

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

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

VOLUME II

Thursday, November 16, 2000

8:30 a.m.

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

## PARTICIPANTS

Stephen R. Bryn, Ph.D., Chairman  
Nancy Chamberlin, Pharm D., Executive Secretary

## VOTING MEMBERS

Kathleen R. Lamborn, Ph.D.  
Gloria L. Anderson, Ph.D., Consumer Representative  
John Doull, M.D., Ph.D.  
Judy Boehlert, Ph.D. Joseph  
Bloom, Ph.D.  
Nair Rodriguez-Hornedo, Ph.D.  
Jurgen Venitz, M.D., Ph.D.

## GUESTS (Non-Voting)

Richard Louis LaLonde, Pharm D.

Diane Renee Mould, Ph.D.

GUEST SPEAKER (Non-Voting) Michael E. Hale, Ph.D.

FDA PARTICIPANTS Mei-Ling Chen, Ph.D. Dale Conner, Pharm D.  
Ajaz Hussain, Ph.D. Peter Lee, Ph.D. Larry Lesko, Ph.D. Vinod  
P. Shah, Ph.D.

Helen Winkle, Acting Director, Office of Pharmaceutical  
Science

## C O N T E N T S

Call to Order Stephen Byrn, Ph.D., Chairman	4
Conflict of Interest Nancy Chamberlin, Pharm D.	4
Welcome, Introduction Helen Winkle	6
GUIDANCE UPDATES	
Biopharmaceutics Classification System Ajaz Hussain, Ph.D.	9
General Bioavailability/Bioequivalence Vinod P. Shah, Ph.D.	30
Average, Population, and Individual Approaches to Establishing Bioequivalence Mei-Ling Chen, Ph.D.	62
CLINICAL PHARMACOLOGY	
Modeling and Simulation Introduction Larry Lesko, Ph.D.	68
Applications of Simulation in Drug Development Michael D. Hale, Ph.D.	74
A Framework of Modeling and Simulation in Regulatory Decision  Peter Lee, Ph.D.	96
Committee Discussion	110
Open Public Hearing	136
Committee Discussion	136
FDA Research Report Product Quality Research Institute Ajaz Hussain, Ph.D.	147
Committee Discussion	177
GENERICS ISSUES	

Failed Bio Studies	
Dale Conner, Pharm D.	179
Committee Discussion	214

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

## 2 Call to Order

3 DR. BYRN: Good morning, everyone. Welcome to the  
4 Pharmaceutical Science Advisory Committee Meeting, the  
5 second day, November the 16th, 2000.

6 I would like to ask Nancy Chamberlin to read the  
7 Conflict of Interest Statement.

## 8 Conflict of Interest Statement

9 DR. CHAMBERLIN: Welcome.

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

14 Based on the submitted agenda for the meeting and  
15 all financial interests reported by the committee  
16 participants, it has been determined that all interests in  
17 firms regulated by the Center for Drug Evaluation and  
18 Research which have been reported by the participants  
19 present no potential for an appearance of a conflict of  
20 interest at this meeting with the following exceptions.

21 Since the issues to be discussed by the Committee  
22 at this meeting will not have a unique impact on any  
23 particular firm or product, but rather may have widespread  
24 implications with respect to an entire class of products, in  
25 accordance with 18 U.S.C. 208(b), each participant has been

1 granted a waiver which permits them to participate in  
2 today's discussions.

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

6 With respect to FDA's invited guests, there are  
7 reported affiliations which we believe should be made public  
8 to allow the participants to objectively evaluate their  
9 comments. Dr. Michael Hale is the Internal Director,  
10 Clinical Pharmacology at Glaxo-Wellcome. Dr. Richard  
11 LaLonde is the Director of Clinical Pharmacokinetics and  
12 Pharmacodynamics, Pfizer Global Research and Development.  
13 Dr. Diane Mould would like to report that she is stockholder  
14 on Pharsight Science Advisory Group. She consults for Xoma,  
15 SmithKline Beecham, and Hoffman LaRoche. Dr. Robert  
16 Hollenbeck is Vice President of University Pharmaceuticals  
17 of Maryland, Inc.

18 With respect to all other participants, we ask in  
19 the interest of fairness that they address any current or  
20 previous financial involvements with any firms whose  
21 products they may wish to comment upon.

22 Thank you.

23 DR. BYRN: Before Helen gives us our welcome and  
24 introduction, I would like the committee, starting on the  
25 left, to introduce themselves.

1 DR. DOULL: John Doull, KU Medical Center.

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

4 DR. CHAMBERLIN: Nancy Chamberlin, Exec. Sec.

5 DR. BYRN: Steve Byrn, Purdue University.

6 DR. LAMBORN: Kathleen Lamborn, University of  
7 California/San Francisco.

8 DR. BOEHLERT: Judy Boehlert. I have my own  
9 consulting business.

10 DR. VENITZ: Jurgen Venitz, Virginia Commonwealth  
11 University.

12 DR. RODRIGUEZ-HORNEDO: Nair Rodriguez, University  
13 of Michigan.

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

16 Welcome, Introduction

17 MS. WINKLE: Good morning, everybody. Hopefully,  
18 you all had a pleasant evening and are ready to start a  
19 second day.

20 Before we talk about today's agenda, I wanted to  
21 thank Dr. Lamborn for doing such a wonderful job yesterday  
22 of chairing the committee. She helped us out at the last  
23 minute and I really appreciate all her help.

24 I also have a few things I want to mention about  
25 yesterday's meeting. I thought the discussion was very

1 good. I thought the discussion on reducing the chemistry  
2 regulatory burden, I think there were some very provocative  
3 questions asked, and I just want to assure everyone on the  
4 committee this is not the last time you will hear about this  
5 particular topic. We are just beginning I think, as Dr.  
6 Chiu said, to address this area, and I wanted to assure  
7 everyone on the committee that we will be looking at every  
8 aspect of the products before we make the decisions, but we  
9 will be bringing those back to you, some of our additional  
10 thoughts on that probably at the next meeting. We are  
11 looking forward to a lot of discussion outside of the Agency  
12 on this and then getting more input from the committee, as  
13 well.

14 I also wanted to mention on the OINDP Subcommittee  
15 report, Dr. Lamborn asked what the next steps were and what  
16 this advisory committee could do to help in those. I wanted  
17 to assure the committee, too, that we are in the process of  
18 still reviewing the issues at hand, and a lot of the data  
19 that came in from the subcommittee, as well as from some of  
20 the comments on the guidance. We have had a lot of  
21 information, and I wanted to let the committee know that we  
22 are not going to move forward with any guidances until we  
23 are sure we have the issues determined on how best to handle  
24 each of them. I think we will probably be bringing this  
25 issue back, as well. I think that we will probably have a



1 subcommittee meeting again to go over some of our questions  
2 that exist after looking at the issues and then come back  
3 and report and get some more input from the advisory  
4 committee, so I just wanted to follow up on that.

5           Today's agenda, I think we have some interesting  
6 topics. We are going to start off with talking about  
7 several of the new guidances that OPS has put out, the first  
8 one being the Biopharmaceutics Classification System. There  
9 has been a lot discussed on this. This guidance has  
10 recently issued and the committee has played an important  
11 part in some of our decision-making as far as the guidance,  
12 so we wanted to tell the committee where we were with it.

13           We are also going to talk about the General BA and  
14 BE guidance and its companion guidance, the average  
15 bioequivalence, and individual approaches to establishing  
16 bioequivalence.

17           The rest of the morning is going to be devoted to  
18 Modeling and Simulation for Clinical Pharmacology. I think  
19 this will be a very interesting discussion and I think there  
20 are a lot of issues here as far as our future direction that  
21 we will want to discuss.

22           After lunch, Dr. Hussain is going to talk about  
23 the FDA research in OPS, as well as Product Quality Research  
24 Institute, and bring the committee up as to what the current  
25 focus of that institute is.



1 Maryland.

2           The research essentially provided the basis for  
3 development of SUPAC guidances, especially the SUPAC-IR  
4 guidance, and the Biopharmaceutics Classification System  
5 base dissolution testing was introduced in the SUPAC  
6 guidance in November of 1995.

7           I joined the Agency in January of '95, so most of  
8 this happened before I joined the Agency, and Larry Lesko  
9 and Vinod Shah led the effort at that point. I was assigned  
10 this task and we put together a working group in April of  
11 '96 to further evaluate the BCS applications and to actually  
12 develop a guidance that outlines methods for classifying a  
13 drug, as well as extend its application beyond SUPAC-IR.

14           We met with the advisory committee in 1996 to  
15 outline our objectives and had an open workshop in 1997 to  
16 discuss our thinking at that time. Based on several  
17 workshops, essentially, we consolidated our thinking and  
18 started towards writing a draft guidance.

19           One key aspect that I want to mention is we put  
20 together an expert panel. At that time, we had several  
21 issues that needed to be discussed, and we put together an  
22 expert panel to discuss those with them, and brought those  
23 decisions back to the advisory committee in 1997.

24           December 1997 was an extended discussion on BCS at  
25 this advisory committee. We then had an AAPS workshop on

1 focusing on permeability methods. What our thinking was and  
2 got feedback from the public discussion at that point, and  
3 then came back to the advisory committee to update our  
4 methods recommendation in the draft guidance.

5 The draft guidance was published in February of  
6 1999, and we received comments from 11 companies. The  
7 comments were not very extensive, but focused primarily on  
8 methodological issues, and I will touch briefly on that  
9 later on.

10 Before we published the final guidance in 2000, we  
11 had an internal training. This was training for our  
12 reviewers, and we generally train our reviewers before we  
13 put the final guidance just to make sure that if there are  
14 any issues, we could correct those, and the external  
15 training occurred in September of 2000.

16 We are at the stage where we have to talk about  
17 next steps, and I will briefly discuss that also.

18 [Slide.]

19 In summary, the BCS guidance has a long title. It  
20 is Waiver of In Vivo Bioequivalence Studies for Immediate  
21 Release Solid Oral Dosage Forms Based on a Biopharmaceutics  
22 Classification System. We call this guidance the BCS  
23 guidance.

24 In summary, what does this guidance provide? It  
25 provides recommendations for methods for classifying a drug

1 substance based on solubility and intestinal permeability.  
2 The way we have defined intestinal permeability is stability  
3 of the drug in the GI fluids as built into that process.

4 The guidance introduces the criteria called rapid  
5 dissolution criteria for solid oral dosage forms, and then  
6 recommends biowaiver for rapidly dissolving solid oral  
7 dosage forms containing drugs that exhibit high solubility,  
8 high permeability, and also has a wide therapeutic index.

9 Obviously, there are safeguards built in with  
10 respect to excipients and this guidance applies when changes  
11 are made that establish the excipients. If there are new  
12 excipients, then, there are different issues that need to be  
13 addressed.

14 [Slide.]

15 When Larry Lesko initiated this work, it was truly  
16 sort of risk based, and some of you have seen some of his  
17 presentation, he laid out how BCS is used to minimize risk.  
18 I am taking a slightly different approach and how to sort of  
19 explain how we look at BCS as a tool for managing risk.

20 When you deal with risk, you have three aspects  
21 to that - assessment of risk, and you need to start with a  
22 clear definition of what the risk is, and in this scenario,  
23 the risk is in terms of bio-in-equivalence.

24 So, you can phrase the question, well, what is the  
25 risk of bio-in-equivalence between two pharmaceutical

1 equivalent products when in vitro dissolution test  
2 comparisons are used for regulatory decisions. So, that is  
3 the question we tried to address.

4 When you assess risk, there are two aspects again  
5 - likelihood of occurrence and the severity of consequences,  
6 so those two aspects have to be dealt with.

7 Then, you have a decision based on the risk  
8 assessment, and I am calling that a regulatory decision.  
9 Here, the key issue that one focuses on is whether or not  
10 the risks are such that the project can be pursued with or  
11 without additional arrangements to mitigate the risk.

12 I think the decision was taken early on that in  
13 vitro dissolution, as we do for quality control, one point  
14 specification was not sufficient, and that is the reason BCS  
15 was developed, and I will share with you the thought  
16 processes behind that.

17 Finally, acceptability of the decision is key. Is  
18 the decision acceptable to society? Because eventually,  
19 what we do here has to be accepted by the public.

20 [Slide.]

21 Bioequivalence, I think has a long and rich  
22 history, and our regulations essentially reflect that  
23 history. If you look at those regulations, one would get a  
24 sense that differences in drug dissolution are generally  
25 considered to be primary reason for bio-in-equivalence. I

1 say that with sort of a question mark, and I say that  
2 because if you look at the regulations as they apply to  
3 solutions, oral solutions, the regulations state that  
4 bioavailability is self-evident for these products, and  
5 simply biowaivers are possible with the caveat that  
6 excipients used in those formulations do not affect  
7 absorption, and that decision is generally based on  
8 historical data of our inactive ingredient guide.

9           When you move toward solid dosage forms, even  
10 suspended solid dosage forms like suspension, chewable  
11 tablets, and so forth, dissolution comes into play, and you  
12 have more rigorous requirements of dissolution testing, as  
13 well as in vivo bioequivalence.

14           If you look at the bottom of the slide, when you  
15 have controlled release and modified release dosage form,  
16 primarily the decisions for bioequivalence are made on in  
17 vivo assessment. For minor changes in formulations, you  
18 could use in vitro dissolution when in vitro in real  
19 correlations have been established, and we have a whole  
20 guidance on how to establish in vitro in real correlation.

21           But everything in between, immediate release or  
22 conventional tablets and capsules, we really don't see in  
23 vitro in real correlations generally. You have a few  
24 examples of such correlations. The primary reason there is  
25 dissolution many times is not the rate-limiting step in the

1 absorption process, and it is very difficult to establish in  
2 vitro in real correlation.

3 We have managed these products differently. For  
4 the pre-1962 drugs, these are the DESI drugs, you had an  
5 option of biowaiver. This is CFR 320.33, which was  
6 essentially the first-class, Biopharm Classification System,  
7 and this dealt with therapeutic index, PK, and  
8 physical/chemical aspects of that, and we have several  
9 products on the market which are approved on that basis.

10 Then, came SUPAC-IR and then dissolution guidance,  
11 and obviously, this is an old slide, the BCS guidance.

12 [Slide.]

13 Let me start at a point in time, 1986. This is  
14 when we had a major FDA bioequivalence hearing. The topic  
15 of in vitro dissolution as a means for establishing  
16 bioequivalence was discussed at this meeting. This was in  
17 Washington.

18 According to significant speakers at this  
19 bioequivalence hearing, Arnold Becketts and others had made  
20 a strong case that in vitro dissolution essentially is  
21 sufficient, and in vivo may not be necessary in all cases.

22 Just to quote one significant quote from that  
23 discussion was, "seems sensible to think that swallowing  
24 something that turns into a solution rapidly would be  
25 difficult to lead to differences from one product to the



1 next." We are talking about bioequivalence here. That was  
2 Dr. Bob Temple from CDER who said that.

3 Towards the end of the workshop or conference,  
4 Professor Milo Gibaldi essentially summarized this, that "I  
5 have learned that there is no support here for attempting to  
6 provide such assurance, namely for bioequivalence, solely  
7 with in vitro data."

8 So, at that point in time, we didn't have  
9 consensus of how do we move forward from that point to the  
10 present day.

11 [Slide.]

12 If you look at how we establish bioequivalence in  
13 in vitro dissolution specifications, what are we looking at  
14 here? You start with pharmaceutical equivalent products.  
15 The definition of pharmaceutical equivalent means you have  
16 the same drug, the same amount, and has to be tablet versus  
17 tablet, not tablet versus capsules, and so forth, so you  
18 have a criteria that the products for bioequivalence testing  
19 have to be similar from a pharmaceutical perspective.

20 So, you have a reference product and a test  
21 product. These could be innovator or generic or it could be  
22 pre-changes versus post-product, and there could be many  
23 differences between the products. For example, the drug  
24 particle size could be different, excipients might be  
25 different, manufacturing process, equipment, size, batch,

1 these are all things that could be different between the two  
2 products.

3 We establish bioequivalence based on the  
4 traditional pharmacokinetic approach, and when these  
5 products are termed bioequivalent, then, they are also of  
6 therapeutic equivalence according to our Orange Book.

7 What you notice here is if you look at all the  
8 products we have approved, generally, for immediate release  
9 dosage forms, there is the same dissolution specification,  
10 and this comes in the USP.

11 So, bioequivalent products provide the same  
12 dissolution specification, but vice versa, not always true.

13 [Slide.]

14 So, if you look at the historical data the last 30  
15 years or so, and simply look at the dissolution  
16 specification that we set for quality control, and try to  
17 estimate how frequently do we see failure of that  
18 dissolution test to signal bio-in-equivalence, what you see  
19 is two dramatic differences.

20 Most of the time you see big differences in  
21 dissolution, but no difference in bio. That means  
22 dissolution is far more sensitive to formulation  
23 differences, the dissolution test in vitro is far more  
24 sensitive to formulation differences, but they do not  
25 translate to biodifferences, and we have used the term

1 "over-discriminating" for that purpose.

2 That is good from one sense, but not good from the  
3 other, but you have a few cases--and I estimated this with  
4 this brief survey of the new drug submissions, that the  
5 failure of dissolution test, the 1-point quality control  
6 test to signal bio-in-equivalence as around roughly 20 to 30  
7 percent, and really, clearly, we have to explain why that is  
8 the case.

9 [Slide.]

10 In the last 30 years, the debates that we have had  
11 on dissolution are essentially summarized here. On one side  
12 you have individuals who argue from the perspective that  
13 dissolution tests are "over-discriminating," and, in fact,  
14 the USP, Roman Number page XI of USP says, "Products that  
15 dissolve about 70 percent in 45 minutes hae no medically  
16 relevant bioequivalence problems."

17 This was based on analysis of all the therapeutic  
18 failures early on that we saw for digoxin, and so forth.  
19 So, that was the basis of what is in the USP, but on the  
20 other hand, I think you have concerns that dissolution tests  
21 are not sufficient to assure bioequivalence, and that has  
22 been reflected in our regulation.

