 understanding and concurrence of all the stakeholders. I  
4 came away from that meeting feeling that many of the  
5 comments directed at me and at the agency were right on and  
6 that we did need to build a better public process for the  
7 debate about moving to this new approach.

8           Towards that end, I think the agency has agreed  
9 to do several things.

10           First of all, as we usually do, we would like  
11 to form an expert committee. The formation of that  
12 committee is occurring right now to help us with some of  
13 the deliberations.

14           We are going to have a public workshop in March  
15 of 1998 where we discuss it publicly, and there will be a  
16 consensus report out of that workshop.

17           We would like to share as much of our data as  
18 possible that forms the basis for the justification for  
19 this new approach. I would argue that we would like to  
20 have a very good, high quality public discussion now about  
21 the science and justification for moving towards individual  
22 bioequivalence, working with all constituencies as best we  
23 can.

24           Then at the end of that process, I would like

1 to repropose the guidance as a level 1 guidance again for  
2 public comment.

3           So, I think you can see that the agency wants  
4 to take a very deliberative approach to this. We recognize  
5 the challenge of it. At the same time I think we're very  
6 convinced that it has a compelling scientific  
7 justification. We want to do the right thing and move  
8 forward in a good way. I might argue to the committee that  
9 at the appropriate time I will certainly bring it back  
10 before the committee for their consideration and discussion  
11 as they wish.

12           Now, I might also say, before I turn to the  
13 issue of narrow therapeutic index drugs, that coupled with  
14 the guidance you'll see also population equivalence  
15 approaches. Those particular approaches are directed  
16 specifically to the pioneer manufacturer during the IND  
17 phase of drug development. Population equivalence  
18 approaches do not require replicate study designs, and in  
19 that sense we do not feel that the population approach  
20 advocated in the guidance adds in any way particularly to  
21 the burden of pioneer manufacturers as they develop new  
22 drugs.

23           The primary reason for recommending population  
24 approaches during the pre-approval period for an NDA is

1 because it doesn't involve switching, and if there's no  
2 switching involved, there's no particular need for  
3 individual bioequivalence. I want to emphasize that, and I  
4 don't see that position changing on the part of the agency.  
5 It's not subject to a scientific debate. It's more a  
6 conceptual understanding that I think we agree on now, and  
7 I can't imagine further discussing changing agreement,  
8 although I would welcome that discussion if it's  
9 appropriate.

10 But individual bioequivalence does apply to  
11 both the generic and pioneer product in the presence of  
12 post-approval change requiring an in vivo study. That's  
13 also very clearly delineated in the guidance document and  
14 it certainly applies to the generic manufacturer at the  
15 time of approval to gain market access.

16 Now, I'd like to turn a little bit and perhaps  
17 close with the issue of goal posts bioequivalence current  
18 approaches and what it all means for narrow therapeutic  
19 index drugs. For those on the committee who've looked on  
20 page 15, you will note that it says we do not have criteria  
21 now for narrow therapeutic index drugs, and that's  
22 absolutely true. For that reason, the agency doesn't feel  
23 that it can comment on which drugs to apply constant  
24 scaling to or not. You'll hear more about our attempts to

1 develop criteria from Dr. Balian when he speaks later on in  
2 the course of this particular part of the session.

3 I want to say a little bit about our goal posts  
4 and perhaps why we are considering scaling for certain  
5 narrow therapeutic index drugs. I apologize to the  
6 committee for going over this and I always wonder, when I  
7 say this, if I'm going to say the right words, not being a  
8 statistician.

9 But essentially what we do now in terms of  
10 declaring bioequivalence is to ask that the ratio of the  
11 means for our bioequivalence metrics, Cmax and AUC, be  
12 within a confidence interval where the goal posts are minus  
13 20 percent of the reference listed drug metric or plus 25  
14 percent of the reference listed drug metric. That's a  
15 symmetrical confidence interval on the log scale, of  
16 course, as the committee knows. We ask that the confidence  
17 interval of the observed ratio of the means be within those  
18 boundary points.

19 Now, let me just run the committee through  
20 something that I'm sure they know quite well. This is an  
21 example of a product that meets the point estimate but  
22 fails the confidence interval, and you can see it does so  
23 because the mean is getting close to .8. And the  
24 confidence interval of the observation falls outside the

1 lower goal post.

2 This is the converse example where it fails on  
3 the upper side.

4 Here's an example of two generic products.

5 This particular representation alludes to the commonplace  
6 statement in the marketplace that two generics can differ  
7 by 40 percent. If one is 20 percent below and one is 20  
8 percent high on the log scale, you can imagine two generics  
9 could be in the marketplace differing by as much as 40  
10 percent in either AUC or Cmax.

11 The agency would not agree that that's a  
12 reasonable possibility because the reality is as you start  
13 to move closer in your point estimate to either boundaries,  
14 the number of subjects required in a study to show  
15 bioequivalence increases. So, you could imagine that a  
16 product could be 19 percent lower but to show equivalence,  
17 if that were truly the situation, it would probably take  
18 hundreds of subjects in that bioequivalence study.

19 Because most bioequivalence studies have, say,  
20 30 to 40 people in them, we actually start to see people  
21 fail the confidence intervals when they differ about 5  
22 percent or 10 percent. Historically the agency, when it  
23 looks at means, usually sees differences of less than 5  
24 percent. So, the agency would not agree that it's possible

1 to see generics in the marketplace differing by as much as  
2 40 percent in their performance metrics, and in fact we  
3 have no instances of that being the case.

4 This, to conclude this part of the  
5 presentation, is an example of a study which in fact shows  
6 bioinequivalence. A lot of times we deal with situations  
7 where the point estimate may be very close to 1, but just  
8 because of variability and numbers of subjects in the  
9 study, they haven't been able to show bioequivalence  
10 according to the goal posts and the confidence interval.