23 Our regulation also says, "Demonstration of in  
24 vitro/in vivo correlation is necessary" with the caveat we  
25 have known for a long time that when you have a correlation,

1 that tends to be product-specific or formulation-specific.  
2 If you change the formulation significantly, then, that  
3 correlation does not hurt, so that is the dilemma here.

4 [Slide.]

5 So, when you look at all the historical data and  
6 try to figure out why did a dissolution test fail to signal  
7 bio-in-equivalence, and you come up with some of the reasons  
8 as follows. One, very common reason tends to be  
9 inappropriate acceptance criteria. This generally refers to  
10 the one-point specification.

11 For quality control, we generally have one-point  
12 acceptance criteria. The dissolution needs to be 70 percent  
13 in 45 minutes or so, so that is the only criteria. To go  
14 with that criteria, that leads to bio-in-equivalence  
15 decisions in some cases.

16 There are reasons other than the acceptance  
17 criteria, and these include inappropriate test method,  
18 primarily the media composition especially the pH. One  
19 lesson that we had learned long ago, but we still tend to  
20 make that mistake, is for weak acids and weak bases with PKA  
21 between ionization constant between, say, 3 to 6, we tend to  
22 use the wrong media. That is where the failure tends to  
23 occur. Media volume and hydrodynamics also can contribute.

24 Clearly, when you look at in vitro dissolution  
25 alone, excipient issues have to be addressed - do excipients

1 affect absorption, so that also needed to be addressed.

2           There are other reasons. Many times  
3 bioequivalence studies fail to establish bioequivalence, but  
4 that does not mean the products were truly bio-in-  
5 equivalent. It was simply a type II error. When you repeat  
6 the study with a larger number of subjects, you have  
7 established bioequivalence.

8           [Slide.]

9           So, the biopharm classification system essentially  
10 starts with the premise that dissolution, solubility,  
11 permeability are the key determining factors that affect  
12 rate and extent of absorption, and simply, the hypothesis is  
13 that if you maintain the same concentration profile of a  
14 drug substance on the intestinal membrane, you have the same  
15 rate and extent of absorption.

16           So, the question is in vitro dissolution, does it  
17 emulate or does it reflect in vivo dissolution process. I  
18 am sure you are aware that traditionally, when we do  
19 dissolution tests we use 900 ml of the media, and simply do  
20 that test.

21           But if you take a look at what are the volumes,  
22 what are the physiologic waivers that impact in vivo  
23 dissolution process, you see some differences here. After  
24 an overnight fast--that is how we do the fasting--what are  
25 the volume estimates?

1           The volume of gastric fluid is highly variable.  
2 You see values from 4 ml to 100 ml depending on how that  
3 volume was collected. You administer the tablet or capsule  
4 with a glass of water, the total volume available is a small  
5 volume, say, about 300 ml. The pH in this fluid ranges from  
6 1 to 3 and if you have a chlorhydrate, it could be higher.

7           The residence time under fasting conditions is  
8 variable. The approximate time to empty, say, 240 ml of  
9 water is about 15 minutes. The permeability of the membrane  
10 in the stomach is low compared to small intestine, and  
11 surface tension is lower than water.

12           Surface tension of gastric fluid tends to be about  
13 30 to 50 times per centimeter. Surface tension of  
14 dissolution of media tends to be around 72 times per  
15 centimeter, and variability is an issue.

16           Clearly, the volume available in the small  
17 intestine is a bit more uncertain, so what gets emptied from  
18 the stomach plus the resident volume, so one could estimate  
19 about 500 ml. The pH ranges from 3 to 8, surface tension is  
20 low. Residence time is between two to four hours, and  
21 permeability is high. Permeability is high because of many  
22 different factors, surface area being one.

23           So, small intestine is the primary area of  
24 absorption. Stomach is not a primary organ for absorption.  
25           The other aspect for dissolution is

1 hydrodynamics, and we don't have a good sense of in vivo  
2 hydrodynamics. So, these are the uncertainties and  
3 complexities that are not captured in in vitro dissolution.

4 [Slide.]

5 So, based on these concerns, we essentially  
6 developed criteria which sort of minimizes the uncertainty  
7 in here. So the Biopharm Classification System primarily  
8 focuses on drug properties, to start with, so you are  
9 looking at solubility of the drug and the permeability of  
10 the drug.

11 The high permeability class boundary is  
12 essentially designed to ensure that the drug is completely  
13 absorbed during the limited transit to the small intestine.  
14 So, you are starting with drugs which essentially have  
15 sufficient rate of permeability across the membrane, so that  
16 absorption is essentially complete within two to four hours.

17 The high solubility criteria is established to  
18 ensure that solubility is not likely to limit dissolution  
19 and, therefore, absorption.

20 So, those are the drug attributes, and overlaid on  
21 that are the product attributes. The rapid dissolution  
22 criteria that was developed was to ensure that in vivo  
23 dissolution is not likely to be a rate-determining step in  
24 the absorption process.

25 [Slide.]

1           So, when you sort of overlay the solubility,  
2 permeability, and dissolution, you can establish certain  
3 aspects of risk management. Drugs that have high  
4 solubility, if you are formulating these drugs, the primary  
5 focus tends to be on manufacturability. If the drug has low  
6 solubility, for example, you have to focus on different  
7 aspects enhancing solubility, enhancing dissolution rate,  
8 and so forth.

9           So, the drugs on the lefthand side, which have  
10 high solubility, the formulations are generally very simple.  
11 On the righthand side, when the solubility is low, you have  
12 to invoke more detailed formulation development plans to  
13 combat low solubility behavior.

14           Now, rapid dissolution is essentially likely the  
15 drug has high solubility. That is sort of inherent. So,  
16 when you have rapid dissolution, and the dissolution tends  
17 to be essentially more rapid than the gastric emptying  
18 process, then dissolution is not likely to be a rate-  
19 limiting step.

20           That simply means that the blood levels you are  
21 measuring are not giving you any information on product  
22 differences. In fact, the variability you see in blood  
23 levels generally comes from variability due to physiology,  
24 not product differences. So, doing bioequivalence studies  
25 under those circumstances really is not adding value.



Similarly, the same case would be argued for Class  
2 III drugs, which have low permeability, but high solubility.  
3 In fact, one of the arguments we have seen is that we should  
4 also apply biowaivers for low permeability drugs that have  
5 high solubility, but we had some concerns, and the concerns  
6 came from the point of view of excipients, as well as  
7 relevance of the volume that we use for in vitro  
8 dissolution.

9 Keep in mind the permeability is the factor which  
10 maintains same conditions in vivo, and in vitro dissolution  
11 volume is 900 ml to emulate the same condition, so we felt  
12 that 900 ml was more appropriate for a highly permeable  
13 drug, but may not be so for a low permeability drug.

14 On the other hand, for Class II drugs, which  
15 exhibit low solubility, there is a high likelihood that  
16 dissolution is likely to be rate determining, and if that  
17 happens, then, in vitro real correlations are possible, and  
18 the argument that these tend to be formulation-specific  
19 stopped us from going in that direction, and Class IV drugs  
20 are generally problem drugs, so we have problems for Class  
21 II and Class III.

22 [Slide.]

23 So, what has been the acceptance of our approach  
24 of BCS-based biowaivers? I think we have had strong support  
25 from the scientific community. We have met with the

1 advisory committee on many occasions, we have met with  
2 expert panel, FDA staff, and public workshops, so the input  
3 we received from these meetings and discussions have been  
4 very positive, however, there is some concerns being  
5 expressed, and the concerns were expressed at the public  
6 workshop, as well as some comments that came to the draft  
7 guidance.

8           Predominantly, the concerns that have been  
9 expressed is that our approach is overly conservative, and  
10 people have argued that we should extend the application of  
11 biowaivers for Class III and Class II drugs. We felt that  
12 it was more prudent at this time to take a more conservative  
13 step because this is such a significant paradigm shift, in  
14 terms of risk, it was felt more prudent to be more  
15 conservative this time.

16           The other concerns that have been expressed are  
17 application to generics. I think of the 11 comments we  
18 received from 11 companies, one was from generic, but 10  
19 were from innovator companies. Of those 10, three expressed  
20 concern that BCS-based biowaivers should only be applied to  
21 innovator, but not for approval of generics.

22           I think we have also heard concerns from  
23 individuals, I think the concern being how can we approve a  
24 product for the first time without doing in vivo testing,  
25 and the answer to that is we do it right now for oral

1 syrups, and so forth, and that concern was impact of  
2 excipients.

3           Analysis of impact of excipients on  
4 bioavailability, in fact, we did find some high-risk  
5 practices with respect to use of some excipients, but that  
6 turned out mainly for oral syrups.

7           I think this afternoon I will briefly mention to  
8 you about a research publication that we have on comparison  
9 between sorbitol and sucrose in oral syrups, and that turned  
10 out to be more of a higher risk because of the large amount  
11 of excipients used in syrups.

12           In terms of excipients for tablets and capsules,  
13 solid oral dosage forms, I think there was some concern with  
14 respect to certain surfactants, but the amount of those  
15 surfactants that we have approved in the Guide would  
16 generally suggest that for a highly permeable drug, they  
17 should not pose a significant problem, but, of course, if  
18 somebody uses excipients in larger amount, and so forth,  
19 that would need to be qualified differently.

20           [Slide.]

21           So, the next steps that we face or the next steps  
22 that we are taking now for further research, this would be  
23 under PQRI, as well as our intramural research which I will  
24 touch upon later this afternoon, and the focus primarily is  
25 on extension of BCS-based biowaivers for Class II and Class

1 III drugs, at the same time, trying to apply BCS-based  
2 biowaivers for "fed" bioequivalence studies.

3           Currently, the guidance applies only for fasting  
4 bioequivalence studies, so the extension would be to "fed"  
5 bioequivalence studies, and significant work and approaches  
6 have been proposed in the literature, especially people like  
7 Azia Karim from Searle have adopted the classification  
8 system to predict the impact of food on bioavailability, and  
9 so forth. So, that information we are looking at, and we  
10 have tried to extend that in that direction.

11           Continuing our educational incentives for  
12 practitioners and public. We feel this is an important  
13 aspect because public confidence, confidence of the  
14 practitioners in our approaches for bioequivalence is  
15 extremely important, and we are planning several meetings  
16 with practitioners and other discussions to promote  
17 understanding of the science and foundation behind this  
18 guidance, and clearly, international harmonization is on our  
19 mind and we are focusing on that aspect also.

20           Thank you.

21           DR. BYRN: Questions for Ajaz? I think maybe we  
22 should questions until the discussion.

23           DR. HUSSAIN: We don't have I think open  
24 discussion.

25           DR. BYRN: Okay. Then, let's have questions now.

1 Any questions for Dr. Hussain?

2 Ajaz, I just have one question relating to the USP  
3 definition and the residence time in the stomach. If the  
4 drug only spends on the average 15 minutes in the stomach  
5 and then passes into the small intestine, the USP statement  
6 seems to have to do with 45 minutes, meaning that the drug  
7 isn't fully dissolved as it is passing into the intestine.

8 Is that a problem?

9 DR. HUSSAIN: Not necessarily in the sense you  
10 have to keep in mind our rapid dissolution criteria that we  
11 built for BCS looked at three different media, and the  
12 reason for that was we don't synchronize the time of  
13 administration with the motility pattern, so there is  
14 always the likelihood that in some subjects, emptying could  
15 be almost instantaneous, so you have to build that concern  
16 in.

17 But 45 minutes from a different perspective I  
18 think is a bit slow, one point specification in 45 minutes.

19 DR. BYRN: Is a bit slow.

20 DR. HUSSAIN: A bit slow, and we have seen example  
21 after example were you see differences.

22 DR. BYRN: When was that USP statement made?

23 DR. HUSSAIN: I don't have ti.

24 DR. BYRN: A long time ago.

25 DR. HUSSAIN: A long time ago, yes.

1 DR. ANDERSON: Would you explain what you are  
2 talking about in the rate-determining step? It is on page  
3 7.

4 DR. HUSSAIN: In the absorption process, a drug  
5 has to dissolve in the media first and then diffuse across  
6 the membrane, so the permeability, the movement across the  
7 intestinal membrane, and the rate at which the drug  
8 dissolves. If the dissolution is slower than the rate it is  
9 possible to have across the membrane, then, that becomes a  
10 rate-limiting step.

11 DR. ANDERSON: Okay. So, it is crossing the  
12 membrane.

13 DR. HUSSAIN: Right.

14 DR. ANDERSON: Thank you.

15 DR. RODRIGUEZ-HORNEDO: Just for clarification.  
16 How are you dealing with weak acids or bases or salts that  
17 span a wide solubility range in the pH range of the GI  
18 tract?

19 DR. HUSSAIN: The solubility criteria that we have  
20 set, we take the minimum solubility across a pH range of 1  
21 to 7.5, and that has been criticized as being overly  
22 conservative because, for example, weak acids, naproxen, and  
23 other drugs, which have poor solubility in acid media, but  
24 have very high solubility in, say, pH 4 and above, would be  
25 a candidate for some of these waivers, because dissolution

1 would be very rapid.

2           The concern we had for drugs like those was that  
3 when dissolution is occurring, the dissolution will occur in  
4 the small intestine, and when it is occurring in small  
5 intestine, the permeability is extremely high for some of  
6 these drugs.

7           So, what we felt was dissolution, even though it  
8 is rapid, could be rate limiting, and when dissolution is  
9 rate limiting, differences between formulations that would  
10 be, say, particle size different, can be important, and we  
11 are not sure whether in vitro dissolution would be  
12 sufficient to cover that. That is the reason we didn't  
13 extend it to those type of drugs.

14           DR. BYRN: Any other questions? Okay. Thank you  
15 very much, Ajaz.

16           Our next speaker is Vinod Shah. He is going to  
17 talk about General Bioavailability/Bioequivalence guidance.

18           General Bioavailability/Bioequivalence

19           DR. SHAH: Good morning. I will be making a  
20 general presentation and provide you an update on the  
21 bioavailability and bioequivalence studies for orally  
22 administered drug products for general consideration.

23           This is a very general guidance which is  
24 applicable for all types of oral drug products.

25           [Slide.]

1           In my presentation, I will first provide you a  
2 very brief outline, then, talk about the chronology,  
3 background information, and the important features of the  
4 guidance and the impact that this guidance would have.

5           [Slide.]

6           In terms of the chronology, we have discussed this  
7 guidance in front of this advisory committee several times  
8 with several different aspects, and then taken that advice  
9 into consideration before we finalize the guidance.

10           The draft guidance was issued in August 1999.  
11 Then, we had an AAPS workshop in Montreal, which was August-  
12 September 1999. The draft guidance had several features  
13 which was very contradictory in nature, and that was the  
14 reason why we had a lot of discussions at this particular  
15 workshop, and it was followed by the discussions at the  
16 advisory committee meeting primarily looking at the  
17 individual bioequivalence issues.

18           We had also the discussions with the Blue Ribbon  
19 Panel, which discussed the values of the individual  
20 bioequivalence, and we have taken all those points into  
21 consideration before we had finalized the guidance.

22           We had also received several comments. All those  
23 comments were reviewed, appropriate changes were made, and  
24 the final guidance is issued in October 2000, just last  
25 month.



1 [Slide.]

2 The major points in the guidance are it uses the  
3 sound scientific principles to reduce the regulatory burden  
4 by lowering in vivo requirements without sacrificing the  
5 product quality. That is the important feature of the  
6 guidance. We have tried to build the guidance based on  
7 science, so that at least we can stand on firm ground as to  
8 what the changes we are making from the existing practice.

9 It defines proportionally similar dosage forms.  
10 Even though we have indicated in our CFR that the products  
11 should be proportionally similar, there was some ambiguity  
12 as to how exactly that needs to be identified, and the  
13 guidance very clearly defines two different ways how it  
14 could be applied.

15 It allows the waivers for the in vivo  
16 bioequivalence of the higher strength of the immediate  
17 release dosage forms. This was something new which was not  
18 done before, but initially, we were allowing the waiver for  
19 the lower strengths, but never for the higher strengths. I  
20 will identify some of the cases where the guidance does  
21 permit that the biowaiver could be provided even for a  
22 higher strength under certain circumstances. It allows the  
23 waivers for the in vivo bioequivalence requirement for the  
24 lower strength of the immediate release dosage form that was  
25 already in existence before, but it also now allows the

1 waiver for the modified release dosage forms under certain  
2 circumstances. Again, that is a new feature in the guidance  
3 which lowers the regulatory burden, and also it eliminates  
4 the multiple-dose bioequivalence study requirements for the  
5 modified release dosage forms. Until now it was required,  
6 but now that would be eliminated, it is not necessary.

7 [Slide.]

8 Now, the guidance does go into the details in  
9 defining the bioequivalence, as well as the bioavailability  
10 issues and trying to give clear differences between the two.

11 In brief, the bioavailability focuses on the  
12 release of the drug substance from the drug product and its  
13 absorption into the systemic circulation, and it provides  
14 the information related to the formulation development, the  
15 rate and extent of drug absorption, its pharmacokinetics,  
16 pharmacodynamics, and the metabolite characteristics of the  
17 drug product.

18 Whereas, on the other hand, bioequivalence issue  
19 or the bioequivalence focuses on the release of the drug  
20 substance from the drug product, and its absorption into the  
21 systemic circulation. It is a comparative test that uses  
22 specified criteria for the comparisons and predetermined  
23 bioequivalence limits. So, bioequivalence is definitely a  
24 comparison with something which is already there.

25 [Slide.]

1           Now, I will try to start defining the  
2 proportionally similar. What do we mean by that?

3           The first definition is all active and inactive  
4 ingredients are exactly in the same proportion. By that we  
5 mean that when you have, say, for example, three different  
6 strengths of products, 100 mg, 50 mg, and 25 mg, then, apart  
7 from the active ingredient, all the inactive ingredients are  
8 also exactly in the same proportion.