11 Now, that leads me to the issue of narrow  
12 therapeutic index drugs and why the agency would be  
13 interested in narrowing the goal posts for narrow  
14 therapeutic index drugs. Let me see if I can speak to that  
15 very briefly.

16 Right now -- and I might use warfarin or  
17 phenytoin as an example -- for the products we let into the  
18 marketplace, as you heard from an earlier speaker, the  
19 point estimate is very close to 1 for the generic relative  
20 to the pioneer product. Of course, we're delighted with  
21 that. It means that the generic is a fine formulation and  
22 it's mimicking the performance of the pioneer in a good  
23 way.

24 However, our current goal posts would allow a

1 product in the marketplace to differ by, say, 10 percent or  
2 more, and for that reason the question arises for these  
3 narrow therapeutic index drugs, should we change our goal  
4 post approach such that that would not occur?

5 Now, the way we would do this, according to the  
6 principles of individual bioequivalence is to let the  
7 variability of the reference product control the goal  
8 posts. You heard an allusion to that somewhat indirectly  
9 earlier today when somebody alluded to phenytoin.

10 Now, let me say, for example, that I think the  
11 pioneer product of phenytoin is a well-manufactured  
12 product. It does show low intra-subject variability for  
13 both the drug substance and the drug product, and our  
14 expectation is that that low variability, if individual  
15 bioequivalence were applied, would drive the goal posts  
16 down to, say, 90 to 111 as opposed to 80 to 125. You can  
17 see I'm using the symmetric approach on the log scale.

18 Now, why would that be a public health  
19 advantage? I think it would be a public health advantage  
20 from the standpoint that we would not allow products in the  
21 marketplace, say, for warfarin to differ in their means by  
22 12 percent. I think if you know the nonlinear kinetics of  
23 warfarin, you can see there's a justification for that. I  
24 don't think we would want a warfarin product where the mean

1 difference truly was 12 percent difference. Because of the  
2 nonlinear kinetics, we could imagine that if it were 12  
3 percent higher, some patients would get in trouble.

4 So, the motivating concept behind always  
5 scaling for a narrow therapeutic index drug, according to  
6 the principles of individual bioequivalence, is to assure  
7 that such products don't get into the marketplace.

8 Now, of course, there is a burden associated  
9 with this because if the true mean difference is within,  
10 say, 90 to 111, more subjects would be needed to pass the  
11 confidence interval boundaries.

12 I look forward to this discussion before the  
13 committee at the appropriate time. If it occurs today,  
14 that's fine, but that's the motivating factor or approach  
15 or concept by saying always scale for a narrow therapeutic  
16 index drug.

17 Now, I might remind the committee that always  
18 scale for narrow therapeutic index drugs means that if you  
19 had a highly variable narrow therapeutic index drug, you  
20 may actually widen the confidence intervals. Again, I  
21 think there's a public health argument for it and a  
22 fairness argument that if the innovator, the pioneer  
23 product, even if it's a narrow therapeutic index drug,  
24 shows a high degree of variability, that the generics

1 shouldn't themselves have to pass a narrower boundary than  
2 the innovator itself would have to pass.

3           Fortunately, we think there are very few  
4 instances of a highly variable narrow therapeutic index  
5 drug because I think you can imagine the therapeutic  
6 challenge of dosing such a drug would be considerable.

7           Now, I want to close, and I apologize to the  
8 Chair for going on perhaps longer than I should have, but I  
9 do think some of these points are so important.

10           There's one last thing I would like to say and  
11 that's this. It's critical for the agency, working with  
12 this committee or other stakeholders as appropriate, to be  
13 able to move to better science. I would be very disturbed  
14 if our discussions, as we move to better science, as we  
15 consider moving to better science, would somehow be used to  
16 attack products that are currently in the marketplace. I  
17 would not want individual bioequivalence concepts that we  
18 are talking about now in a very preliminary way to be used  
19 to suggest that any product in the marketplace, either  
20 pioneer or generic, is somehow not a good product. This is  
21 a very important point for the agency, and as a matter of  
22 fact, it has been discussed in the courts and the courts  
23 certainly endorse that.

24           I might also argue that all products -- you

1 know, it's true of an agency and an industry that over time  
2 products become outdated in the way they're manufactured,  
3 and the products that were approved 25 or 50 years ago in  
4 this country would not perhaps be manufactured and  
5 controlled in the same way as they would be if they were  
6 approved today.

7 I might draw the committee's attention to the  
8 fact that for both the ICH stability document and the ICH  
9 impurity document, Q1A and Q3A, it has been a particular  
10 challenge for the agency, working with industry, to not  
11 make those guidances apply retroactively. It's very  
12 burdensome and the justification for it is difficult.

13 So, as I say, we always want to do better, but  
14 it does not imply that currently available products in any  
15 way have problems associated with them. I think it's  
16 important for the agency to endorse this not only for  
17 generics but also for pioneer manufacturers.

18 Now, having said all that, I will turn it back  
19 to the committee. I guess, Dr. Zimmerman, thank you very  
20 much. I do apologize for going over, but I think you can  
21 see there were some very important things I had to get on  
22 the table.

23 DR. MAYERSOHN: Cheryl?

24 DR. ZIMMERMAN: Dr. Mayersohn has a question

1 for you, Dr. Williams.

2 DR. MAYERSOHN: Roger, this isn't so much a  
3 question as a comment. I think you know early on I was  
4 fairly skeptical about the concerns leading to the issue of  
5 individual bioequivalence, and I look forward to seeing the  
6 documentation of the problem. However, I must say that  
7 from my understanding of what you just said, you are taking  
8 a very healthy view of the problem and the approach to its  
9 solution. So, maybe being beaten up once in a while isn't  
10 so bad.

11 (Laughter.)