9           If you take 50 mg as the standard, then, the 100  
10 mg tablet will have all the ingredients, which is twice that  
11 of the 50 mg, and for a 25 mg tablet, all the ingredients,  
12 active, as well as inactive, will be exactly half of that,  
13 and that is the classical definition of how we say that  
14 everything is proportionally similar.

15           But the second definition is saying that the total  
16 weight remains nearly the same for all the strengths and the  
17 change in strength is obtained by altering the amount of the  
18 active ingredient because it has to be, since you are  
19 changing the strength, and one or more of the inactive  
20 ingredients.

21           Now, here is the case where it is generally meant  
22 for very small tablets or small amount of the active  
23 ingredients, for example, if the ingredients is 1 mg, half a  
24 mg, or 2 mg, then, in those cases, it is very difficult to  
25 obtain everything which is proportional to one another, and

1 we say that all the ingredients, everything remains nearly  
2 the same, and the only change, if the change in the amount  
3 of the active ingredient plus maybe minor adjustments with  
4 respect to the inactive ingredient, which will be replacing  
5 for the active.

6 So, this is how we have defined the two different  
7 ways of proportionally similar drug products.

8 [Slide.]

9 Once we have these definitions, as it is defined  
10 in our regulations, in terms of documenting the  
11 bioequivalence, in the descending order or preference of the  
12 methods, are the pharmacokinetic methods, pharmacodynamic  
13 methods, comparative clinical trials, and in vitro studies.

14 For most of the bioavailability, as well as the  
15 bioequivalence, primarily, the bioequivalence studies, the  
16 method of choice is the pharmacokinetic methods. I will go  
17 slightly in more detail into it.

18 [Slide.]

19 In terms of pharmacokinetic studies, the guidance  
20 does provide information on the general considerations and  
21 the study conduct, how the study needs to be performed. It  
22 also provides the definitions for the pilot study and the  
23 pivotal study, how and what it needs to be done.

24 The study design is a single-dose design. With  
25 respect to that, there are several different types of it.

1 The simplest one is the crossover design for all immediate  
2 release products, and the data analysis is done using the  
3 ABE, meaning the average bioequivalence.

4 That is our standard way, how the studies are  
5 conducted today, how the data are analyzed, and there is no  
6 change in that particular aspect. It is a single-dose,  
7 crossover study for all immediate release dosage products  
8 except one exception, coming down here, and the data  
9 analysis is average bioequivalence.

10 Again, I would like to point out that this was the  
11 area which was heavily discussed and debated in front of  
12 this committee for last three, four years probably, and we  
13 took the advice of these committee members plus the expert  
14 members, and have come to these conclusions.

15 So, for the immediate release dosage forms,  
16 crossover, single-dose study, using the average  
17 bioequivalence criteria.

18 For the modified release dosage forms, again, it  
19 is a single-dose study, but we are recommending a replicate  
20 study design, but still the calculation is based on the  
21 average bioequivalence, because it was felt that if at all  
22 we are going to see any subject by formulation interactions  
23 or any other issue for which the replicate study would be  
24 useful, this would be the best scenario.

25 That was the recommendation again that came from

1 this panel, as well as the Blue Ribbon Expert Panel  
2 Committee, and we decided to go with that, that we will use  
3 the replicate design and still request the same way of drug  
4 approval as it is being done now, and that is to use the  
5 average bioequivalence criteria for the drug approval  
6 purposes.

7           The area where we felt--and that was again the  
8 recommendations--that the individual bioequivalence would be  
9 very useful using a replicate design, would be to use for  
10 the highly variable drug products.

11           This is a scenario where if you want to do the  
12 standard single-dose, crossover study design, then, it may  
13 require, depending upon the variability, anywhere between 60  
14 to 100 to 150 subjects. In order to avoid that, the  
15 replicate study design and the use of the individual  
16 bioequivalence criteria will definitely lower the number of  
17 subjects needed, and it will make it easier for the drug  
18 approval purposes.

19           So, those are the three different types of the  
20 studies and the analysis that will be done in terms of the  
21 pharmacokinetic studies, and they are defined in detail in  
22 the general guidance.

23           Also, with respect to the pharmacokinetic measures  
24 of the systemic exposure and the total exposure, the  
25 guidance is also trying to move away from the classical

1 terms of define the rate and extent of bioavailability into  
2 the systemic exposure terms of bioavailability. I think I  
3 have a slide for that, too.

4           What it is talking about is three different ways  
5 of exposure measures. One is called the early exposure,  
6 which is an area under the curve, truncated maybe up to the  
7 T<sub>max</sub> of the median reference product. The peak exposure  
8 would give the same as the C<sub>max</sub>, and the total exposure,  
9 meaning the area under the curve. So, these are the three  
10 different terms of exposure measures which is described in  
11 detail in the guidance.

12           [Slide.]

13           The last two measures, the peak and the total, are  
14 the same as we are doing it today, and we feel that the  
15 early exposure might be useful in some cases of the  
16 immediate release products where you would like to have a  
17 very rapid onset of the drug product, of the drug, for  
18 example, in cases of the nonsteroidal anti-inflammatory  
19 agents, you would like to have a very slow drug  
20 administration, and not a very rapid total dose to be  
21 released at the same time.

22           So, those are the cases where the early exposure  
23 criteria might be useful.

24           [Slide.]

25           For the immediate release products, the general

1 considerations, the focus is on the release of the drug  
2 substance from the drug product into the systemic  
3 circulation, and the requirements are the in vivo single-  
4 dose study, they need to perform the in vitro dissolution  
5 study, and the exposure measures as the total exposure and  
6 the peak exposure, and since it is an immediate release, if  
7 there is a need then, and early exposure measures need to be  
8 defined here.

9 [Slide.]

10 For the biowaivers, as you heard from the previous  
11 speaker, Dr. Ajaz Hussain, that for products which are  
12 highly soluble, highly permeable, and rapidly dissolving,  
13 you don't need to do any in vivo bioequivalence studies.  
14 You can get the biowaivers, and for the lower strengths for  
15 the immediate release products, you can get the biowaivers  
16 as long as they are proportionally similar, and you need to  
17 perform the dissolution profile comparisons.

18 Whenever we use the word "dissolution profile  
19 comparison," we are again talking about the total profile  
20 determination, and using simple statistical calculation  
21 using the criteria, what we have defined as the f2 criteria,  
22 which is a simulated factor, and the value has to be either  
23 50 or greater when you apply these equations.

24 Now, if the product is very rapidly dissolving  
25 like in the case of the BCS Classification, one where the



1 dissolution is more than 85 percent in 15 minutes, then, you  
2 do not need to have the profile. Otherwise, in every case  
3 we need to have the profile and the profile comparison to be  
4 done using the f2 criteria. So, you provide that type of  
5 comparison.

6 [Slide.]

7 For the modified release dosage forms, just to  
8 summarize it, for the bioavailability studies, which is for  
9 the new drug applications, is single-dose fasting study on  
10 all the strengths, a single-dose food-effect study at the  
11 highest strength, and a steady state study using the highest  
12 strength. These would be the minimum requirements for the  
13 new drug applications.

14 For the bioequivalence studies, which is primarily  
15 the ND applications, a single-dose replicate bioequivalence  
16 study at the highest strength comparing the test and the  
17 reference product, and a food-effect study at the highest  
18 strength.

19 Please note here that there is no requirement for  
20 a multiple-dose study in the case of the bioequivalence  
21 studies.

22 [Slide.]

23 Why do we do that? Because we feel that a single-  
24 dose study is considered more sensitive in assessing the  
25 primary question in a bioequivalence study, that if the

1 release of the drug substance from the drug product into the  
2 systemic circulation, we feel that the multiple-dose study  
3 is not generally needed, and therefore it is not  
4 recommended, and that is the reason why we recommend only a  
5 single-dose study for the modified release, extended release  
6 dosage forms.

7 [Slide.]

8 The studies are done only at the highest strength,  
9 while the lower strength provide the biowaivers. In the  
10 case of the beaded capsules, the only difference between the  
11 different strengths is the number of the active beads, and  
12 therefore, you need to do the dissolution profile comparison  
13 of different strengths under the approved single dissolution  
14 best conditions.

15 For the tablets, it needs to be again the same  
16 dosage form, should be proportionally similar in the active  
17 and inactive ingredients, and should be having the same drug  
18 release mechanism.

19 Under those circumstances, you need to do the  
20 dissolution profile comparison at least in three media,  
21 namely, pH 1.2, 4.5, and 6.8, so that we can get an  
22 assurance that even the different strengths will be behaving  
23 in the same manner as the highest strength, and again in  
24 this case, you need to do the profile comparisons.

25 This particular system would be also applicable

1 for the approval of the biowaivers for the postapproval  
2 cases.

3 [Slide.]

4 There are three other features which are also  
5 clearly discussed in the guidance, one being the parent drug  
6 versus the metabolites. Should metabolite be measured for  
7 the bioequivalence studies or not, and if so, then, under  
8 what circumstances?

9 It clearly says that as far as the bioavailability  
10 studies are concerned, both the parent drug and the  
11 metabolite should be measured and quantitated, but the  
12 reduction in burden comes when we go into the bioequivalence  
13 study requirements, where the recommendation is you measure  
14 only the parent drug.

15 There are some cases where you may not be able to  
16 measure the parent drug, and you may have to measure the  
17 metabolites. Now, those are identified here. The  
18 measurement of a metabolite is preferred when the parent  
19 drug levels are too low to allow the reliable measurements  
20 in the biological fluids.

21 In that particular case, you measure the  
22 metabolites and all the bioequivalence criterias of the drug  
23 approval should be made based on the metabolite itself.

24 In the second case, when the metabolite  
25 contributes significantly to the safety and/or the efficacy

1 of the drug product, then both the parent drug and the  
2 metabolite should be measured. But in this particular  
3 scenario, the parent drug would be the prime criteria for  
4 the bioequivalence evaluation and determination, and the  
5 metabolite would be providing supporting information for the  
6 drug approval process.

7 [Slide.]

8 The second situation is the measurements of the  
9 enantiomers versus the racemates. There have been some  
10 cases where people are indicating that even for the  
11 bioequivalence study, you need to measure all the  
12 enantiomers which are present in the compound, but the  
13 guidance now provides a clear-cut definition that that is  
14 not necessarily a requirement.

15 For the bioavailability studies, the measurements  
16 of both the enantiomers should be done, but for the  
17 bioequivalence study, the racemates, using a chiral assay,  
18 is recommended unless all these following four criterias are  
19 met, and those are the enantiomers exhibit different  
20 pharmacodynamic characteristics, enantiomers exhibit  
21 different pharmacokinetic characteristics, the primary  
22 efficacy or the safety resides with the minor enantiomer,  
23 and the nonlinear absorption is present for at least one of  
24 the enantiomers.

25 If all these four criterias are in existence,

1 then, both the enantiomers should be measured for the  
2 bioequivalence study, and in that particular case, the  
3 bioequivalence criteria of confidence interval would be  
4 applied to both the enantiomers.

5 [Slide.]

6 The third important factor in the guidance is for  
7 the long half-life drugs. Again, here, for the  
8 bioavailability purposes, there should be a complete total  
9 characterization of the half-life of the drug and total area  
10 under the co-measurements, but for the bioequivalence  
11 purposes, it was felt that that is not necessary.

12 The partial area under the curve, truncated to a  
13 certain point, could be used for the calculations of the  
14 bioequivalence, and those are the collection of adequate  
15 sampling time to ensure the completion of the GI transit  
16 time of the drug product and the absorption of the drug  
17 substance, and generally, that is considered to be 72 hours  
18 will be sufficient enough, and therefore, area under the  
19 curve could be truncated up to 72 hours.

20 [Slide.]

21 So, these are the general features of our BA and  
22 BE guidance, and now these old guidances, which were there,  
23 would be eliminated because now the general BA/BE guidance  
24 supersedes that and those are the two guidelines which came  
25 out in 1984 and 1993 for the extended release dosage forms

1 and the statistical guidelines, and also several drug-  
2 specific bioequivalence guidances which were put out, all  
3 these guidances would be removed from the web page  
4 eventually.

5 [Slide.]

6 Now, the impact of this guidance is it reduces the  
7 regulatory burden while maintaining the sound scientific  
8 principles consistent with the public health objectives of  
9 maintaining the optimally performing drug product on the  
10 market.

11 In brief, it provides the biowaivers for the lower  
12 strengths of the immediate release products, modified  
13 release beaded capsules, and modified release tablet dosage  
14 forms, biowaiver for the higher strength of the immediate  
15 release product.

16 In some cases, if you find, for the new drug  
17 applications, after the studies are done, and you find that  
18 there is a need to increase the dose once the product is on  
19 the market, then, provided you have studied that higher dose  
20 one way or the other in your initial clinical studies, then,  
21 the higher dose waiver could be provided based on the  
22 dissolution profile comparison it provides.

23 It also eliminates the multiple-dose  
24 bioequivalence study requirements for the modified release  
25 dosage forms, and there is a reduced emphasis on measuring

1 the metabolites in bioequivalence studies. We think that  
2 all these features do help in reducing the regulatory burden  
3 without lowering or minimizing the quality of the product.

4 Thank you very much. I will be happy to answer  
5 any questions.

6 DR. BYRN: Questions for Vinod?

7 DR. VENITZ: I am interested in this issue of  
8 parent compound versus metabolite measurement. Let me give  
9 you two scenarios, and if you could explain to me how the  
10 guidance would handle that.

11 You have a drug that is known to be a prodrug, so  
12 the parent compound presumably is inactive. The metabolite  
13 carries efficacy and safety issues. You can measure both of  
14 them.

15 Let's assume you do a study and you find that in  
16 terms of the parent compound, the product fails, but in  
17 terms of metabolite, the product passes. What would that  
18 mean?

19 DR. SHAH: Now, let me go back. Are you able to  
20 measure the parent drug?

21 DR. VENITZ: I am able to measure both of them,  
22 yes.

23 DR. SHAH: You are able to measure the parent  
24 drug. Then, it will be the parent drug itself that we will  
25 be measuring for the bioequivalence purposes.

1 DR. VENITZ: Even though the parent compound has  
2 no pharmacologic activity? I am saying it is a prodrug, so  
3 the parent drug itself is inactive. The metabolite has the  
4 pharmacologic activity.

5 DR. SHAH: In that particular case, you measure  
6 all the metabolite. If you are not able to measure the  
7 parent drug completely and quantify that in terms of its  
8 absorption and elimination characteristics, if you are not  
9 able to get a total profile for that parent drug, whether it  
10 is a prodrug or not, then, you go into the metabolite.

11 DR. VENITZ: But if the metabolite and the parent  
12 compound tell me opposite things as far as the  
13 bioavailability or bioequivalence assessment is concerned,  
14 how do you handle that? Which one counts more or do they  
15 count equal? You could have a scenario where one of the two  
16 fails, and one passes, and what does that mean with respect  
17 to the product, is that a bioequivalent product or not?

18 DR. SHAH: If you have to measure a metabolite  
19 under the circumstance of 10, it should pass both the  
20 requirement of parent drug and the metabolite, if you have  
21 to measure the metabolite.

22 DR. VENITZ: If I am able to measure both, and one  
23 passes, the other one does not, what does that mean with  
24 respect to the product that you are testing?

25 DR. SHAH: Then, only the parent drug is required,



1 not the metabolite.

2 DR. VENITZ: Even if the parent compound is  
3 completely inactive?

4 DR. SHAH: Yes.

5 DR. VENITZ: So, you could have a scenario where  
6 you are basing the equivalence on an inactive moiety.

7 DR. SHAH: Because what is happening is something  
8 is changing in the body rather than the molecule itself,  
9 because what are we really interested here, we are comparing  
10 the two products, where the only difference is in the  
11 formulation, and not difference anywhere else.

12 So, that should be easily picked up by the parent  
13 drug itself, and if you are able to measure that. We are  
14 interested in the drug release of the product until it goes  
15 into the systemic circulation. That is what we are  
16 measuring, yes.

17 DR. VENITZ: Could I just follow up? I would make  
18 the argument that the parent compound, if it is inactive, is  
19 clinically irrelevant.

20 DR. SHAH: Okay.

21 DR. LAMBORN: I think I wanted to follow up. I  
22 can't believe that the circumstances, if it is feasible to  
23 have the parent pass, and the other not pass, if that could  
24 occur, I am sure that the requirement would be that they  
25 both must pass, because it is just not--maybe you are

1 thinking of it in terms of the fact that it would never  
2 happen, but if it did happen, then, clearly, the active  
3 metabolite has to be equivalent in order to have  
4 bioequivalence.

5 DR. VENITZ: That is basically what I am saying.

6 DR. BYRN: I thought the question was the reverse,  
7 but it is the question the parent passes, the metabolite  
8 doesn't, or is it the reverse?

9 DR. VENITZ: Or vice versa. If you get  
10 conflicting results by looking at parent compound versus  
11 metabolite, which one counts more? What he is saying, I  
12 think, is that the parent compounds, if you can measure,  
13 counts more, it overrides even though it might be  
14 pharmacologically inactive.

15 I am saying clinically, that doesn't make sense.

16 DR. LAMBORN: I think it has to be a  
17 misunderstanding for you to answer the way you answered.

18 MS. WINKLE: Larry is co-chair of the  
19 Bioequivalence Coordinating Committee, and we have several  
20 clarifications that we want to make on this, as well as on  
21 our recommendations for IBE.

22 DR. LESKO: Thanks, Steve. Thanks, Helen. I am  
23 Larry Lesko from FDA. I chair the BCC, Biopharm  
24 Coordinating Committee with Dale Conner from Office of  
25 Generic Drugs.

1 I do want to make a correction to a slide that Dr.  
2 Shah showed, which I think is a very critical correction.  
3 He had a slide which recommended replicate design studies  
4 for modified release products and for highly variable drugs.

5 Part of the slide was correct, but part of it was  
6 incorrect. I don't know if you want to flip to that slide,  
7 Steve, to bring it back up on the screen.

8 [Slide.]