12 DR. WILLIAMS: Thank you.

13 DR. ZIMMERMAN: Yes, Dr. Goldberg.

14 DR. GOLDBERG: Roger, after the discussion we  
15 had this morning on the BCS, I was wondering whether that  
16 could be tied in with this rather than therapeutic range.  
17 I think that if a drug is problematical in absorption, then  
18 I think the need for something like individual  
19 bioequivalence is much greater than if there's no question  
20 or problem with absorption of the drug. So, I think a tie-  
21 in between the BCS and this would be a good approach rather  
22 than narrow therapeutic window. For example, warfarin  
23 doesn't seem to have any problem with absorption, but I'm  
24 sure some of the drugs on the NTI, as well as other drugs,

1       may have.

2                   DR. WILLIAMS: I think it's an excellent point,  
3       Dr. Goldberg. I might say that I think the committee  
4       probably has noticed that as we work to kind of move away  
5       from what I call the one-size-fits-all -- you know, life is  
6       easier when everything is the same, and we're going to get  
7       caught up in challenges that we need to work together on  
8       hopefully in a productive and positive way. I would say a  
9       specific challenge is what you alluded to.

10                   Now, you saw from Dr. Hussain's presentation  
11       this morning that we are going to say that the  
12       biopharmaceutic classification would not apply to a narrow  
13       therapeutic index drug. Yet, at the same time you heard  
14       Dr. Rhodes point out that warfarin is a highly soluble,  
15       highly permeable drug and perhaps could be approved on the  
16       basis of dissolution only. Now, this is what makes life  
17       interesting in Washington, and it's why I get a high  
18       salary.

19                   (Laughter.)

20                   DR. WILLIAMS: So, it's a hard challenge and we  
21       have to work together on it. I don't have an answer to it  
22       right now, but I thank you for pointing it out.

23                   DR. ZIMMERMAN: Well, I think we'll move on to  
24       our next speaker who is Douglas Sporn who is going to talk

1 to us about the SUPAC approach and issues involved there.

2 MR. SPORN: Fortunately, because of what the  
3 previous speakers have covered, my job is going to be  
4 relatively easy. I'm mostly going to fill in a few blank  
5 spots and underline some of the things that were said  
6 earlier. I want to talk about what is the list, just to  
7 make sure everybody has seen it and knows what we're  
8 talking about. Marv Meyer already talked about the generic  
9 drug scandal. I want to discuss that a little more. I'll  
10 show you the regulatory definition and actually talk about  
11 how --

12 DR. ZIMMERMAN: Mr. Sporn, would you move your  
13 slide up?

14 MR. SPORN: Then actually talk about the  
15 application in the SUPAC.

16 I haven't been here for the entire meeting  
17 today, but I've heard a number of people mention SUPAC and  
18 I'm not sure everyone knows what that stands for: scale-up  
19 and post-approval changes. It's a concept that Roger  
20 coined and it basically is a series of guidances the Center  
21 is putting out for the pharmaceutical industry and for our  
22 reviewers that gives our best opinion of what tests and  
23 filing requirements would be for various changes depending  
24 on the dosage form. As Roger mentioned, we have three that

1 are out now: one for immediate release, one for semi-  
2 solids, and one for modified release. And we have two or  
3 three more that are in the wings being developed.

4 Just real quickly, this is the list. You may  
5 not be able to read it in back. I think it is in your  
6 handouts. This is probably the list that Marv was looking  
7 for. I stole it at lunch.

8 (Laughter.)

9 MR. SPORN: Let me give you a little more  
10 background about how this came about during the scandal  
11 because everything Marv said is correct. You have to kind  
12 of put yourself back at the time of the scandal when there  
13 was really a national scare about what was going on because  
14 the investigations were just getting started and people  
15 really didn't know the extent of the problem in the generic  
16 industry.

17 Partly to get a quick snapshot of what was  
18 going on, it was decided that FDA headquarters and the  
19 field would do a survey of products and test them against  
20 USP and other standards, compendial and application  
21 standards, to see if they were in compliance or not. It  
22 was decided this had to be done very, very fast.

23 There is a regulatory definition of narrow  
24 therapeutic index drugs. I'll show it to you in a minute.

1 I can tell you it is not the definition that was applied.  
2 There wasn't time to be that thoughtful.

3 What happened, Dr. Bruce Burlington, who was  
4 head of the Office of Generic Drugs at that time, basically  
5 went to all the new drug clinical division directors and  
6 said, give me a list of drugs that you'd be concerned about  
7 if there was a problem somewhere out there. This was done  
8 like on the back of an envelope overnight. That's the  
9 list. That is how it was put together.

10 It's just unfortunate that it has sort of taken  
11 a life of its own on now, and we have people coming into my  
12 office volunteering to be declared narrow therapeutic  
13 because they think it will in some ways help in the world  
14 of competition.

15 This is the regulatory definition. It somehow  
16 got in the CFR. You're going to hear more about what is  
17 going on to really define what the criteria should be. I  
18 will say this definition and the issues associated with the  
19 terminology, and what it implies has been discussed with  
20 the Medical Policy Coordinating Committee which Roger and  
21 Bob Temple head, and you'll be hearing more about that.

22 Now, I just wanted to wrap up by giving you a  
23 couple of examples. You've heard what Roger said about  
24 there are places in the SUPAC where we have said, okay, if

1 you have a narrow therapeutic index drug, you do something  
2 different. In both IR and MR, that mostly takes into  
3 account a change in components or composition, things that  
4 you would allow to be changed and then testing using  
5 dissolution wouldn't be allowed if it was a narrow  
6 therapeutic index drug, whatever that means.

7 For example, here we have under level 2 and  
8 level 3, which is a certain amount of change in the  
9 excipients of an immediate release product. For an IR  
10 product, we're saying if there's a change in grade or if  
11 there's any qualitative or quantitative change in the  
12 excipients, we're recommending that an in vivo  
13 bioequivalence study be done. That's the type of  
14 additional safeguards we're putting in on these SUPAC  
15 documents.