9 DR. LESKO: In the guidance, if you look at the  
10 section of the slide on Study Design - Single Dose, the  
11 guidance is correct and it recommends crossover design for  
12 most immediate release drug products.

13 The slide is also correct when it states that the  
14 guidance recommends replicate design for modified release  
15 products and highly variable drug products whether they are  
16 immediate or modified release.

17 I won't go into the reasons for that, but they are  
18 delineated in the guidance on page 7 as to why we have  
19 recommended replicate designs for these particular drug  
20 products, and we felt there were significant advantages to  
21 the information that we would acquire from these types of  
22 studies. That is in the guidance. I think we put five or  
23 six reasons.

24 I think the key point people need to understand,  
25 however is that the analysis of these bioequivalence

1 studies, not matter what they are, should be average  
2 bioequivalence. We do not recommend in the guidance  
3 individual bioequivalence for any of these replicate design  
4 studies.

5           What we do say, however, is if a sponsor or an  
6 applicant has a strong rationale for proposing an  
7 alternative method for analyzing these replicate design  
8 studies, whether it be individual bioequivalence or anything  
9 else, they could come in and discuss that on a case-by-case  
10 basis with the Agency.

11           So, that is a difference then in what Dr. Shah  
12 presented in that presentation. That is important to  
13 clarify. So, in a sense, we expect average bioequivalence  
14 as a routine, but the sponsor does have that option to come  
15 in and make a case and rationale for an individual  
16 bioequivalence approach or a population bioequivalence  
17 approach, or whatever else they feel would be appropriate  
18 for their product, and they should do that most likely in  
19 advance before the study is conducted, and not after the  
20 fact.

21           So, that was the clarification.

22           DR. SHAH: So, they can do either individual or  
23 average, right?

24           DR. LESKO: No. You are making it seem like the  
25 company can make that choice. We are recommending average

1 bioequivalence as a routine. They don't have to come in and  
2 ask the FDA, they can just do the analysis of the replicate  
3 design using average bioequivalence. We are recommending  
4 that as the default procedure, if you will.

5           The guidance says, however, a sponsor may have a  
6 strong argument or a strong rationale to feel they can use  
7 another method, IBE, population BE, or however else they  
8 want to analyze that data, but then they need to come in and  
9 explain that prior to conducting their study. There is a  
10 difference.

11           DR. SHAH: Okay. Sorry.

12           DR. ANDERSON: In your statement on general  
13 considerations, you indicated that this method I suppose  
14 uses sound scientific principles, et cetera, et cetera, you  
15 see where I am?

16           There is a process up here which was followed to  
17 reach the final guidance in October 2000. I want to  
18 concentrate on without sacrificing product quality.

19           Was there anything in the process for getting to  
20 the final guidance that would give you evidence that you are  
21 not sacrificing product quality?

22           DR. SHAH: Yes, like we had the discussions at  
23 this advisory committee meeting. We also had the  
24 discussions at the expert panel meetings. We also had the  
25 discussions at the annual AAPS meeting. We also had the

1 discussions with the international meetings of that nature  
2 where we had discussed the general guidance and the  
3 principles behind that. The summary of all that is that is  
4 what we came to the conclusion.

5 DR. ANDERSON: I guess one thing I left out. Did  
6 you have any laboratory science data?

7 DR. SHAH: No, we did not have any laboratory  
8 science data, but that is why we are adding the dissolution  
9 profile comparisons rather than having a single-dose and the  
10 multiple-dose studies, or single time point studies. We are  
11 saying that if you have the total profile comparison between  
12 the two different strengths, then, we would be at ease to  
13 provide the biowaiver for the lower strengths.

14 DR. ANDERSON: I think I understand the individual  
15 elements, but when you put everything together, you don't  
16 really have the laboratory data that suggests that there is  
17 no sacrifice in the product quality.

18 DR. SHAH: We did not have the in vivo data, but  
19 all the data that we have in the Agency, we have taken a  
20 look at it, and all will meet the dose criteria. That is  
21 why we came to that conclusion. Those were the studies  
22 which has passed before, and there was nothing that we need  
23 to worry about.

24 DR. LESKO: I wanted to maybe clarify the question  
25 that Dr. Venitz raised on metabolite, because I feel there

1 is sort of confusion about that, and some logical confusion.

2           The first principle that we worked with in terms  
3 of a parent drug and a metabolite, and the parent drug is  
4 called in our regulations the "active moiety" in the dosage  
5 form even though it may not be pharmacologically active.

6           We have a footnote in the guidance that kind of  
7 gets into that, the dosage form may contain an active and an  
8 inactive ingredient. The active ingredient may be a prodrug  
9 that requires transformation to an in vivo metabolite or  
10 active metabolite, or something like that, so it gets a  
11 little confusing with the terminology.

12           Let's just talk about it practically. If you had  
13 a prodrug that was administered and then converted into an  
14 active metabolite, there are a number of issues that would  
15 come up there. The first question might be is that prodrug  
16 measurable with reliable analytical methods, and can you  
17 look at it over time as would be necessary in a  
18 bioequivalence study.

19           If that were yes, I think we would look at that  
20 prodrug as a measure of bioequivalence separate and apart  
21 from the fact that it is not pharmacologically active. The  
22 reason is that the goal of a bioequivalence study is to look  
23 at the release of the active ingredient as defined in our  
24 regulations which include a prodrug from the dosage form,  
25 and the prodrug would then be the marker for the release of

1 a drug substance from a dosage form.

2           If you said no, I am not going to look at a  
3 prodrug, I am going to look at a metabolite, you confound  
4 the bioequivalence determination to the degree that the  
5 metabolite profile is a function of two things, its release,  
6 the release of its parent, and its conversion to a  
7 metabolite, as well as the clearance of the metabolite.

8           So, the question is what are you measuring when  
9 you measure the area under the curve of a metabolite. It is  
10 confounded by both absorption, as well as elimination, and  
11 it is not a clear indicator of bioequivalence.

12           So, I would say that we would prefer to look at  
13 the prodrug when it could be measured adequately and over  
14 time.

15           Now, there is a second part to the story. If  
16 there is a metabolite that contributes significantly to  
17 safety or efficacy, we recommend that that metabolite be  
18 measured, and we say in the guidance that the measurement of  
19 that metabolite can be used as supportive information  
20 relative to the determination of bioequivalence. So, we  
21 don't ignore an active metabolite. We do recommend that you  
22 measure it.

23           The last part of that is, well, how do you make a  
24 regulatory decision on bioequivalence, and if the metabolite  
25 is the reliable entity that you are measuring in the blood,



1 the prodrug is too low, you can't measure it, we would use  
2 confidence intervals on the metabolite.

3 On the other hand, if you had both prodrug and  
4 metabolite, measurable adequately over time, we would put  
5 confidence intervals on the prodrug, because we feel that  
6 measures the dosage form performance, and we would look at  
7 the metabolite for any significant differences, and if there  
8 were some, it would raise some questions.

9 So, I hope that sort of addresses your question to  
10 some degree.

11 DR. SHAH: I guess that is what it is on the slide  
12 and is consistent with what Larry has indicated and what we  
13 discussed.

14 DR. BYRN: Any other questions? I am sure, like  
15 in other cases on this matter, that the Agency, if you are  
16 getting conflicting data like the question raised, that that  
17 would be a strong indication that you would communicate with  
18 the Agency immediately and discuss the issue in a meeting or  
19 a conference call.

20 Any other questions? Identify yourself, please.

21 MR. RASHID: I am Abdur Rashid from Pharma  
22 Kinetics Labs.

23 What is the requirement for food studies for  
24 immediate release products?

25 DR. SHAH: I suggest you wait until the food

1 effect guidance comes out.

2 MR. RASHID: Okay. I have another question. You  
3 did not discuss the population requirement for these kinds  
4 of studies, and this is much different from we used to see  
5 in the standard guidances.

6 Now, the recommendation for enrollment of women  
7 and elderly?

8 DR. SHAH: Well, this was just a brief update, but  
9 what we are recommending in the guidance is you need to try  
10 and get as many different subjects as possible, different  
11 types of subjects, different races and all, but the main  
12 statistical analysis is to be only between the products.  
13 You do not have to do the subsections and subcriterias,  
14 subcategorizing with respect to the statistical analysis.

15 If you have a product that is going to be  
16 administered, let's say, primarily in elderly patients,  
17 then, we would recommend that you try and get at least 60  
18 percent of the population which would be of that particular  
19 age.

20 So, that is a recommendation. Again, we are  
21 indicating you need to try your level best to get that type  
22 of population rather than just using under normal, healthy  
23 subjects, which normally, the studies are done in the  
24 students of 18 to 24 years of age primarily.

25 DR. BYRN: Dr. Lesko.

1 DR. LESKO: I would like to just elaborate on the  
2 answer that Dr. Shah provided on the food studies, because  
3 not everyone may be aware of the situation with the food  
4 study guidance.

5 Currently, as the question was posed, I would  
6 recommend that the people that do food studies and  
7 bioequivalence follow the current procedures that FDA has in  
8 place, which are the traditional procedures. We haven't  
9 changed anything with respect to food studies at the moment.

10 Dr. Shah was referring to a food study guidance  
11 that we have published on the Internet for public comment,  
12 and we are currently reviewing those comments and trying to  
13 rewrite our guidance on food studies in light of those  
14 comments.

15 That process isn't done yet, and you can't, at  
16 this point, for example, conduct food studies as was  
17 described in our draft guidance that we put on the Internet,  
18 because after the public comment period, we did make some  
19 changes in that guidance, so it is going to be different  
20 than what was on the Internet, but it is not complete and we  
21 don't anticipate completing that until the first quarter of  
22 next year.

23 So, my sense at this point is we are going to put  
24 that guidance out again for public comment on the Internet,  
25 and then after that, we will proceed to finish it. So, I

1 think it is important people realize that the food study  
2 requirements are those that were currently in place.

3           While I am here, I am might as well elaborate a  
4 little bit on our thinking since I was involved with it on  
5 the population. We felt in the recruitment of subjects for  
6 bioequivalence studies, it is important to capture test  
7 subjects that are as close to the actual patients that will  
8 be involved with switchability in terms of generic drugs,  
9 for example, and we have recommended to sponsors to broaden  
10 the recruitment of subjects into these bioequivalence  
11 studies.

12           What that means is we would not want necessarily  
13 to see exclusion criteria for certain parts of our  
14 population as has been done sometimes in the past where it  
15 was male volunteers between a certain age, and so on, and so  
16 forth. We would hope that sponsors would not exclude  
17 certain subpopulations or subsets of the population, but  
18 make an attempt to include a representative population in  
19 these types of studies.

20           DR. BYRN: Any other questions?

21           MR. AGRAWAL: I am Mukal Agrawal from Roxanne  
22 Labs.

23           When the labeling for an innovative product says  
24 that there is no documented food effect, and a generic firm  
25 is trying to develop a product, what is the requirement for

1 a food effect bioequivalence study?

2 DR. SHAH: Is it immediate release or modified  
3 release?

4 MR. AGRAWAL: Immediate release.

5 DR. SHAH: Then, if there is a labeling which says  
6 no food effect, then, you don't need to do any food effect  
7 studies. That is our current standards.

8 Just one clarification again coming up from the  
9 two different BCC chairs.

10 DR. LESKO: I apologize for these corrections, but  
11 I think they are necessary, so there is no confusion, and  
12 both Dale and I are both at the microphone. We are co-  
13 chairs of the Biopharmaceutics Coordinating Committee.

14 If a label, in fact, says what the gentleman said,  
15 my understanding is that for a generic product, they would  
16 have to conduct a food study for a generic product. If the  
17 label says there is no food effect, that means the test  
18 product would also have to have a confirmation study that  
19 demonstrates no food effect, and therefore, a fasting and a  
20 food study would be required for that generic product.

21 DR. CONNER: Requested for the product.

22 Just another clarification or addition to what  
23 Larry said before, and what he said about what we ask for,  
24 for food. Only one small thing changed in this guidance  
25 about food studies, and this one is to the sponsor's

1 benefit, in that if you will recall, before, we did a three-  
2 say food study, so we had the test under fed conditions, the  
3 reference under fed conditions, and we also did an  
4 additional arm of the test under fasting conditions.

5 The original thought was, well, we will figure out  
6 how much of a food effect between fasting and fed there is,  
7 but when you really think about it, that is kind of a nice  
8 to know, and not necessary for making a judgment whether  
9 this product is truly equivalent in the fed state.

10 I think it is probably two sentences or so that  
11 deal with food studies in this guidance. That actually has  
12 been changed. So, in effect now we have a two-way study,  
13 fed test versus fed reference, and that third arm, the nice-  
14 to-know arm has been eliminated by this guidance.

15 We have other changes in the works, as Larry  
16 referred to, but it will be a considerable amount of time  
17 before those are finalized.

18 DR. BYRN: One more time. Are there any more  
19 questions?

20 [No response.]

21 DR. BYRN: These comments are excellent to clarify  
22 the guidance, so I think this is very worthwhile, so thanks  
23 to everybody for their comments.

24 We will go to the next discussion, which is an  
25 update on a guidance. Mei-Ling Chen is going to give us an

1 update on the Average, Population, and Individual Approaches  
2 to Establishing Bioequivalence.

3 Average, Population, and Individual Approaches  
4 to Establishing Bioequivalence

5 DR. CHEN: Chairman and members of the advisory  
6 committee, it is my pleasure to give you an update on the  
7 guidance for industry.

8 [Slide.]

9 Over the last decade with the advances in  
10 knowledge and the methodology, the FDA has published three  
11 statistical guidances on bioequivalence, and they are listed  
12 on this slide.

13 The first guidance, published in 1992, focused on  
14 the average bioequivalence using standard two-treatment  
15 crossover design.

16 The second guidance, issued in 1997, the  
17 preliminary draft guidance, it talked about population and  
18 individual bioequivalence approaches.

19 In the third guidance, published in 1999, last  
20 year, that was the most recent document on the topic.

21 [Slide.]

22 As reflected in the title, the 1999 draft guidance  
23 incorporates the 1992 guidance, updates the 1997 preliminary  
24 draft guidance. It focuses on the various study designs,  
25 statistical criteria, and the methodologies for establishing

1 bioequivalence. However, this guidance does not deal with  
2 the question of when to use a specific criterion. As you  
3 know, this question has been addressed in a general  
4 bioavailability and bioequivalence guidance that was  
5 discussed by the previous speaker, Dr. Vinod Shah.

6 [Slide.]

7 In terms of regulatory application, as you all  
8 have heard, that the Agency has essentially followed the  
9 recommendation of this advisory committee from the last  
10 committee meeting in September 1999.

11 Replicate designs are recommended for modified  
12 release dosage forms and highly variable drugs. Average  
13 bioequivalence is recommended for most bioequivalence  
14 studies, however, sponsors and applicants have the  
15 opportunity to provide rationale for using another  
16 criterion, for example, individual bioequivalence for highly  
17 variable drug products.

18 Currently, population bioequivalence is proposed  
19 for use in the in vitro testing of nasal and oral inhalation  
20 drug products.

21 [Slide.]

22 This slide shows the outline of the guidance. The  
23 guidance covers three criteria and talks about the various  
24 study designs including replicate study designs, non-  
25 replicate study designs, and parallel designs.



1           This guidance also includes a section that deals  
2 with the miscellaneous issues that are often encountered  
3 during analysis of bioequivalence studies, such as studies  
4 in multiple groups, carryover effect, and outlier questions.

5           At the end of the document, there are eight  
6 appendices that provide further details of all the  
7 statistical methods.

8           [Slide.]

9           For the benefit of new members on this advisory  
10 committee, I would like to briefly go over the general  
11 principles and the concepts for these three criteria, and  
12 then highlight the changes to the draft guidance.

13           The main differences among the three criteria is  
14 that the current approach, average bioequivalence, focuses  
15 on a comparison of population means between the test and the  
16 reference product.

17           The population bioequivalence and the individual  
18 bioequivalence compare both means and variances.

19           [Slide.]

20           So, in general, an equivalence approach relies on  
21 a criterion to allow comparison, a confidence interval for  
22 this criterion and a predetermined bioequivalence limit, and  
23 this slide outlines the corresponding formula for the three  
24 bioequivalence criteria.

25           [Slide.]

1           A key concept for the proposed population and  
2 individual bioequivalence criteria is to compare the  
3 distance measure between the test and reference  
4 formulations, T-R, with that of the reference formulation  
5 against itself, R-R-prime. So, the distance measure is  
6 expressed by the expected squared difference and this  
7 comparison is denoted as a ratio of the two distance  
8 measures indicated on this slide.

9           [Slide.]

10           Derived from the distance concept, you can see  
11 that both population and individual bioequivalence criteria  
12 compare the distribution, that is, the combination of the  
13 mean and the variance between the test and the reference  
14 products, and that result in a general form as shown on this  
15 slide.

16           So, you may have noted that the general form  
17 appears as a comparison to the reference variance, and that  
18 is why it is often referred to as reference scaling.  
19 Reference scaling means that both criteria are scaled to the  
20 variability of the reference product, and it is logical in  
21 the way that reference to a product has been demonstrated to  
22 be safe and effective clinically, so its variability, well  
23 defined to therapeutic window and therefore, it should  
24 determine the bioequivalence limit of the drug product.

25           [Slide.]

1           However, some comment has expressed concerns that  
2 this criterion with both means and variance in one equation  
3 also with the reference scaling, a test product with a large  
4 average difference might be approved.

5           To address this point, the current guidance  
6 indicates that further constraint on the point estimate of  
7 the geometric test and reference mean ratio to fall within  
8 80 to 125 percent. So, in addition to the bioequivalence  
9 limit based on the confidence intervals, we will require  
10 constraint on the mean difference.

11           [Slide.]

12           After the publication of this draft guidance in  
13 August 1999, we only received a dozen or so public comments.  
14 The Working Group has reviewed these public comments. The  
15 draft guidance has been revised by the Working Group and the  
16 Biopharmaceutics Coordinating Committee.

17           The guidance is now going through the internal  
18 clearance, and we hope that we can publish the final  
19 guidance soon.

20           That is my update today. Thank you.

21           DR. BYRN: Questions for Dr. Chen? Yes, Kathleen.

22           DR. LAMBORN: I was interested in your statement  
23 about where this use of the population bioequivalence stood.

24           In the one slide it says that population bioequivalence is  
25 used in the in vitro testing of the nasal and oral

1 inhalation, and when you spoke, you said it is proposed for  
2 use.

3 Is it currently the method in place or is it just  
4 part of the proposed guidance?

5 DR. CHEN: It is included in the draft guidance  
6 for nasal and oral inhalation products, and the draft  
7 guidance has been published on Internet, and that is the  
8 guidance that Dr. Wally Adams discussed yesterday.

9 DR. LAMBORN: That is why I asked. So it is, in  
10 fact, not part of an existing approved guidance, it is part  
11 of a proposed guidance.

12 DR. CHEN: Correct.

13 DR. LAMBORN: I just wanted to make sure I  
14 understood.

15 DR. BYRN: Other questions for Dr. Chen?

16 [No response.]

17 DR. BYRN: Thank you very much.

18 Let's take a 10-minute break. We have gone over a  
19 little bit, so I think we can take a 10-minute break and  
20 resume here within 10 minutes, by 10:25 by my watch.

21 [Recess.]

22 DR. BYRN: Technically, we are not supposed to  
23 have questions from the floor during this part of the  
24 meeting, however, we have deviated from that on occasion  
25 when it seemed important, and we did do that this morning.

1 We don't have major regrets about that, but we are not  
2 supposed to do it.

3 So, what we are going to do on this part of the  
4 meeting, since we have a discussion and then an open hearing  
5 after lunch, is we will go ahead with the presentations.  
6 Then, the committee will discuss. Then, after lunch, we can  
7 have questions.

8 Unless there is some question that you just can  
9 absolutely not stand it any further and must interrupt the  
10 meeting, then, we will recognize you, but we will try to  
11 follow that procedure. Then, we will be more in line with  
12 the guidances that we operate under because we don't want to  
13 deviate from those.

14 This is going to be a very interesting session on  
15 Clinical Pharmacology. The first speaker is Dr. Larry  
16 Lesko, and he is going to speak on Modeling and Simulation  
17 Introduction.

#### 18 CLINICAL PHARMACOLOGY

#### 19 Modeling and Simulation Introduction

20 DR. LESKO: Thank you, Steve, and good morning,  
21 everybody.

22 I think everyone, at least up on the stage, has a  
23 copy of the slides that I will showing to introduce this  
24 topic for discussion before the committee. Those in the  
25 audience will have the advantage of looking at 3D blurry

1 slides, it looks like. I see a lot of shadows on those  
2 slides, but we will have to bear with it.

3 [Slide.]

4 This is a topic that we like to bring before the  
5 committee to have some discussion that probably is part of a  
6 foundation of further discussion on the applications of  
7 modeling and simulation in the future as we move with the  
8 trends in technology and applications in drug development,  
9 to modeling and simulation becoming a more important part of  
10 regulatory review and decision-making.

11 [Slide.]

12 I would first say that this is not a revolutionary  
13 topic for public discussion. In the past, modeling and  
14 simulation has been an integral part of the way FDA conducts  
15 business.

16 There are many applications of modeling and  
17 simulation in the disciplines of clinical pharmacology,  
18 biostatistics, and clinical medicine. They range from PK/PD  
19 modeling to power analysis to study design.

20 But I think that there is within the Agency is a  
21 consensus view of need, that we have to move from the  
22 stovepipes, if I can call it that, of modeling and  
23 simulation in respective disciplines to a more broad  
24 consensus view of the need for modeling and simulation in  
25 the regulatory environment.

1           So, I see the need then for better integration of  
2 modeling and simulation across discipline lines, and I think  
3 of clin pharm biostat in clinical medicine as those  
4 discipline lines, and a development of a common technical  
5 framework to ensure that models and simulation are useful  
6 and meets the needs of biostatisticians, clinical  
7 pharmacologists, and clinicians.

8           [Slide.]

9           Now, over the past, as I said, modeling and  
10 simulation has been a routine part of regulatory decision-  
11 making, and I have many examples of this from the past five  
12 years. I will call them success stories. Of course, there  
13 are also unsuccessful stories, which I won't present today,  
14 but, for example, some of the success stories are the  
15 bioequivalence of metered dose inhaler products and topical  
16 corticosteroid products, which involve modeling and, in some  
17 cases, simulation, to make a determination of bioequivalence  
18 of innovator and test products.

19           Over the years, the Office of Clinical  
20 Pharmacology and Biopharmaceutics has contributed to  
21 decisions on the approval of products for over-the-counter  
22 use, for prescription use, where there were specific safety  
23 questions related to exposure-response relationships, where  
24 clinicians would pose "what if" questions, and we would use  
25 modeling and simulation to provide the options to the

1 physician or decision-making on approval.

2           Also, over the last couple of years we have had  
3 many cases of approving changes in doses of previously  
4 approved products, dosing regimens or route of  
5 administration on the basis of a modeling and simulation  
6 exercise that answered the questions about relative risk and  
7 efficacy and safety.

8           Also, in the past we have had a number of  
9 guidances in the clinical pharmacology master plan--I will  
10 call it that. We have brought some of those guidances for  
11 discussion before this committee on drug interactions, how  
12 to conduct and analyze renal studies, hepatic studies,  
13 population PK, and in all those guidances, we put in a  
14 component about modeling and simulation to build a  
15 groundswell, if you will, of quantitative analysis based on  
16 modeling and simulation for interpreting the outcome of  
17 these studies.

18           [Slide.]

19           So, we have a future vision for modeling and  
20 simulation that is a growing enthusiastic vision where we  
21 would have, in the Agency, an integrated environment for  
22 modeling and simulation where we can develop in some cases,  
23 apply in other cases, or in other cases, still rely upon  
24 models and simulation that support a number of things.

25           Modeling and simulation, we envision in an



1 integrated way can support the regulatory decision-making  
2 process in some current and new ways, can support drug  
3 development activities when we are asked to comment on a  
4 drug development plan that involves modeling and simulation,  
5 and also there are occasions when we meet with companies who  
6 are doing some advance planning for clinical trials, for  
7 example, Phase III trials, where they specifically request  
8 some input on the plans for those clinical trials, which may  
9 be based in turn upon modeling and simulation.

10 [Slide.]

11 If you look at the trends in modeling and  
12 simulation, there are significant opportunities really  
13 across the whole spectrum of activities in drug development  
14 and regulatory decision.

15 They range from using animal PK/TK data,  
16 pharmacokinetics/toxicokinetics data, to support the first  
17 dose in man, dose-response data to develop and refine the  
18 process by which doses are selected for Phase III clinical  
19 trials, using PK/PD relationships to interpret changes in  
20 pharmacokinetics in patient subsets, such as patients with  
21 renal and hepatic disease, and more recently, modeling and  
22 simulation has become more and more sort of linked to  
23 clinical trial simulation, CTS, to explore the range of  
24 critical study design issues that allow for the designers of  
25 clinical trials to look at tradeoffs in terms of subject

1 number, study design, doses, and so on. So, the opportunity  
2 to look at many variables simultaneously and their impact on  
3 projected clinical trial outcomes is another application.

4 So, the opportunities are there, the technology is  
5 certainly there, and the payoffs may be there or potentially  
6 may be there in the years to come, but one can imagine very  
7 easily some high potential payoffs from a concerted effort  
8 to pursue modeling and simulation in this environment,  
9 reduce cost in terms of time and money of the drug  
10 development process, for us in FDA, I think an increased  
11 assurance and quality of our regulatory decisions, and those  
12 two things in turn I think lead to the final outcome, which  
13 is better drug products and information on how to use those  
14 drug products in package inserts made available to the  
15 American public.

16 [Slide.]

17 With that little background, here is what we plan  
18 today for the committee. We have invited Mike Hale to  
19 present the current trends in modeling and simulation in the  
20 drug development process. We are as interested to know this  
21 as anyone, and Mike will give us an up-to-date perspective  
22 on where things currently are in drug development.

23 Next, we are going to have a presentation by Peter  
24 Lee. He is co-chair, along with Stella Machado, from  
25 Biostatistics, of an FDA Working Group that is looking into

1 modeling and simulation technology and standards with the  
2 eye towards a future modeling and simulation environment  
3 within FDA.

4           Finally, we have two experts at the tables, Diane  
5 Mould and Richard LaLonde. These are experts in this field.  
6 They are advanced users of this technology, and they are  
7 going to participate and share some of their expertise, as  
8 well.

9           I think with that, Steve, I will turn it back to  
10 you, and if there is any questions, I would be happy to  
11 answer them.

12           DR. BYRN: Thank you very much, Larry.

13           We will just go ahead with the first speaker,  
14 which is Dr. Michael Hale from Glaxo Wellcome.

15           The Applications of Simulation in Drug Development

16           DR. HALE: Thank you.

17           [Slide.]

18           It is a pleasure to be here today and talk about  
19 this topic. It is one that has been very controversial for  
20 many years, and I think we are moving in a direction,  
21 hopefully, of better agreement.

22           One note for those of you with the handouts, there  
23 are largely progressive disclosure slides, and some of them  
24 may be a bit confusing if you are just looking at the paper.

25           [Slide.]

1           I would like to start off with just briefly  
2 looking at how we generate information. If you will look at  
3 the right, this is the traditional collect data stage. This  
4 is the summarize, analyze, interpret stage. We are very  
5 familiar with those in the drug development process because  
6 it is a very visible process. That is what is obvious to  
7 anybody looking at our business. So, we won't do these in a  
8 very open, publicly available manner.

9           The FDA also participates in those two areas in  
10 terms of reviewing, evaluating, approving, rejecting, and so  
11 we have a long history of working together, although from  
12 somewhat different perspectives.

13           But we have this third region, the region where we  
14 model, simulate, predict, and I am calling this the Grey  
15 Zone, because we use this area heavily in the pharmaceutical  
16 industry, but it seldom gets out of the door very much for  
17 face-to-face discussions with FDA or other people.

18           It does, and Larry has indicated some successes,  
19 and there are some. Unfortunately, they tend to be the  
20 exception rather than the rule. Part of it is because we  
21 haven't yet developed an effective language to speak with  
22 one another. We haven't developed common shared  
23 expectations, and it is my understanding that is one reason  
24 that this topic is on the agenda today, to ask the question  
25 what we need to do to develop a better shared understanding

1 of this grey zone.

2 [Slide.]

3 I would like to start with definitions.

4 Basically, I am taking the point of view that modeling and  
5 simulation are the way that we have a technical expression  
6 or articulation of what we understand or what we think we  
7 understand.

8 Within that context, within the context of our  
9 science, we used modeling as a way that we describe existing  
10 data. That is, we have phenomena, we want to explain why it  
11 works or how it works, so modeling is the mechanism we use  
12 for explaining what we observe, whereas, on other hand,  
13 simulation is what we use to try to express our believe  
14 about the future. It is used in a mostly predictive sense  
15 or saying this is what I think is going to happen.

16 [Slide.]

17 Why do we do it? Well, we do it because we think  
18 that it is necessary to provide improved patient therapy,  
19 first of all, so that we can get better clinical beneficial  
20 effects, better safety for patients, and perhaps improved  
21 convenience of dosing and robustness.

22 One of the unfortunate things that happens is a  
23 drug that appears very effective in the clinic, goes out  
24 into the real world, and people take it too frequently or  
25 not frequently enough, or they take it with some other drug

1 that they shouldn't, and we have a drug that looked really  
2 good in the clinical development that is a disaster once it  
3 is introduced.

4 So, we would be very interested in finding ways  
5 that we can produce more robust drugs.

6 The other is to have a more effective and  
7 efficient use of limited resources. Anybody that keeps up  
8 with the news knows that the cost of drug development have  
9 been exploding.

10 Please don't take this as a firm figure, I don't  
11 know that there is really a good, firm figure, but rule of  
12 thumb is you are looking at half a billion dollars or so to  
13 get a drug to market nowadays, just in the R&D part of it.  
14 It is very expensive just in dollars terms and in terms of  
15 number of patients that are exposed to therapy.

16 We would like to find ways to reduce the cost, but  
17 we don't want to do it at compromise, compromise with  
18 respect to either safety or suboptimal therapy. So, we  
19 would like to have our cake and eat it, too, basically.

20 [Slide.]

21 Primary areas of use.

22 I forgot to thank my many colleagues that helped  
23 me. I do have to specifically mention Mark Sale, Keith  
24 Muir, Paul Mudd, and Misba Beerah, some of my colleagues  
25 at Glaxo Wellcome, because they did loan me a few of the

1 graphics you will see today.

2           One of the comments I got on this slide in  
3 particular was, well, why not just put up everything we do,  
4 and I said, okay, fine. It is virtually everything we do in  
5 drug development. There is almost no area of drug  
6 development that is untouched by modeling and simulation.

7           [Slide.]

8           In preparing for this, I sent a note to several of  
9 my preclinical and nonclinical colleagues, and I said can  
10 you tell me some of the areas where you are currently using  
11 modeling and simulation, and I got back these replies just  
12 from a very small group of people. This is just barely  
13 scratching the surface.

14           It is used very heavily in lead optimization, lead  
15 selection. It is used very heavily in the manufacturing and  
16 analytical stability. These are all areas where modeling  
17 and simulation has been used for many years.

18           I can tell you my personal background. Before I  
19 entered the dark forest of clinical pharmacology, I did a  
20 lot of CMC work in process optimization and analytical  
21 development, and those tools have been in that area for many  
22 years, and we would not have the ability of manufacturing  
23 processes we have today without it.

24           [Slide.]

25           One of my colleagues, Anne Hersey, gave me this

1 slide. This is a conceptual model of how the data elements  
2 come together. That is, we take some statistical and  
3 mathematical tools, and they are very diverse, ranging from  
4 simply algebra to cellular automata, and neural networks.

5 We add in some simple physiochemical descriptors,  
6 and we also do some animal work, simply animal ADME, and  
7 then we try to develop common themes, so that we can do a  
8 better job of some of our lead development.

9 [Slide.]

10 In early clinical development, I would go ahead  
11 and make a bold claim here, and perhaps it is not bold, that  
12 virtually every drug that we take into human beings is  
13 thoroughly modeled before we even get to base one.

14 Now, when I say "thoroughly modeled," I mean we  
15 will use animal models to figure out what kind of doses to  
16 start at and what we expect to look for in terms of safety.  
17 These are not necessarily precise models, I will not claim  
18 that, but I will say very clearly that we do not take drugs  
19 into human beings without a pretty thorough look in terms of  
20 modeling.

21 We do use those models to select a PK sampling  
22 schedule, and we also use those to figure out how much  
23 efficacy--or I should say beneficial effect--we can expect  
24 from a drug and what kind of safety issues we might be  
25 facing.



1           I would also point out to this group at this time  
2 that safety is probably the biggest unknown at this time in  
3 modeling and simulation, because for clinical or beneficial  
4 effect, we know what we are looking for.

5           We can say we want to reduce blood pressure, we  
6 want to lose weight, these other things, it is a very well-  
7 specified target in advance, whereas, safety is all comers,  
8 and that makes it very difficult to build models when you  
9 are in that kind of situation.

10           The last one, and the one that we actually use  
11 heavily, is comparing new compounds with existing compounds,  
12 compounds we are either developing in-house or compounds  
13 that are already on the market.

14           [Slide.]

15           To give you some kind of what a model actually  
16 looks like, we often have to break a model down into  
17 component pieces and collect data defining each of the  
18 connections.

19           For example, this illustrates how we put together  
20 a model for a drug for diabetic use. We started basically  
21 with the dose of the drug and figured out how that affected  
22 the pharmacokinetics, if you increase the dose, what blood  
23 concentrations of drug do you see.

24           We then looked at the relationship between the  
25 concentration in the blood and a biomarker, in this case

1 glucose. We looked at the relationship between glucose and  
2 an accepted regulatory surrogate glycosylated hemoglobin.

3 Then, we looked at the relationship between  
4 glycosylated hemoglobin and the clinical response, that is,  
5 the consequences of diabetes. On the end, the  
6 pharmacoeconomic people might take the rest of this model  
7 and try to project it into the market.

8 Basically, we build these pieces by, in this case,  
9 we actually used animal data for some of these, we used  
10 human data for some of these, and for some others we even  
11 went to other drugs in the same class.

12 These all are not necessarily a logical  
13 progression of one drug. We kind of take bits and pieces  
14 and stitch them together. That is realistically the only  
15 way we can do a lot of this now.

16 [Slide.]

17 This is another example, and I want to thank Misba  
18 Beeraher for providing this one. In this case, we were  
19 looking at safety because contrary to what I told you a  
20 moment ago, for this particular compound we did pretty much  
21 know what to expect for safety, and, in fact, there was a  
22 drug already on the market.

23 It had, if you look at the blue squares here, this  
24 was the fitted safety relationship to concentration, and the  
25 data you see here, the red dots and the black dots, are

1 actual observed safety versus concentration data in humans  
2 at two different doses.

3           Now, we had a new lead compound, and the people in  
4 Early Discovery asked us, is this a compound worth taking  
5 forward into humans, and so we looked at some animal data.  
6 The animal data gave us this green curve, and so we were  
7 able to superimpose those two curves and then compare out  
8 new lead versus the existing drug on the market, and make an  
9 evaluation based on sensitivity and specificity as to  
10 whether this was a drug worth advancing or not.

11           [Slide.]

12           Here is another example. This one is fairly  
13 simple, but I think it is also insightful in that we are  
14 looking at how half-life and how dose impact the use of this  
15 drug.

16           For example, the first one is rather obvious. We  
17 have a plot here of clinical effect, in this case percent of  
18 maximum increase in effect versus daily drug dose, and we  
19 have a typical sigmoidal curve here. We have one for a 12-  
20 hour half-life and one for a 6-hour.