16 Probably we would continue to apply this once  
17 we identify what is a true narrow therapeutic index drug,  
18 but all that is open to reconsideration as well. I think  
19 this is going to be a long, interesting process to really  
20 determine what is the criteria, what are the products that  
21 meet the criteria, and then decide with your help what sort  
22 of restrictions should we put in the post-approval world to  
23 make sure these products perform as they're supposed to.

24 Thank you.

1 DR. ZIMMERMAN: Are there questions from the  
2 committee? Dr. Byrn?

3 DR. BYRN: I had a question about the generic  
4 drug problems of 1989 to 1994. Two kind of summary  
5 questions. Did all of those problems involve drugs that  
6 were on the list? Essentially all?

7 MR. SPORN: No. In fact, a survey was done of  
8 many drugs, including almost all the ones that were on the  
9 list, and no problem was found.

10 DR. BYRN: Okay. So, what were the main drugs  
11 that were involved in those problems?

12 MR. SPORN: It would be a long list. Don Hare  
13 is probably out here who could answer --

14 DR. BYRN: Because I had heard, for example,  
15 carbamazepine was one of them.

16 MR. SPORN: I don't know if carbamazepine was  
17 caught up. There was a problem at one time. I don't know  
18 if it was associated with the scandal or not.

19 DR. BYRN: What I'm really curious about is,  
20 was manufacturing inequivalence the cause of the generic  
21 drug problems from 1989 to 1994?

22 MR. SPORN: There were a number of things that  
23 happened, but the bottom line was there was essentially  
24 fraud committed. There was selective reporting,

1 nonreporting.

2 DR. BYRN: And were those on lots that weren't  
3 passing that were inequivalent? That was my understanding  
4 but --

5 MR. SPORN: These products were approved based  
6 on the assumption that the data submitted to the agency was  
7 truthful, and in many cases it was ont truthful.

8 DR. BYRN: So, it really involved the  
9 submissions, not passing lots --

10 MR. SPORN: Right.

11 DR. BYRN: -- not submitting correct data. I  
12 guess another way, not submitting correct data that it's  
13 bioequivalent and then later passing lots that were not  
14 equivalent.

15 MR. SPORN: Right.

16 DR. BYRN: It was actually having inequivalent  
17 lots to start with.

18 MR. SPORN: In one very notable case, the  
19 innovator was compared against the innovator, but it was  
20 disguised as being the generic firm's application.

21 DR. BYRN: I guess I'm trying to understand  
22 more of the background. We don't know I guess the  
23 motivation, but in your opinion was that done because the  
24 particular lots that the generic company made would not

1 pass?

2 MR. SPORN: The motivation was money.

3 (Laughter.)

4 MR. SPORN: Anytime a blockbuster drug is  
5 coming off patent, generally I think the feeling is that  
6 the first person to get an approval is going to capture the  
7 biggest share of the market. So, it is believed a number  
8 of firms, in order to get there first, said this is the  
9 quickest route to get FDA's approval and really worry about  
10 how to manufacture it later. So, in some cases two sets of  
11 books were kept.

12 Was there another question?

13 DR. BYRN: No, those were the two questions.

14 DR. ZIMMERMAN: Other comments, questions?

15 (No response.)

16 DR. ZIMMERMAN: Thank you.

17 I think we're going to take our afternoon  
18 break. We will reconvene in 20 minutes.

19 MR. SPORN: Can I say one other thing since one  
20 of the speakers alluded to the Medwatch reports that had  
21 been submitted to the agency about warfarin? That is true.  
22 DuPont-Merck provided 26 such reports. We looked at all  
23 reports like that. We take them very seriously. There is  
24 a group inside CDER that is convened just to look at

1 alleged therapeutic inequivalence cases, to analyze them,  
2 and find out what is behind them, if we can.

3 We have not finished looking at those 26, but I  
4 can tell you preliminarily, based on the data we provided,  
5 we're not able to conclude because the patient was switched  
6 to a generic that that was the source of the problem. Now,  
7 maybe when we dig deeper, it will come out differently, but  
8 that's the early indication that I have.

9 DR. ZIMMERMAN: Thank you.

10 (Recess.)

11 DR. ZIMMERMAN: Ladies and gentlemen, we'd like  
12 to get started. Our first speaker for the afternoon will  
13 be Dr. Rabi Patnaik, and he will be speaking about  
14 individual bioequivalence.

15 DR. PATNAIK: Thank you, Dr. Zimmerman.

16 Dr. Williams has already set, so to speak, the  
17 table for me, so I will probably skip a few of the slides  
18 which I have given to the committee.

19 The objective of my presentation is not to  
20 focus on the methodology of individual bioequivalence or  
21 the concept and to discuss that, but the discussion will be  
22 as it pertains to drugs in general and specifically to so-  
23 called, quote/unquote, narrow therapeutic index drugs.

24 What I plan to do is to introduce a little bit

1 of the concept and the criteria which Dr. Williams already  
2 sort of briefly presented to the committee, and then I will  
3 show you some examples of what I'm talking about. Then  
4 afterwards, I will discuss what are the next steps to the  
5 whole issue of individual bioequivalence as it pertains to  
6 drugs in general as well as to, quote/unquote, narrow  
7 therapeutic index drugs.

8 Now, for consideration for assessment of  
9 bioequivalence of drug products, what one should consider  
10 maybe -- Dr. Williams has already alluded to these two  
11 concepts of prescribability and switchability. Individual  
12 bioequivalence is more concerned with the switchability end  
13 so that we can assure, when the drug products are switched  
14 within one patient, safety and efficacy are assured.

15 The other factor that needs to be considered  
16 maybe and important is reference variability which is very  
17 important when switching should occur.

18 And thirdly, to some extent, therapeutic index  
19 of the drug should also be considered.

20 These are the three salient factors one should  
21 consider.

22 Now, currently we are having average  
23 bioequivalence concept. You might have heard about it, and  
24 probably you have heard -- several times these committee

1 must have gone through this subject. It focuses on the  
2 population averages of the test and reference, but it  
3 doesn't say anything about distribution of the metric  
4 between the test and reference. In other words, we don't  
5 know anything about the statistical parameters. It also  
6 ignores the subject-by-formulation interaction.