21           At this point in time, we only had animal data,  
22 and the animal data told us it might be as low as 6 hours,  
23 it might be as long as 12 hours, we weren't sure, so let's  
24 look at those two possibilities and project what we might  
25 expect in man in terms of dose.

1           So, you can look at the dose curve and figure out  
2 what kind of effect you can expect based on dose for either  
3 12- or 6-hour half-life.

4           Now, if you don't want to go along the dose axis,  
5 you can go vertically. In other words, for a fixed dose,  
6 how does half-life impact effect? So, this is a very  
7 interesting kind of figure in that we can either go  
8 horizontally and figure out for fixed effect what does the  
9 dose need to be given half-life, or we can go vertically and  
10 ask how does half-life impact this for a given dose in terms  
11 of effect.

12           [Slide.]

13           Now, later in clinical development--and by "later  
14 clinical development," I mean proof of concept, region and  
15 after, Phase III postmarketing--we use it to try to optimize  
16 our dose. We use it to try to extend to populations that  
17 may not have been directly studied.

18           We also want to look at alternate dosing regimens.  
19 As it turns out, there is an infinity of dosing regimens,  
20 and we only realistically can look at maybe a couple, maybe  
21 three in late stage clinical development.

22           Optimal times and measures for evaluation. This  
23 might mean how often does the patient need to come into the  
24 clinic for evaluation. If we are talking about blood  
25 sampling, it might be is it one hour, two hours, six hours,

1 whatever post-dose.

2           It might regard surrogate markers. This is  
3 actually one of the very large areas where we use simulation  
4 in terms of evaluating sampling times and what measures to  
5 look at.

6           Individualization of therapy, a very controversial  
7 area, or examination of statistical test. This is the  
8 classic use of simulation. Statisticians for years have  
9 used simulation to evaluate statistical properties of  
10 various tests.

11           You may have noticed I have not specifically  
12 mentioned clinical trials simulation. Part of that is  
13 because it is going to be so well mentioned elsewhere,  
14 particularly in Peter's talk, but we do use clinical trial  
15 simulation on occasion to project what our expected trial  
16 outcomes are, and it is actually probably one of the  
17 toughest things to do in this whole area, but we certainly  
18 do it.

19           [Slide.]

20           I want to show you one example here where we use  
21 simulation to try to examine how therapeutic drug monitoring  
22 might or might not be useful for a group of patients.

23           In this case, this involved an approved drug.

24 There is a PK/PD relationship that had been demonstrated in  
25 the literature, and it was also the case that people in the

1 clinic were saying why don't we use therapeutic drug  
2 monitoring, we have a PK/PD relationship that is published,  
3 why don't we use it, so that we monitor our patients, and  
4 those that are at AUC levels, that are very low on the PK/PD  
5 curve, why don't we boost them up higher on the PK/PD curve.

6 That met with quite a bit of opposition from the  
7 health economists. They said we are not sure it is  
8 worthwhile to do that from a cost point of view, how many  
9 people would actually benefit from that. Maybe people are  
10 already largely at high enough AUCs, why should we bring  
11 them into the clinic and sampling.

12 So, what we did here was looked at the  
13 relationship between patient AUC on this axis, and this is  
14 in terms of population percentile. So, if you go to the  
15 right, these would be patients that have a very high AUC,  
16 and at the left, these would be patients that have a very  
17 low AUC. On the vertical axis, we have a probability of  
18 achieving a beneficial effect.

19 What the simulation showed here, when you get  
20 these two curves, the blue curve is what happens when you  
21 follow a fixed dosing schedule, and the dashed curve there  
22 is what happens when you use therapeutic drug monitoring.

23 What this shows is that the curves converge  
24 somewhere around 60 percent. Now, what that means is that  
25 people at the population 60th percentile and above get no

1 benefit from therapeutic drug monitoring in terms of  
2 effectiveness. They are already achieving sufficient AUCs  
3 to give them the full benefit of the drug.

4           The people at the very lowest ends--and I haven't  
5 shown that part of the curve, they just fall like a rock  
6 almost here--also don't benefit, but the people in this  
7 region right in here do benefit, people from about 10  
8 percent to 30 percent, we can really substantially increase  
9 their expected therapeutic outcome by therapeutic drug  
10 monitoring, so at that point it becomes a decision for the  
11 clinicians and the economists to decide is it worth doing.

12           I should point out the reason we did this was  
13 because this allowed us to look at a huge variety of  
14 different ways of therapeutic drug monitoring. In this  
15 case, we actually used a quality control kind of scheme  
16 where we had action limits, warning limits, two out of  
17 three, things like that, and the simulation enabled us to  
18 look at a wide variety of different schedules.

19           [Slide.]

20           When I was told about the purpose of this meeting,  
21 I talked with a number of people, and they said you really  
22 need to make sure you look at some of the key issues, don't  
23 just go tell them what we do, also, tell them some of the  
24 key issues we face.

25           So I would like to ask the question: Why wouldn't

1 a rational person accept modeling and simulation?

2 I would propose that there are three legitimate  
3 reasons to challenge a modeling and simulation project.

4 The first is the premises or the assumptions. You  
5 might legitimately say I don't accept your results because I  
6 don't accept your assumptions.

7 You also might challenge the implementation. You  
8 might say your assumptions are fine, you are just not doing  
9 a very good job of implementing your assumptions.

10 Lastly, we could fail in interpretation.

11 [Slide.]

12 I want to look just briefly at a way forward. The  
13 premises I will propose fall into two classes. The first  
14 class of premises is those that are verifiable. By  
15 "verifiable," I mean that there is some way that we can  
16 reach expert agreement, that there is some basis for experts  
17 getting together and said yes, we agree on this assumption.

18 Usually, that will involve some supporting data,  
19 compelling plausibility, accepted theory in models, common  
20 understanding of science, things like that.

21 The second category would be areas where we  
22 legitimately disagree, and I would propose that those are  
23 the subject of a simulation study, that if experts disagree,  
24 if we disagree widely on our assumptions, let's put those  
25 off the table, over into the area of uncertainty, and



1 explicitly study them as factors in our simulation.

2           So, I would propose the key difference on  
3 assumptions is areas where experts agree and where experts  
4 disagree, use that as a classification as to whether we  
5 ought to include an assumption as a given or include an  
6 assumption as something that we are studying.

7           [Slide.]

8           Now, one way you can determine which class it  
9 falls into, things we consider to be more certain fall in  
10 the left column, the verifiable. Things that are less  
11 certain, if we disagree, take it out of the left column, put  
12 it in the right column.

13           How does it get out of the right column into the  
14 left? Well, over time, as we get smarter, as we get more  
15 data, more knowledge, as the science advances, we will move  
16 things out of the right column into the left column. It is  
17 just the natural progression of science.

18           [Slide.]

19           For implementation, there is really only one  
20 question, and that is: Do the modeling and simulation plan  
21 and software faithfully embody the premises? It is a  
22 question easily asked, but it is difficult to answer.

23           [Slide.]

24           So, how do we gain confidence in implementation?  
25 Actually, I think this is one of the key questions that a

group, such as this, needs to give some thought to.

2           I would propose there are two ways that we  
3 approach this. First of all, there is a general framework  
4 that needs to be addressed, that is, that we need some  
5 standardized accepted tools, some industry standard tools  
6 that we can use.

7           This would also involve validated model libraries.  
8 There are already some efforts like this in the preclinical  
9 area where some people are trying to get together some  
10 molecular models that are validated and widely accepted.  
11 These would need to be public and available for all to use.

12           Next, would be traditional software validation.  
13 We need to make sure that the tools and the models we have  
14 are thoroughly validated, and lastly, we will need some  
15 benchmark case studies, some accepted examples that we can  
16 through our models and software to make sure things work  
17 correctly.

18           On the other side of the table, we have specific  
19 applications. So, for a specific drug indication or a  
20 specific compound, we need to look at the credibility of the  
21 implementers, are these people that are expert in the art.

22           Frankly, I would prefer Picasso with crayons to an  
23 ape with oil paints.

24           We also need to think about independent review. A  
25 lot of times we do that through peer presentation. We

1 present at meetings, we have face-to-face meetings with FDA  
2 or other regulators.

3 Another possibility might be a third party. It  
4 could be that regulators and industry get together and agree  
5 on premises, agree on an implementation, but then contract  
6 that to an independent third party is a possibility.

7 Another possibility is a line-by-line checking,  
8 which is hugely labor intensive.

9 [Slide.]

10 The last area, interpretation, requires that we  
11 collaborate. It means we need subject matter specialists,  
12 those that are expert in clinical applications or clinical  
13 pharmacology, statistical expertise, I am told  
14 pharmacometricians, people that really know about simulation  
15 science.

16 We need to ask about relevance. If the  
17 simulation, if the model is not relevant to the question  
18 being asked, that is a big issue.

19 And what about scope? Interpolation versus  
20 extrapolation? Those are fundamentally different issues  
21 that need to be addressed.

22 And precedence, do we have a precedented mechanism  
23 of action, do we have experience in models in this drug  
24 class, do we have experience in models for this drug  
25 indication?

1           Probably one of the biggest needs we have right  
2 now is, as I said before, a model library, a validated model  
3 library. We also need models for disease progression. Many  
4 times when we go to do a simulation, we lack a good model of  
5 disease progression. As you know, bad input gives bad  
6 outputs.

7           The assumptions we use for our simulations hugely  
8 affect the conclusions, and I think that has been the  
9 biggest single complaint about modeling and simulation, and  
10 that is to simply say since all of our outputs depend on  
11 your inputs, I am not sure I want to look at it, I am not  
12 sure I buy into your assumptions, particularly when a lot of  
13 the work that goes on, goes on in a black box or behind the  
14 curtain.

15           So, we need a process that is visible, that is  
16 open, where there is accepted validated tools, et cetera, so  
17 that we can actually have a process that people trust. This  
18 is actually going to require working together, so we get out  
19 of the grey zone and get industry and FDA talking together,  
20 as we are doing today, to get agreement on these things.

21           [Slide.]

22           To summarize here, why not simulate?

23           I am going to claim, first of all, that the  
24 assumptions is a manageable issue, that basically, we can  
25 negotiate agreement up-front before we do a lot of the

1 modeling and simulation, or we can actually negotiate which  
2 premises we will accept and which of those have to be  
3 checked further.

4           We need to be careful, though, because if we put  
5 too many things in the right column of less certain, things  
6 which we must simulate, then, we are not going to be able to  
7 reach many conclusions.

8           In terms of implementation, this is achievable,  
9 but it is going to be an intensive ongoing effort, in other  
10 words, even once we have validated models, we are still  
11 going to have to case-by-case look at whether the specific  
12 application was done well.

13           Interpretation. It has been suggested this is no  
14 different than interpreting standard clinical trials. That  
15 is not entirely true because with simulation we can actually  
16 do lots of replication under varying conditions, but the  
17 principle is the same. That is, you need statistical  
18 expertise, subject matter expertise, et cetera, but it is  
19 essentially the same kind of intellectual activity.

20           [Slide.]

21           Lastly, I do want to provide you with a few  
22 references. Annual reviews in Pharmacology and Toxicology  
23 this year had two very relevant articles, one on simulation  
24 of clinical trials, and one on PK/PD modeling in drug  
25 development.

1           The FDA this year has had two advisory committees  
2 on this topic. The Antiviral Committee back on July 25th  
3 talked about PK/PD for antiviral applications and looked at  
4 different measures of exposure and how those related to  
5 outcome.

6           There is another one I don't have on here, that is  
7 very recent, that is Cardiovascular Advisory Committee.  
8 They also looked at PK/PD, and I will call that modeling  
9 kinds of issues.

10           There was also a Good Practices Conference early  
11 in 1999, and following that conference, we developed a  
12 consensus paper, and that was published on the web at the  
13 Georgetown home page.

14           There are numerous FDA guidances, and I will just  
15 mention one here, the one on Population and  
16 Pharmacokinetics, which actually has a substantial amount of  
17 discussion about modeling and simulation.

18           One of the things--and I will for a few seconds  
19 digress here--we need to get out of the mindset that  
20 modeling and simulation is the same as PK/PD modeling. Many  
21 people, when you mention simulation, automatically jump to  
22 clinical trial simulation, and when you say "modeling,"  
23 automatically think PK/PD modeling.

24           Those things are not synonymous, and we need to  
25 think in terms of a broader framework, and when we talk

1 about models, we think to think more about assumptions, and  
2 less about a mathematical Emax or statistical model.

3 [Slide.]

4 Just real briefly, I want to point out to you  
5 there is a FDA guidance that, in principle, says modeling  
6 and simulation is the kind of thing we need to be doing. It  
7 doesn't say it in those words, you don't find the word  
8 "model," you don't find "simulation," what it talks about is  
9 what do we need for quantitative and qualitative standards  
10 for demonstrating effectiveness, and how can we use existing  
11 data to move to new applications.

12 Now, it does talk about extrapolating entirely  
13 from existing studies, and it does say that we can actually  
14 move into some new areas and have an adequate demonstration  
15 without additional trials. So, this guidance actually is  
16 right on target in terms of laying down some broad  
17 principles, the principles being we should be able to make  
18 rational use of existing data and apply expertise to extend  
19 into new areas where it would be in the common interest.

20 Some of the examples that were provided in that  
21 guidance were pediatric bioequivalence, et cetera.

22 [Slide.]

23 I have got one last slide before my summary, and  
24 that is, do we currently combine premise, data, and analysis  
25 for regulatory approvals?

1           I am going to claim that absolutely, and we have  
2 done so for years. In this case, if you look at the premise  
3 that equivalent rate and extent gives you an equivalent  
4 drug, then, we add in some data, data from one, well-  
5 controlled pharmacokinetic clinical trial. Then, we add in  
6 one statistical analysis including a decision criteria.

7           So, we take those three elements, a presumption,  
8 some data, and an analysis, and the conclusion we draw from  
9 that is equivalent effect and safety, and this is done  
10 without a clinical test of safety and effectiveness, which  
11 leads to an approval of a generic drug or bioequivalence.

12           So, I would propose to you that this concept is  
13 already well established in the regulatory domain, and what  
14 we are talking about now is actually developing a new  
15 language, a new way we speak to one another, setting a new  
16 level of expectation, so that industry and regulatory  
17 agencies may actually get together and have more or less a  
18 common way of talking.

19           [Slide.]

20           So, in conclusion, modeling and simulation are  
21 natural, they are necessary for advancing the scientific  
22 understanding of drug characteristics. One of the things  
23 that is very important to remember is a lot of the early  
24 uses right now are private and proprietary, that is, drug  
25 companies are using these methods largely for developing



1 lead optimization, selecting which candidates to take  
2 forward, et cetera, and the methods that are being used  
3 there are largely considered to give competitive advantage,  
4 and they are not considered to really impact the final  
5 effectiveness or safety. Basically, we cover all those  
6 hurdles well before we get to the discussion point with  
7 others.

8           Lastly, combining premise, data, and analysis for  
9 agreed conclusions is not new.

10           Thank you very much.

11           DR. BYRN: Thanks.

12           Our next speaker will be Dr. Peter Lee, who is  
13 going to speak on A Framework of Modeling and Simulation in  
14 Regulatory Decision.

15           A Framework of Modeling and Simulation in  
16                           Regulatory Decision

17           DR. LEE: Thank you, Steve.

18           [Slide.]

19           I think what we heard from Dr. Mike Hale is the  
20 advocacy of modeling and simulation in drug development  
21 process. What I would like to do is to describe to you a  
22 framework of modeling and simulation for regulatory  
23 decision.

24           [Slide.]

25           I want to start out with a terminology slide. I

1 think everybody may have heard many different definitions of  
2 modeling and simulation. As a matter of fact, just a few  
3 minutes ago, Dr. Mike Hale just gave a slightly different  
4 version of the definitions, but I think we all talk about  
5 the same things.

6 I want to give this definition, so that we can  
7 clarify the terminology at least for my presentations. I  
8 think modeling is an activity to determine the mathematical  
9 equations that can appropriately describe the data, and the  
10 data can be described in different fashions. For example,  
11 it can be described as a mechanism of action, and it can be  
12 described by the smoothness of the data.

13 Simulation is a process to predict outcomes of  
14 specified conditions and using the model that has been  
15 established previously.

16 Clinical trial simulation is actually a specific  
17 form of simulation. It is used to predict the outcome of  
18 clinical trials.

19 My presentation is going to focus on simulation  
20 and clinical trial simulations, however, it is not possible  
21 to review simulation without evaluating modeling process,  
22 because in a simulation we are using models, and we have to  
23 know how good the model is.

24 [Slide.]

25 So, the topic for my presentation today include

1 the following. First, I want to talk about what is the  
2 trend of modeling and simulation in current regulatory  
3 submissions. Then, I will talk about how modeling and  
4 simulation submission have been used for regulatory decision  
5 in the past.

6 I will move into specifically a clinical trial  
7 simulation, what is the potential utility of clinical trial  
8 simulations. Finally, I will talk a little what are the  
9 directions and next steps for evaluating the clinical trial  
10 simulation or modeling simulations.

11 At the end of my talk, I will pose an additional  
12 question to the committee, and hopefully, we can get  
13 direction from the committee regarding how we should  
14 proceed.

15 [Slide.]

16 So, how good is the current drug development  
17 process? Here, I present several surveys by different  
18 researchers. The first survey is conducted by Dr. Carl Peck  
19 in CDDS Georgetown University.

20 Basically, what he shows is about 22 percent of  
21 approved NDA require post-marketing dose adjustment.  
22 Although we don't know too much background about this NDA,  
23 so we need to interpret the data with cautions,  
24 nevertheless, I think Dr. Carl Peck concluded in the  
25 Cardiorenal Advisory Committee meeting earlier this month

1 that pre-market drug development is improvable regarding a  
2 safe dose.

3 Another survey by CMR International shows that the  
4 average NDA required 12 years and 350 to \$600 million, it is  
5 very costly and time-consuming.

6 The last survey done by Price Waterhouse Cooper  
7 shows that 30 percent of NDAs is non-approvable and 15  
8 percent of the Phase III study failed.

9 [Slide.]