7 The second factor is the issue of switchability  
8 is not addressed in average bioequivalence.

9 As we heard from Dr. Williams, one size fits  
10 all. We have the same standard for highly variable drugs,  
11 for narrow therapeutic index drugs, quote/unquote, and also  
12 for other drugs.

13 The concept which I will be just presenting as  
14 an example to just explain to you the concept, it will have  
15 more incentive for the generic or any drug manufacturer to  
16 manufacture less variable formulations.

17 What essentially the concept is, it has got  
18 three components. One is the difference in the averages of  
19 the two products, test and reference. This is the variable  
20 and variance component. These two components add together,  
21 we say that they should be less than some bioequivalence  
22 limit.

23 Now, what are those parameters? This is the  
24 test and reference mean. This is the difference in the

1 within-subject variability of the test and reference  
2 product, and this is the subject-by-formulation  
3 interaction. This is the upper bioequivalence limit which  
4 is similar to the average bioequivalence limit which we  
5 have currently with respect to the mean differences.

6 Now, when we add some variance terms to this  
7 concept, we have a variance allowance given in the  
8 bioequivalence and it is scaled to the within-subject  
9 reference variability.

10 So, essentially we are not diverting that much  
11 in this concept from the average bioequivalence concept  
12 except that we assume that the test variance of the within-  
13 subject of test and reference are similar, so it cancels  
14 out. And there is no subject-by-formulation interaction.  
15 So, this is also nonexistent. So, ultimately we come  
16 across with an expression where we only consider the mean  
17 differences.

18 Now, in this concept, this equation, when you  
19 plot it, the upper limit of the bioequivalence criterion  
20 versus the within-subject standard deviation of the  
21 reference product on a log scale, it becomes the CV. You  
22 get a relationship like that, that more is the variability,  
23 higher will be the upper limit. So, what happens, if the  
24 variability is high, one can get the bioequivalence limit

1 raised.

2           So, this concept was worked on by the working  
3 group of the individual bioequivalence project. We first  
4 thought over that products which have a difficult product  
5 or problematic product but shows lower bioequivalence --  
6 lower within-subject variance will have to have stricter  
7 goal posts. So, what the working group developed is that  
8 will have a reference scaling of all the products whose  
9 variability is more than a certain specified number, and  
10 below that the goal post will not be reduced. It will  
11 remain constant. So, some of the drug products which show  
12 less than -- in this case it's .2 -- will remain as the  
13 .125, and those which have got more than .2 will be scaled  
14 to the reference listed drug variance.

15           So, we have two scales but conceptually one can  
16 think, as Dr. Williams suggested, that for certain products  
17 which have got so-called narrow therapeutic index drugs,  
18 one can make it much stricter for bioequivalence  
19 assessment. So, we are pretty sure that it will not pose  
20 any safety risks.

21           But depending upon what are the drugs, one has  
22 to look at what variability it is. If a drug which has got  
23 high variability, intra-subject variability, but it is  
24 narrow therapeutic, if we govern our policy with respect to

1 the intra-subject variability of the reference product,  
2 then it has to be scaled and it might be widened.

3 So, we are in a very preliminary stage and we  
4 have to look at various drug products. We have a very  
5 limited data set to look at. So, what we did -- some of  
6 you might have also seen this data set, but I just wanted  
7 for the benefit of this committee that we have very limited  
8 12 studies which are having 34 data sets which have been  
9 analyzed using this criteria. What I will do is to show  
10 you what kind of values we got and how it really comes out  
11 to be interesting enough.

12 They're all replicate design studies and most  
13 of them are healthy subject and some of them have got  
14 target populations. They represent different dosage forms.

15 Just for the interest of time, I will just look  
16 at the Cmax. We have analyzed both AUC and Cmax, but I  
17 will just show some selected data analyzed on Cmax.

18 Now, what this is is this is the plot in order  
19 of the lowest value. Over here is the test/reference ratio  
20 on a log scale for the Cmax. The test is much lower. The  
21 test value is much lower than the reference which is 13-14  
22 percent. On the right-hand side, it goes as high as 15  
23 percent higher than the reference.

24 So, we can see in 34 data sets there's a whole

1 gamut of values one gets in terms of the mean values and  
2 the averages -- differences. So, a lot of Cmax value, you  
3 can see that the ratios are very close to 1. Some of them  
4 are, the test is higher than reference, and here the test  
5 is lower than reference.

6 In average bioequivalence, this is what we see,  
7 but when you add the variance terms, the point I'm making  
8 here is that you always assume the test variability and  
9 reference variability, within-subject variability are  
10 almost similar. So, we shouldn't even consider it because  
11 the subject is its own control, and also there should not  
12 be any variability between the two formulations.

13 But as you can see here, here is about 50  
14 percent lower test variability, 50 percent lower than the  
15 reference, as high as about 70 percent higher than the  
16 reference. A whole gamut of variability differences we  
17 have seen. This is the same thing, test/reference ratio of  
18 the within-subject variability for Cmax.

19 Now, this is another term. The term  $\sigma_D$  is  
20 the subject-by-formulation interactions. This is again  
21 rank order from the lowest value to the highest value. The  
22 statistical experts in our working group suggested that any  
23 value less than .15 probably is not that important from  
24 this interaction behavior, the subject-by-formulation

1 interaction behavior. Anything above .15 is quite  
2 important.

3 So, you can see out of about 9 data sets out of  
4 34, we saw subject-by-formulation interaction more than  
5 .15. But this is just the observations.

6 Finally, which is very interesting here, it is  
7 the within-subject variability of the reference product.  
8 Now, it starts from about 10 percent all the way to 50  
9 percent within-subject variability of the reference  
10 product.