10 With all that, I think Price Waterhouse Cooper  
11 come out with Pharma 2005 report. In that report, they  
12 indicate that in the next five years, pharmaceutical  
13 companies are going to use simulation to help them develop  
14 drugs. Actually, the simulation will be in the center part  
15 of the drug development process.

16 It will establish a knowledge database, and this  
17 knowledge database will be used to design protocol and then  
18 study will be countdown, and data will come back and use  
19 simulation to analyze the data. Eventually, the result will  
20 go back to the knowledge database for the next study  
21 designs.

22 [Slide.]

23 So, this is a vision by the Price Waterhouse  
24 Cooper for the next five years, and let's take a look at  
25 what is going on at this time. Basically, this table shows

1 the application of simulation in different area of drug  
2 discovery and development, starting from discovery,  
3 preclinical, clinical, and outcomes.

4 The only point I want to show here is in every  
5 single drug development process, there are some sort of  
6 simulation being used, modeling and simulation being used to  
7 support the process.

8 [Slide.]

9 So, the current environment is that computer-aided  
10 trial design has been used by 17 out of 20 PhRMA companies,  
11 and there are 1,200 different users. There are over 15  
12 different software packages that can be used for simulation  
13 and modeling.

14 We also have past experience with modeling and  
15 simulation in regulatory decisions. We also see emerging  
16 submissions using simulation to support trial designs.

17 [Slide.]

18 This is another survey. According to Dr. Carl  
19 Peck, there were over 100 clinical trial submissions have  
20 been conducted in the last couple of years. On a survey by  
21 Dr. Dan Weiner shows that the number of clinical trial  
22 simulation in different therapeutic areas.

23 Basically, what he shows here, the simulation has  
24 been done on any therapeutic area from pain relief,  
25 cardiovascular, CNS, diabetes, cancer, almost any different

1 therapeutic area, so it is not really limited by the  
2 indication of the drugs.

3 [Slide.]

4 Here, I just want to show you some of the past  
5 experience we have in FDA in terms of using modeling and  
6 simulation to make decisions. I just want to go through  
7 this really quickly. PK simulation has been used quite  
8 often. We use single-dose data, modeling with those data.  
9 We do that all the time.

10 PD simulations, one example that Larry has  
11 mentioned is the Albuterol bioequivalent. We use modeling  
12 and simulation to analyze the data and test bioequivalence  
13 based on pharmacodynamic rather than pharmacokinetics.

14 Population PK is another area we used modeling and  
15 simulation, about 40 percent our NDAs currently contains  
16 some sort of population PK analysis, and it is used to  
17 identify subpopulation that may have different PKs. Quite  
18 often this information ends up in the label.

19 PK/PD simulation has a lot of utility, as Larry  
20 alluded in his slides, can be used to bridging different  
21 subpopulations, different formulations, determine the dose  
22 selections. We have another exposure response guidance  
23 coming out to address some of this.

24 [Slide.]

25 We also have some new experience specifically in

1 the clinical trial simulation area. Although this is a very  
2 new area, we don't have many examples, but basically, we see  
3 some physiologic and disease models in Alzheimer's areas.  
4 We have a physiological model to describe QTc prolongation,  
5 also, in diabetes areas.

6 We also see clinical trial simulation to support  
7 Phase III protocol design.

8 [Slide.]

9 I just want to give you what I thought are good  
10 examples. This is an example in clinical trial simulation  
11 specifically. It is Drug X, and the drug shows only  
12 marginal efficacy in your Phase II studies.

13 [Slide.]

14 Similar background. The drug is given as an IV  
15 infusion, and the reason for marginal results in Phase II is  
16 believed to be the drug concentration may not be optimal.

17 [Slide.]

18 Here is a reason for the marginal Phase II  
19 results. This is concentration-effect relationship. Effect  
20 is plotted at different concentrations. Here is the  
21 placebo. When you see the concentration increase, you see  
22 the efficacy increase, however, up to a certain point,  
23 further increase of concentration actually resulting in a  
24 decrease of efficacy.

25 [Slide.]

1           If you look at a number of patients with different  
2 concentrations, you see about 15 percent of patients  
3 actually underdose, and another 44 percent of patients  
4 actually overdose.

5           So, you have about 60 percent of patients which  
6 didn't get the appropriate concentrations.

7           So, the idea of Phase III studies is to move these  
8 two extremes into the center, so that everybody can get  
9 appropriate concentrations.

10           The company actually see this so-called inverse U-  
11 shape, not only in the Phase II study, but also in Phase I  
12 biomarker study in humans, as well as in preclinical animal  
13 data.

14           If you look at the overdose patients, this is  
15 simulated data, and these two lines shows therapeutic  
16 windows. You see the concentration increase quickly and  
17 over the therapeutic windows.

18           The proposed new dosing regimen is that we will  
19 reduce at a certain time point the concentration will be  
20 determined, and if the concentration is over the therapeutic  
21 window, it will be reduced, so that it can fall into the  
22 therapeutic window, and then another assay or second assay  
23 can be conducted. Again, if the concentration is above  
24 therapeutic window, it will be reduced again.

25           [Slide.]



1           Now, if we look at those patients, and this is a  
2 concentration profile, you will get into the therapeutic  
3 window with time. Again, one of the proposals is giving a  
4 loading dose, so that the concentration will get into the  
5 therapeutic window and increase the infusion rate, so you  
6 will maintain there.

7           So, this is all very nice theoretically. The  
8 problem is the company hasn't conducted any clinical trials  
9 to verify this will work.

10          [Slide.]

11          There are several design issues to interpret the  
12 answer, for example, when do we do these assays, four hours,  
13 three hours, two hours post-dose. Once we determine the  
14 concentration is over the therapeutic window, how much did  
15 you reduce the infusion rate, so that the concentration can  
16 fall into the therapeutic windows.

17          How about the dropout rate, 10 percent dropout, 20  
18 percent dropout. There are different severities. A patient  
19 may respond to a drug differently. There is the compliance  
20 issues, and so on, and so forth, and this is a 2D6, how  
21 about the phenotyping of the patients.

22          [Slide.]

23          So, the company considered all these factors I  
24 just talk about and put it into a simulation, and trying to  
25 identify different type of study design, and eventually they

end up with three best study designs. The probability of  
2 success rate is actually over 85 percent with these optimum  
3 study designs.

4 So, if the company used the Phase II study design,  
5 there will be 60 percent of patients who may not benefit  
6 from the Phase II design, only 40 percent will benefit, and  
7 it ends up with very little power.

8 The clinical trial simulation, the company  
9 actually identified a good study design, a good way to  
10 conduct the study, so that we have a good, successful rate  
11 for the Phase III studies.

12 To summarize the utilities of clinical trial  
13 simulations, I just wanted to talk about simulation  
14 actually, and clinical trial simulation is just one form of  
15 simulations.

16 This simulation can be used to predict PK under  
17 conditions not studied, a single dose to multiple dose, can  
18 be used to select optimum dose, can be used to design study.  
19 There is a large number of publications out there to use  
20 simulation to design population PK, to design exposure  
21 response studies.

22 Can be used to evaluate change of pharmacodynamics  
23 due to the change in formulation, dose regimen, and dosing  
24 routes. They also provide bridging information for  
25 subpopulations, such as pediatric populations.

1 All this actually is being used to develop  
2 informative labeling language in a package insert, so the  
3 prescriber will be able to more effectively prescribe the  
4 drugs.

5 [Slide.]

6 As we saw, there may be additional utilities of  
7 simulation, and this is more specifically for clinical trial  
8 simulation. I think clinical trial simulation can be used  
9 to integrate preclinical, clinical pharmacology, and  
10 biopharmaceuticals study results into a late-phase clinical  
11 trial design to ensure safe and effective study designs.

12 Also, it can be used to design unbiased, powered,  
13 and robust studies to maximize the treatment benefits-risk  
14 ratio in the patients.

15 It can be used to explore "what if" scenarios and  
16 compare different study designs.

17 Finally, I think it is also important that it can  
18 be used to combine multiple discipline expertise in  
19 reviewing IND and NDAs.

20 By "multiple discipline," I mean clinical  
21 pharmacology, biostatisticians, and clinicians.

22 [Slide.]

23 I think the key factors to successful simulation  
24 projects include the following. There has to be prospective  
25 planning, just like any other project in the review process.

1           It should have some kind of a well-understood  
2 mechanism of action, because a lot of the simulations are  
3 used to predict something else, and with a good, honest-  
4 ending mechanism of action, the prediction or extrapolation  
5 can be more accurate.

6           Also, the robust model is not overly sensitive to  
7 assumption. I think Mike has talked about that.

8           Disease progression model is also important. We  
9 see a lot of failed simulation in the past just because  
10 there is a lack of disease progression models.

11           Availability of exposure-response data is  
12 important because exposure-response data typically is the  
13 center of the simulations.

14           We should have a balanced input from relevant  
15 disciplines. I think that is important.

16           Finally, it also depend on how far the simulation  
17 extrapolated. We see an example where people may use  
18 preclinical data to predict Phase III results. It is  
19 probably not going to be very accurate. However, if you  
20 have a Phase II study, and use that information to predict  
21 Phase III, the result may be more reliable.

22           [Slide.]

23           So, what are the issues at this time? I think the  
24 issues are there is no consistent approach for CDER review  
25 to assure the quality of modeling and simulation projects.

1 We also have other FDA guidance talk about using  
2 simulations, however, we never address the "best practice"  
3 for simulations.

4 We also believe that proper review of modeling and  
5 simulation submissions may require FDA guidance for  
6 industry.

7 [Slide.]

8 So, we have formed an MPCC Modeling and Simulation  
9 Working Group just a couple months ago, and the goal of the  
10 Working Group is to assess the current state of art of  
11 modeling and simulation, to explore potential for regulatory  
12 applications of modeling and simulation, and determine  
13 standards to assess the utility.

14 Also, develop a standard for modeling and  
15 simulation output, which is a report. Another is develop a  
16 guidance as a standard for reviewing and critiquing modeling  
17 and simulation reports. Finally, prepare a guidance for  
18 industry for reporting modeling and simulation results.

19 [Slide.]

20 At this time, I just want to summarize actually my  
21 position and pose the following questions to the advisory  
22 committee members.

23 I think the first question is: How does industry  
24 use simulation to help the drug development process? I  
25 think Mike has addressed that question.

1           The second question is: Are modeling and  
2 simulation appropriate for drug development and regulatory  
3 decisions? That is in Mike's presentation, and hopefully,  
4 my presentation has addressed that question, as well.

5           The third question is: What are the important  
6 attributes for a meaningful simulation practice?

7           [Slide.]

8           The next question is: Do we need an FDA guidance  
9 to industry regarding the best practice of modeling and  
10 simulation for regulatory applications?

11           If the answer is yes to the prior question, then:  
12 What important information should be included in the  
13 guidance?

14           If the answer is no: What are the critical issues  
15 that need to be addressed before we move forward to the  
16 guidance?

17           With that, I will turn the floor back to the  
18 chairman.

19           DR. BYRN: Thank you very much.

20           For the committee, if you would get your agenda  
21 out, the last two pages of your agenda are the questions  
22 that have started to be addressed. I guess that is really  
23 our job, at least one of our jobs as a committee is to start  
24 to address these questions.

25           Before we do that, are there any questions that

1 arose that people would like to ask the speakers, the  
2 committee now that would like to ask the speakers to clarify  
3 any issues of concern or of interest to them?

4 [No response.]

5 DR. BYRN: Let me introduce the guests or why  
6 don't the guests that are here introduce yourselves and just  
7 say where you are from. Diane, do you want to start?

8 DR. MOULD: I am Diane Mould, Georgetown  
9 University, CDDS.

10 DR. LaLONDE: My name is Richard LaLonde. I am at  
11 Pfizer Global Research and Development in Ann Arbor,  
12 Michigan.

13 DR. BYRN: We hope you will participate. Did you  
14 guys have any questions for the speakers or any comments you  
15 would like to make before we start on these questions?

16 [No response.]

17 Committee Discussion

18 DR. BYRN: Let's go ahead and start on the  
19 questions. Obviously, the first one we have had a summary  
20 of. The first question is: How does industry use  
21 simulation to help the drug development process? Obviously,  
22 we had talks that summarized that, but are there clarifying  
23 issues or points that somebody would like to make?

24 DR. VENITZ: Just a recommendation. It might be  
25 useful to go beyond individual case reports and perform some

1 kind of a survey to see what companies in general do and  
2 what kind of internal practices they have. Part of what  
3 your working group is going to do is to come up with  
4 guidances to address practices, and it might be worthwhile  
5 to figure out what the current practices are.

6 DR. BYRN: Yes, go ahead.

7 DR. MOULD: I would also like to just point out  
8 that modeling and simulation actually are almost impossible  
9 to differentiate anymore. Simulation actually is used in  
10 qualifying and validating model performance, and so if  
11 people do modeling, invariably, they are doing simulation,  
12 as well, so it is a difficult concept to really separate any  
13 longer.

14 DR. LAMBORN: I guess I do in a sense have a  
15 question that goes back to the FDA for bringing this  
16 forward. To me, it is not an issue of whether modeling and  
17 simulation have a role, as has already been pointed out.  
18 They are clearly an integral part of what is being done now  
19 in a range of ways. I mean everything from animal modeling  
20 to the use of pharmacokinetics to predict.

21 Also, I am a little bit confused as to why there  
22 is a thought that there should be a single guidance on  
23 modeling and simulation. It would seem to me obvious that  
24 what you would need to do is to approach each of the  
25 guidances that address either the disease-specific or the



1 bioavailability/bioequivalence, any specific topic, and you  
2 would, within that context, talk about how modeling and  
3 simulation could be used.

4           In fact, the guidance that would come out on what  
5 would be needed for each component, whether it is what  
6 assumptions are reasonable, what kinds of validation needs  
7 to be done on the simulation would potentially be different  
8 in each of those contexts.

9           I would be interested in what sort of a situation  
10 you would expect that would override that distinction,  
11 because I would have thought it would be much more effective  
12 to approach these in the context in which they are going to  
13 be used.

14           DR. LESKO: I think that is a good point, and  
15 actually, got me to sort of a broader question, which isn't  
16 part of the slide questions necessarily, and that is why  
17 should a regulatory agency care about modeling and  
18 simulation at all, in other words, should it be in a  
19 position of being reactive to these kind of models and  
20 simulations that come forward from industry, in other words,  
21 be prepared to comment on them or critique them, or what we  
22 heard from Mike was a lot of internal decision-making that  
23 goes on, based on modeling and simulation, and the question  
24 becomes at what point does this become something that is  
25 important to FDA to either react to or whatever.

1           I think the other aspect of it is should the  
2 agency be proactive in sort of advancing the notion that we  
3 have good science, we have good technology, and being more  
4 of an advocate than we have been in the past for encouraging  
5 the use of good modeling and simulation in the drug  
6 development and certainly within our own regulatory decision  
7 sort of practice.

8           So, there is really two approaches in a sense for  
9 us, I think, to modeling and simulation.

10           That being said, I guess the question about it is  
11 kind of case-by-case, do you apply modeling and simulation  
12 principles to case-by-case. I always think of case-by-case  
13 as being maybe prone to some inconsistencies across the  
14 different units, at least within FDA.

15           That is one of the concerns I would have that if  
16 we are dealing with bioequivalence, you are dealing with  
17 generic drugs. If you are dealing with cardiovascular  
18 drugs, it is the cardiovascular division, and the same  
19 things with the biostatisticians.

20           Is it possible to get at least a general framework  
21 of agreement on the characteristics or attributes of models  
22 and the implementation of simulation to verify them, that  
23 would be a standard that would cut across different offices  
24 and different divisions, so that you don't have to go back  
25 and sort of repeat that stuff in each case.

1           So, I guess I envisioned a sort of best practices  
2 framework that was very generalized in terms of--and I don't  
3 know how general it would be--maybe it is a matter of these  
4 are the key characteristics of a good modeling simulation  
5 exercise. You have got to clearly state your assumptions  
6 that we understand. You have got to clearly define some  
7 characteristics of the model that represent a good fit to  
8 the model or something like that, where everybody would say,  
9 yes, I agree with that, now, let me look at my specific  
10 application in this particular case.

11           Sometimes I am afraid we are going to have to sort  
12 of reinvent that with each particular case-by-case  
13 application of the modeling and simulation.

14           DR. LAMBORN: I think, if I could comment, first  
15 of all, I think it would be great if the Agency could be  
16 proactive and help in bringing about use of this. I think  
17 that whenever we have interactions across all groups that  
18 have potential interest, we gain something and we move  
19 forward faster.

20           I think the other thing that I was trying to say  
21 is I think that when it comes to setting some guidelines,  
22 they are probably going to have to be very broad and just  
23 sort of state the kinds of issues that have to be thought  
24 about, but that the actual best approach and any of the  
25 details are probably going to inevitably--they may be that

1 there are some clinical trials ones that could cross  
2 multiple disease areas, but the issues may be very different  
3 from things that might be done that would be bioequivalence,  
4 and there may not be too much detail that can be considered  
5 to be common to those.

6 DR. LESKO: I would say we haven't gotten to the  
7 point where we decide we are going to write a guide, this is  
8 part of the exploring of this process, this committee  
9 meeting and Peter's working group.

10 There is an analogy. I was thinking about the  
11 guidances that we have worked on in the past, and some of  
12 you may be aware of or recall the in vitro drug metabolism  
13 drug interaction guidance we put out in 1995, which at the  
14 time, in 1995, was really just a very general guidance both  
15 to increase awareness of the science that had evolved, and  
16 it was very general guidance that five years later has led  
17 to in vitro drug interaction studies that are a routine part  
18 of every submission we get virtually.

19 So, maybe my thought was that this would be more  
20 of a general guidance to perhaps serve to encourage sponsors  
21 to look at this as a tool, and then maybe some general  
22 framework that could then be elaborated on as things evolved  
23 and we begin to learn more about the subtleties and what  
24 have you of modeling and simulation.