11 So, just looking at this data, if we say from  
12 20 percent is our regulatory cutoff point from which we'll  
13 start scaling with respect to the reference listed product,  
14 you can see there are a lot of data sets in which we scale  
15 it to the reference listed drug, within-subject  
16 variability, and below .2, irrespective of whether it is  
17 low or high, we'll keep it as constant .2.

18 So, the observations that we have seen that in  
19 data sets, which is very limited, we have this variability  
20 differences in test and reference. We have to some extent  
21 observed some subject-by-formulation interactions, and we  
22 see that the reference variability actually ranges from 10  
23 percent to 50 percent depending upon the type of drug.

24 Some of the assumptions which we make for

1 average bioequivalence may not be true, and here we see  
2 about 8 out of 34 data sets within-subject variability,  
3 reference more than 20 percent, and the within-subject  
4 variability ratio test/reference, you can see 50 percent  
5 lower than the reference to 200 percent higher than the  
6 reference. And in 8 of 34 subject-by-formulation  
7 interaction, we see for AUC, and 10 out of 34 we see for  
8 Cmax.

9           So, this is very limited. I'm just showing  
10 this just that the committee will appreciate that with this  
11 very limited data set, we have observed this, which is that  
12 for narrow therapeutic index drugs we can reference scale  
13 it to make it tighter so that if there is a concern about  
14 safety and efficacy by using this concept.

15           Now, what we are saying essentially -- and Dr.  
16 Williams has already alluded to this fact -- is that it  
17 addresses the correct question, this concept, which is the  
18 switchability, and it considers the subject-by-formulation  
19 interactions, which is important because I have some  
20 interaction with the two different formulations that's not  
21 very ideal for that subject or that patient.

22           Now, there will be an incentive for less  
23 variable drug product because the question is such that  
24 this test variability is lower than the reference

1 variability. That is much easier for the criteria to pass  
2 the bioequivalence testing.

3           The scaling method which we discussed with  
4 respect to the reference product, it will be for both  
5 highly variable drugs, as well as for certain agency-  
6 specified or defined narrow therapeutic index drugs. So,  
7 it has got the benefit of a whole diverse classes of drug,  
8 drugs in general, but we can pay specific attention to  
9 special classes of drug.

10           Here also, because we are looking at all kinds  
11 of intrinsic factors in the formulation drug substance, as  
12 well as the type of product, the way we are assessing  
13 bioequivalence we can use more common general population  
14 rather than a very fixed, healthy general population. So,  
15 it will be easier for people to do this study.

16           Now here, as all of you know, yesterday it went  
17 on the Internet and today the guidance, preliminary rough  
18 draft guidance, has been published, and there will be a  
19 Federal Register notice about the availability of this  
20 guidance. It is available for public comment. So, we are  
21 planning to get and we are hoping that we will get a lot of  
22 comments about this and then act on it and consider it and  
23 review it. Then the working group will go through it very  
24 carefully, and then we'll do whatever we can do to get it

1       into a modified version.

2                   What are the next steps in this whole  
3       development of individual bioequivalence? We have  
4       published it, so number 1 is already done.

5                   The agency has broadly shared the data  
6       publicly, whatever data the agency has in house, how to  
7       share the data so that people can have an appreciation who  
8       wants to look at the data.

9                   Then as Dr. Williams alluded to the fact that  
10      expert committee is forming to look into all sorts of --  
11      the implication of the individual bioequivalence concept  
12      and how it should be applied. We'll get a whole gamut of  
13      advice from this expert committee.

14                  On March 16th to 18th, a joint FDA/AAPS  
15      workshop has been scheduled to discuss about narrow  
16      therapeutic index drugs and individual bioequivalence and  
17      that will help us to develop public consensus.

18                  Then afterwards, after the meeting, then the  
19      expert committee will probably reconvene and offer their  
20      recommendation.

21                  Then the agency may repropose the guidance  
22      based on the whole gamut of activities and then have it  
23      again for public comments.

24                  Just to see the last one, this is the working

1 group of individual bioequivalence. All of the working  
2 group has worked very hard from 1992 onwards and especially  
3 more emphatically for 1994 down to come up with the  
4 guidance as well as all the analysis and developing the  
5 concept and deciding on this scaling system. We're looking  
6 forward to getting the comments from everybody.

7 Thank you very much.

8 DR. ZIMMERMAN: Thank you.

9 Are there questions from the committee? Dr.  
10 Mayersohn first.

11 DR. MAYERSOHN: Rabi, you said there were 12  
12 studies in the files. This represents one of them? What  
13 you just presented represents one of those studies?

14 DR. PATNAIK: These are all 34 data sets of 12  
15 studies. Some of them have got more than one analysis.

16 DR. MAYERSOHN: I see. Is there any way to  
17 characterize them in terms of the classification system we  
18 talked about today?

19 DR. PATNAIK: Not all of them we can do it.  
20 For some of them we can do.

21 DR. MAYERSOHN: Is there at least a rank order  
22 correlation between those that are most troublesome and  
23 classification 4 or 3 or 2? Do you understand my question?

24 DR. PATNAIK: Yes, I understand about the BCS

1 classification 1, 2, 3, 4.

2 DR. MAYERSOHN: Yes.

3 DR. PATNAIK: We are planning to do that and  
4 look at if there is an absorption problem. For some of the  
5 data, we haven't looked at it, but I'm sure that the  
6 working group is going to look at, from a BCS standpoint,  
7 what kind of drugs and how they relate.

8 DR. MAYERSOHN: I would hope there would be  
9 some common characteristics shared by those that are most  
10 troublesome that have the greatest variability, and I  
11 encourage you to look at them.

12 DR. PATNAIK: Yes, but I can tell you that just  
13 looking at the data sets -- because we have worked on these  
14 data sets so much, I can say that some of the data there,  
15 they pass average bioequivalence, they pass individual  
16 bioequivalence, and they're highly permeable/soluble drugs.

17 DR. MAYERSOHN: All of these compounds?

18 DR. PATNAIK: No. I can tell you a few of them  
19 which I can recall.

20 DR. MAYERSOHN: That are troublesome?

21 DR. PATNAIK: That are easy. They're non-  
22 troublesome. They can easily pass both.

23 DR. MAYERSOHN: And that's what you would have  
24 expected.

1 DR. PATNAIK: Yes.

2 DR. MAYERSOHN: Okay.

3 DR. ZIMMERMAN: Dr. Goldberg?

4 DR. GOLDBERG: Dr. Patnaik, you talk about the  
5 agency defining NTI drugs.

6 DR. PATNAIK: Yes.

7 DR. GOLDBERG: Will that be based upon the CFR  
8 classification or on Dr. Burlington's list? How is the  
9 classification going to be done?

10 DR. PATNAIK: Dr. Goldberg, I cannot say  
11 because it's all up in the air what will be the criteria,  
12 how it will be developed, and the process to be followed,  
13 what will be the criteria. I think really John Balian is  
14 going to talk about it. I do not know how the whole list  
15 will be developed, by what definitions or what criteria to  
16 be used at this time at least.

17 DR. GOLDBERG: Assuming that the agency does  
18 classify some drugs as NTI, will they require retrospective  
19 studies?

20 DR. PATNAIK: I guess not, but I'm not really  
21 in a position to tell you which are already on the market  
22 -- that's what you mean. Those that are already on the  
23 market, whether to do another study, even the new criteria  
24 on this individual bioequivalence, whatever form it takes,

1 to show that they are still bioequivalent by the new  
2 methodology. Is that your question?

3 DR. GOLDBERG: Yes.

4 DR. PATNAIK: I do not know. I don't think so,  
5 but again I'm not the person to make that decision.

6 DR. GOLDBERG: Okay. Thank you.

7 DR. ZIMMERMAN: Dr. Branch?

8 DR. BRANCH: I got very confused as to the  
9 mathematical analysis and the linkage to NTI. Essentially  
10 as I heard Roger talking about it earlier, there was an  
11 idea that with the narrow therapeutic index drugs, you  
12 would allow the pioneer drug to set the variance, and if it  
13 was tight, then the competitor would have to be equally  
14 tight.

15 But what you presented was actually a variance  
16 to upper limit relationship in which you said if it was  
17 below 20 percent variance, then it would become fixed. It  
18 seems to me that what you've actually proposed is exactly  
19 the opposite of what you stated. What you have proposed is  
20 easing the criteria on any drug where the pioneer/reference  
21 has a bigger variance than 20 percent. If it's tighter  
22 than 20 percent, you're just keeping the status quo as it  
23 is right now. So, it seems to me that the linkage between  
24 this analysis and NTI is arbitrary and nothing to do with

1 that.

2 Can you help clarify?

3 DR. PATNAIK: Yes. Probably you misunderstood  
4 what I said. Currently for all drugs if we apply the  
5 individual bioequivalence criteria, irrespective of  
6 whatever classification you have got, then what we'll have  
7 that the working group has come up with the concept of  
8 constant scaling and reference scaling.

9 By that, what I mean is for all drug products  
10 as a conceptual basis, that when within-subject variability  
11 is of the reference listed drug, pioneer drug, innovator  
12 drug, is .2 or less than .2, if one uses this criteria and  
13 the upper limit is controlled by the magnitude of the  
14 within-subject variability of the reference product, then  
15 if it is less than .2, then it will be narrowed if it is  
16 less than 1.25.

17 So, to avoid that, the drugs which have no  
18 problem but they have intrinsically lower within-subject  
19 variability, there is no reason for the narrowing the upper  
20 limit.

21 DR. BRANCH: Your point is taken. Warfarin is  
22 a good example.

23 But my point is that essentially the narrow  
24 therapeutic index drugs -- we've just heard today the vast

1 majority of them are right down in that box which is going  
2 to stay exactly the same as it is now. The implications of  
3 what you're proposing has nothing to do with what's going  
4 be down in the bottom left-hand corner. It has everything  
5 to do with what's going to be in that graph that goes up on  
6 the opposite extension. According to what you're saying,  
7 any drug that has a large variance in the pioneer drug, you  
8 will be able to have wider goal posts.

9 DR. PATNAIK: Yes.

10 DR. BRANCH: So, the focus of this initiative  
11 has nothing to do with narrow therapeutic index drugs. It  
12 has to do with changing the goal posts for drugs that have  
13 inherent variability.

14 DR. PATNAIK: You will make it much more  
15 tighter for accepting -- for determining bioequivalence  
16 because now instead of the higher limit to be 1.25, you are  
17 going to make it less.

18 DR. BRANCH: But you said that that's going to  
19 be fixed. You're not going to change --

20 DR. PATNAIK: No, no. I mean currently for the  
21 majority of drugs that's what I'm saying, for special,  
22 whatever the agency comes up with, a list of drugs or how  
23 to identify certain drugs. Whether they will call it a  
24 narrow therapeutic index drug or a special class of drugs I

1 do not know, but for special drugs which needs to pay  
2 careful attention, they may be assessed to a lower  
3 bioequivalence standard --

4 DR. BRANCH: But if you apply the data that we  
5 saw for warfarin earlier today to that graph, can you  
6 interpret what change, if any, this new analysis would  
7 provide for that specific instance, given that the variance  
8 that we saw was in the region of between 5 and 10 percent  
9 in those studies?

10 DR. PATNAIK: If you see that -- now, if it is  
11 less than 20 percent, which is over here --

12 DR. BRANCH: I think the data we saw earlier  
13 today was around about 10 percent. So, it's the extreme  
14 left-hand bar that would be represented by warfarin in that  
15 if it was in that data set.

16 DR. PATNAIK: So, what will happen is that it  
17 will probably come towards the lower than .2. What we are  
18 saying here, irrespective of whatever it is, below .2 will  
19 keep it as constant but it's not going to --

20 DR. BRANCH: So, it will make no difference to  
21 the narrow therapeutic index drugs, which is what I was  
22 saying.

23 DR. PATNAIK: It makes a difference because it  
24 will be lower. The bioequivalence limit will be lower

1 because we'll not constant scale it. We'll scale it to  
2 whatever reference variability shows.

3 DR. LAMBORN: Could I ask perhaps the same  
4 question in a different way? If I understand it, you're  
5 saying that for the non-narrow therapeutic index you would  
6 use this lower bound, but for the narrow therapeutic index  
7 you would not have a lower bound, but would allow them to  
8 go further down the line?

9 DR. PATNAIK: Yes.

10 DR. LAMBORN: So, the solid line that you're  
11 proposing there would not be employed for the narrow  
12 therapeutic index at the lower end. You would continue  
13 down that line below.

14 DR. PATNAIK: Yes, that is the point. The  
15 point is now for all drugs -- what is the thinking is that  
16 for all drugs we'll have the concept to a constant scaling  
17 as well as the reference scaling. But for certain drugs  
18 which have been identified, instead of going to this level,  
19 it will be dictated by whatever within-subject variability  
20 dictates.

21 DR. ZIMMERMAN: Dr. Byrn.

22 DR. BYRN: I just wanted to go on. I was  
23 talking earlier about not -- I think one of the goals of  
24 manufacturing should be to minimize the variation in

1 pharmaceutical manufacturing. In other words, the  
2 manufacturing people don't want to add to the already  
3 existing clinical variation any more variation. So, I'm  
4 not sure that we shouldn't have the dotted line for all  
5 drugs.

6 One of the problems you may get into from going  
7 across with some, say, non-narrow therapeutic index drug is  
8 that it would reduce the incentive to control manufacturing  
9 of the reference drug product. I think it might ultimately  
10 benefit the public health to put as many incentives as we  
11 could on innovators as they're developing the drug and  
12 marketing it during the period that's on their patent to  
13 tighten up their manufacturing as much as possible.

14 Now, maybe there's a decision, well, it's going  
15 to cost more and this improved cost isn't gaining anything  
16 in the public health. But to me it seems like we want to  
17 use the dotted line for all drugs. It would be an  
18 incentive then to do the very best job we can in the  
19 manufacturing end and that way any variation that you're  
20 seeing is just due to patient variation.

21 DR. PATNAIK: Yes, but here there are two  
22 things. One issue is that by following the reference  
23 listed drug variability, we become too restrictive for  
24 every drug which should not be that restrictive because now

1 we are having 1.25 which is like an average bioequivalence  
2 criteria.

3 DR. BYRN: Right.

4 DR. PATNAIK: So, most of the drugs have no  
5 problem. Some of the drugs are highly variable drugs which  
6 where you see that one can maybe safely widen the goal  
7 posts, the bioequivalence limit. For certain drugs also on  
8 the same token a difficult drug or some drugs which need to  
9 be restricted, we can reduce it.

10 DR. BYRN: I think you're arguing in effect  
11 what I said, that going along the line at 1.25 for a non-  
12 narrow therapeutic index drug is the most cost effective  
13 drug product and you're not gaining anything by staying on  
14 the dotted line.

15 But myself -- and I don't know how much we're  
16 talking about in cost and maybe that's a way to determine  
17 it. It seems like in the perfect world, if we could build  
18 in an incentive to manufacture the drug exactly the same  
19 every time, even a non-narrow therapeutic index, that would  
20 be in the best interest of public health.

21 DR. PATNAIK: Yes. That is we're saying of the  
22 reference listed drug having the less variability.

23 DR. BYRN: Right. I'm just trying to argue for  
24 moving the concept of less variability from narrow

1 therapeutic index drugs, which I very much favor, to all  
2 drugs.

3 DR. PATNAIK: But what is happening right now,  
4 if a product has got high variability in the reference  
5 listed drug or the innovator drug has got high variability,  
6 the generic or another multi-source product should have  
7 either that variability or should match that variability --

8 DR. BYRN: Right.

9 DR. PATNAIK: -- so that they can show  
10 bioequivalence.

11 But with this new concept, you can see that if  
12 your variability of the test is lower than the reference,  
13 so this becomes a negative value, then this is a higher  
14 value than if it is lower than the test. So, the whole  
15 thing, keeping the rest of the thing constant, might have a  
16 lower value. It is easier for the firm which is conducting  
17 this test to pass the bioequivalence limit.

18 So, here is a big incentive for the  
19 manufacturer of a multi-source product or if they're trying  
20 to change the formulation to have as good a formulation as  
21 they can manufacture.

22 DR. BYRN: Now, one other question. Is this  
23 concept in the draft guidance?

24 DR. PATNAIK: Yes.

1 DR. BYRN: This concept of going across?

2 DR. PATNAIK: Constantly.

3 DR. BYRN: Okay.

4 DR. ZIMMERMAN: Dr. Brazeau?

5 DR. BRAZEAU: I'm wondering if you would be  
6 better off, because I think we got confused in your  
7 nomenclature, if you would subdivide drugs like they did  
8 with the biochemical classification system to maybe having  
9 different classes of drugs with narrow therapeutic windows,  
10 a high variability, low variability, narrow. Because what  
11 we were doing was getting confused in the different  
12 nomenclature. So, I think if you differentiate.

13 Now, in the study data that you showed us, I  
14 think it would also help if you showed us which of those  
15 drugs, or maybe just by colors of those graphs, of those  
16 bars that you showed us, correspond to different types of  
17 drugs, like you were talking narrow therapeutic window or  
18 highly variable. Because it's hard to follow that and the  
19 data is from multiple studies. You said there were some  
20 controls. There were some normals and there were some test  
21 subjects. I have a hard time to interpret all that.

22 DR. PATNAIK: The objective was not to really  
23 focus on the application of the data with respect to the  
24 narrow therapeutic index drugs. The reason was that we

1 have not yet defined what should be criteria for  
2 identifying or saying narrow therapeutic index drugs. All  
3 I