25 DR. LaLONDE: I was wondering if maybe the

1 experience with population of pharmacokinetics may be a good  
2 guide in this area, because there was a guidance prepared a  
3 couple of years ago, I guess, or a year ago, and as you all  
4 probably know, population pharmacokinetics were used for  
5 quite a while starting in the eighties. There were a lot of  
6 submissions, I guess increasing over time, and I think as  
7 the FDA saw more and more of this information coming in,  
8 they were saying, well, maybe we want to have our staff  
9 better trained in this area, and with time, say, well, maybe  
10 we want to offer some general guideline, not necessarily  
11 really be very, very specific, but offer some general  
12 recommendations of the elements that should be part of a  
13 population analysis, the validation.

14 We may not be there yet with clinical trial  
15 simulations, but as we gain experience, maybe we will learn  
16 a little bit more about the things that we need to pay  
17 attention to as you get more and more of this information  
18 submitted to the Agency.

19 So, there may be some lessons to learn there from  
20 that experience.

21 DR. LESKO: There are some lessons to be learned.  
22 The guidance that you are referring to, the so-called  
23 population pharmacokinetics guidance, you know, to me, it is  
24 one of those stovepipe guidances, you know, it was developed  
25 really in the field of clinical pharmacology, and we used

1 it, we analyzed the data, and then we sort of recommend the  
2 outcome to the medical staff.

3           There wasn't a lot of debate about that because  
4 nobody really cared that much about the inside part of  
5 population PK, you know, what is the bottom line, but I  
6 think when we get to broader applications of modeling and  
7 simulation that begin, like you say, to get into more  
8 sophisticated applications, clinical trial simulation, there  
9 are a lot more questions being asked. It is not one of the  
10 stovepipes anymore. I see it as really three overlapping  
11 circles - biostat, clin pharm, and clinical.

12           The problem has been, you know, when you listen to  
13 all the stories, and you can't argue with the value of it,  
14 it is that implementation of it that we need to sort of move  
15 forward on, and we need some steps to implementing it, such  
16 that the needs of statisticians, clinicians, and clinical  
17 pharmacology folks are met, and if moving to a guidance can  
18 do that, you know, in a consensus way, then, that might be a  
19 way to advance the field.

20           DR. BYRN: Could I ask Michael a question, and  
21 then raise an issue. On stability simulation or modeling in  
22 the CMC area, is it, in your view, without divulging--I know  
23 this is getting into the more confidential areas--is it  
24 possible to simulate or model stability, predict stability  
25 results from small amounts of data? In your opinion, is

1 that possible now or does a lot more work--this is in the  
2 CMC area?

3 DR. HALE: I believe it is routinely done, in  
4 fact. We often use accelerated testing, things like  
5 arrhenius modeling, et cetera, to project shelf life, so,  
6 yes.

7 DR. BYRN: Okay. Now, if we go on with that, and  
8 we could take a scenario where if you had a good model and  
9 it followed the guidance or something, you have a good  
10 model, you run a couple points, yes, it is fitting the  
11 model, now, we don't need to do any more stability studies.  
12 I am not saying that that could happen initially, but I  
13 assume that this kind of thing, if you could do this, would  
14 tremendously reduce time to market.

15 You could reduce time to market, and if you could  
16 do the same thing in clinical trials, which is an area that  
17 I am not an expert in, but you could get a model and then  
18 you could see a few patients were following that model,  
19 obviously, you could reduce time to market greatly.

20 Clearly, if there is anything like this being  
21 contemplated, then, it would be I think the Agency would  
22 have to validate those models and make sure that they were  
23 correct because a lot would be dependent on those.

24 DR. LESKO: You reminded me of one of the  
25 applications of modeling and perhaps simulation, and that is

1 the extrapolation of adult efficacy data to pediatric  
2 populations.

3 DR. BYRN: Yes.

4 DR. LESKO: And there are certain prerequisites to  
5 do that, but when it is done, it benefits from having a good  
6 exposure-response relationship, some prior understanding of  
7 what is going on in kids and adults, but then the actual  
8 implementation of a simulation or a modeling exercise really  
9 brings some credibility to the ability to make a decision.

10 You don't have to go on to repeat efficacy trials  
11 and safety trials in this pediatric population. One of the  
12 hang-ups, not in that necessarily, but in general, in using  
13 models to simulate, say, new populations or new dosage  
14 forms, is frequently the issue of, well, is this--and this  
15 is what we hear frequently--is this a validated model, and,  
16 you know, what is validation of one of these models mean.

17 And if you can't really get to that point with  
18 some general characteristics or attributes, you really  
19 sometimes will run into a difficulty--

20 DR. BYRN: We are having trouble validating a  
21 spreadsheet.

22 DR. LESKO: So, another issue is what does  
23 validation of a model mean in terms of simulation.

24 DR. BYRN: I don't know whether we should even be  
25 using the word "validation," because we could slow down the



1 development.

2 DR. LESKO: I often thought verification would be  
3 a better word.

4 DR. BYRN: Maybe that is a better word, because I  
5 don't think we really want to apply the word "validation" in  
6 this area yet.

7 DR. HALE: I think you have actually hit on one of  
8 the key points that some people don't think about, that we  
9 actually are not talking about something that is purely an  
10 abstract exercise, that we actually want data to go along  
11 with the models or the simulations.

12 The next to the last slide I showed you, I was  
13 hoping to make that very clear that we are talking about the  
14 models or premises plus data, plus the careful analysis.  
15 One of the things that we have to think a little bit about  
16 is, is the model supporting the data, or is the data  
17 supporting the model.

18 It is a little tricky distinction, but, in fact,  
19 in the modeling and simulation, I think it becomes more  
20 perhaps the model supporting the data, so that instead of  
21 this crushing weight of evidence, we actually blast mix to  
22 support the data.

23 DR. BYRN: Also, we are going to talk about the  
24 public. We have to be able to assure the public that the  
25 model is supporting the data, that it is not making up

1 something that we can't verify in any of these areas, but  
2 certainly if we could do this or even think about doing it,  
3 we are talking about reducing time to market.

4           There is a huge public benefit to that, because  
5 therapies are going to get on the market quicker, so there  
6 is a major benefit to doing this.

7           DR. LAMBORN: If I might make a comment on the  
8 issue of clinical trials where I think we are more likely to  
9 be of benefit in the near term, there has been a lot of  
10 discussion in that environment about the difficulties with  
11 surrogate markers even and any kind of prediction where  
12 people are at a level that they are going to be comfortable  
13 of approval based on models.

14           I think the concept of using simulations to  
15 identify endpoints, to identify the most likely successes,  
16 but then to ultimately have to validate them in the more  
17 classic clinical trials environment is probably going to be  
18 the first place that we are going to be benefitted, is to  
19 focus in more quickly, but then have to validate with data.  
20 I think it would be great if we could get to the other, but  
21 I think that is going to be further down the line, because  
22 people are always saying, but this one could be different.

23           DR. BYRN: Just to add, and then we will get to  
24 Dr. Mould, certainly in the stability area, sometimes  
25 arrhenius plots don't work, and so you have to have some

1 data. It is great to have a model, but you can't do it  
2 without some data. I think what we are really talking about  
3 is reducing the amount of data, and I think that is what you  
4 are talking about, too, how much real data do we need if we  
5 have a good model.

6 Dr. Mould.

7 DR. MOULD: I was just going to add that I think  
8 currently for simulation, we often use it for things like  
9 line extension or refinement of dose. As Dr. Peck pointed  
10 out earlier, there are quite a number of compounds that come  
11 back for label adjustment, and simulation is often something  
12 that is used to help understand and pick a better dose  
13 strategy.

14 So, it is not really the pivotal trial, it is not  
15 replacing a pivotal trial per se, but it is helping to  
16 streamline the process and facilitate your understanding of  
17 the data.

18 DR. BYRN: Thank you. That is what I was trying  
19 to say.

20 DR. VENITZ: I would like to make the comment that  
21 lots of times it is not only the results of the modeling  
22 exercise that is important, but the process itself in terms  
23 of identifying what we don't know usually more than it is  
24 important for us to identify what we do know, and for the  
25 parts that we don't know, how much confidence, how wide are

1 our guesses.

2           So, I think when you talk about best practices,  
3 Larry, it is not only a matter of identifying attributes and  
4 some specification, how those attributes should be met. I  
5 think that really depends on the purpose of this whole  
6 exercise, and it is one thing to say I want to use this kind  
7 of modeling to approve a drug in a certain population that  
8 has never been tested for safety and efficacy. Then, we  
9 would put the standard up very high.

10           But if you want to support dosing changes or  
11 special population kinetic change that you observe, then,  
12 you might have much less of a burden to overcome in terms of  
13 the specifications of the model.

14           DR. LESKO: So, an example of modeling and  
15 simulation, then, that would be sort of lower down than  
16 approving a drug would be to approve label language based on  
17 a suitable modeling and simulation exercise.

18           DR. VENITZ: Right. In my mind, it would depend  
19 on what the claim is that you want to take out of the  
20 results that you get and how wrong can you be, and what are  
21 the consequences of being wrong that determine the rigor  
22 that you put in, in the modeling exercise, in the first  
23 place, because otherwise, you are back to, well, if you have  
24 all the data in the world, we can model everything, but then  
25 why would you model in the first place, let's just use the

1 data.

2 DR. BYRN: Dr. Doull.

3 DR. DOULL: I think it would be interesting if we  
4 could begin to put some parameters on extrapolation. In  
5 toxicology, for example, we have two major problems in  
6 extrapolation. We want to use the results of one species to  
7 predict what is going to happen with another.

8 We also want to extrapolate from very high doses  
9 that we do our tests in to the very low doses that humans  
10 are exposed to. We tend to do that without much guidance in  
11 terms of how one does extrapolation. We don't have any  
12 problems with interpolation, but with extrapolation, we do a  
13 lot.

14 The Nonclinical Subcommittee, of course, is  
15 looking at the utility of biomarkers as a way of predicting,  
16 and according to your description, toxicology and use of  
17 biomarkers, and so on, all of those are really modeling  
18 techniques.

19 So, the issue for the biomarker use, for example,  
20 is really how predictive it is. You know, is it really  
21 giving you the right answer. I hear what Kathleen is saying  
22 about validation, but the bottom line comes to that question  
23 of does it give you the right answer, and I don't know  
24 whether that is validation or verification or whatever, but  
25 if it isn't doing that, we are wasting our time.

1 DR. LESKO: I tend to agree with that. I think  
2 the animal-to-human bridging is more often than not done on  
3 an exposure basis and PK/PD or at least TK/TD relationship,  
4 and I think it is actually one of the more advanced areas  
5 for modeling and simulation, for estimating first dose in  
6 man. So, in some ways, that is a little bit ahead of, say,  
7 clinical trial simulation.

8 DR. BYRN: I would like to focus on these four  
9 questions now, because I do think that we need to try to get  
10 some kind of answers to these, and then we will have a  
11 chance to discuss them.

12 The first question, I think we have pretty well  
13 addressed, is how industry uses simulation to help the drug  
14 development process. I think Michael has simply summarized  
15 it, everywhere probably is a fair statement.

16 Let's have some discussion on the committee, just  
17 opinions: Are modeling and simulation appropriate for drug  
18 development and regulatory decisions? Are there points that  
19 the committee would like to bring up?

20 DR. LAMBORN: I guess I would just think that for  
21 the same reasons that were just stated in answer to 1, the  
22 answer is yes, modeling and simulation are appropriate for  
23 drug development and regulatory decisions.

24 I mean they are not appropriate everywhere, but  
25 there is a place for them many places in that process.

1 DR. BYRN: Other comments? Does everybody agree  
2 with Kathleen?

3 DR. BOEHLERT: Just to follow up on your comments  
4 with regard to technical CMC kinds of decisions, in fact,  
5 they are used now. Submissions are made based on limited  
6 stability data for generic products or innovator products,  
7 and so they have been in use for many years, this is not  
8 new, so definitely the answer there is yes.

9 DR. BYRN: Gloria.

10 DR. ANDERSON: As a strong supporter of computer-  
11 assisted drug design prior to getting to where you guys are  
12 with clinical, I certainly would think that we ought to be  
13 involved in it.

14 It seems to me--and this is probably particularly  
15 more true in the future than now--it seems to me like it  
16 would be difficult to regulate an industry that is using  
17 something that you are not familiar with, so if no other  
18 reason, it is probably important to do that.

19 It also may--getting back to the Nonclinical Study  
20 Subcommittee--I suspect that at some point, there could be a  
21 link between what is being done now with the computer-  
22 assisted modeling and the information they collect, and what  
23 goes on after that, and our job is to look at ways to make  
24 this more efficient and to link these in order to shorten  
25 the amount of time that is required to get the drug to

1 market.

2 DR. BYRN: That is Question 2. Question 3. What  
3 are the important attributes of a meaningful simulation  
4 practice? I think we have been talking about one of them, I  
5 think is verification and use of data to verify the  
6 simulation or the model.

7 Can we have some discussion about other ones? Dr.  
8 Mould.

9 DR. MOULD: I would like to suggest or strongly  
10 support the use of some kind of a simulation analysis plan  
11 being put in place prior to the simulation, because I think  
12 it adds a lot of scientific veracity to the work, and it  
13 allows a more team-based approach, which has been mentioned  
14 before, so that you have more than just the modeler working  
15 on it.

16 DR. BYRN: Can you explain a little bit a  
17 simulation analysis plan?

18 DR. MOULD: Actually, to define the scope of the  
19 simulation, to define what it is you want to know, what you  
20 expect to get out of it, and how you anticipate to do the  
21 work.

22 DR. BYRN: So, you don't just start out with a  
23 simulation, you outline what you want first, and then you  
24 get the simulation.

25 DR. MOULD: Exactly, a protocol, if you will, or



1 an analysis plan.

2 DR. BYRN: It is a protocol. Does everybody feel  
3 comfortable with that? Now, we are talking about at least  
4 two things, a simulation analysis plan and then a  
5 verification, if you will, a verification activity involved  
6 in that, whether it is using real data or some other source  
7 of data, but some kind of verification process.

8 Other attributes?

9 DR. LAMBORN: Beyond that it has to have the three  
10 components that Michael mentioned earlier, I mean the list  
11 of clear assumptions, the statement about the  
12 implementation, so really, it is documentation and  
13 clarification of exactly what is involved, and again, the  
14 things that have been said about the full team participation  
15 in the interpretation to assure that there is consensus and  
16 understanding from all the different aspects of it.

17 So, I think it is just a synthesis of things  
18 already said.

19 DR. BOEHLERT: One additional comment that I might  
20 add. I think any analysis plan, where at all possible,  
21 should have predetermined exceptions criteria, so you know  
22 exactly what it is you are aiming for in advance, and that  
23 these aren't determined after the fact, well, this is what  
24 we got, so this is what it should be.

25 DR. LAMBORN: Basically, the thing that you would

1 expect from any research project, whatever it is.

2 DR. BYRN: Larry.

3 DR. LESKO: I just want to make a sub-question to  
4 that question. I think we recognize that applications of  
5 modeling and simulation are going to range from something  
6 that would be at the lower end of the scale to a higher end  
7 of the scale.

8 As an example, if you are going to extrapolate,  
9 let's say, some efficacy and safety data from one population  
10 to another using some modeling of exposure response data, et  
11 cetera, it may have a different standard than, say, another  
12 situation where you might want to use an exposure-response  
13 relationship to make a judgment on the significance of an  
14 exposure increase and a drug interaction for the purposes of  
15 labeling the product.

16 So, in one case, you are approving a drug for a  
17 new population. In the other case, you are labeling the  
18 product based on a model and a simulation.

19 I wonder if there are attributes of the modeling  
20 and simulation exercise that would be used to distinguish  
21 between the credibility of those applications. In other  
22 words, would there be certain characteristics of the  
23 modeling and simulation that would distinguish these  
24 applications?

25 DR. VENITZ: I think for the latter, meaning you

1 are trying to approve a subpopulation for safety and  
2 efficacy, it is the very thing that we were talking about,  
3 you have to have a prospective plan in place. You cannot do  
4 some study and then go on a fishing expedition, which is  
5 what a lot of people, a lot of statisticians particularly,  
6 look at modeling and simulation in the clinical pharmacology  
7 area. So, it is the equivalent of a meta-analysis, and you  
8 really have no control of the final outcome.

9           So, if the standard that you are trying to meet is  
10 very high, you are trying to look for approval, I think it  
11 has to be prospectively designed and according to protocol.

12           For the former case, that might not be the case.  
13 You might have retrospective analysis of data that you have  
14 in your safety database and see whether a certain change in  
15 exposure really leads to a change or expected change in  
16 dynamics.

17           DR. BYRN: Other comments? Maybe we will go to  
18 Question 4. I think we will review these again and have  
19 public comment after lunch, so we will have time to come  
20 back and comment some more, but let's cover Question 4 right  
21 before we break.

22           Do we need an FDA guidance to industry regarding  
23 the best practice of modeling and simulation for regulatory  
24 applications? I think we have kind of covered the first  
25 bullet.

1           If yes, what is the important information that  
2 should be in the guidance? If no, what are the critical  
3 issues that need to be addressed before developing a  
4 guidance?

5           I think Kathleen already addressed this to some  
6 extent. Do you want to say anything more?

7           DR. LAMBORN: I guess what I would argue is that  
8 at the moment, that there are guidances which include  
9 information that is specific to them, and it sounds to me  
10 like it would take some more defining to come up with  
11 something that would be a broad guidance, that would go  
12 across all the different kinds of applications.

13           DR. VENITZ: I am wondering about the scope of the  
14 guidance, would it include things like what Mike was  
15 mentioning, that are used primarily in the discovery  
16 process, trying to predict based on structure, certain  
17 physical, chemical, or biological activities.

18           Would that be part of what this guidance is all  
19 about, or is it more of the traditional clinical trials  
20 simulation type?

21           DR. LAMBORN: It seems to me we have got two  
22 things. We tend to think of a guidance as being something  
23 that is what you are expected to do in order to meet  
24 regulatory approval, and I think, Larry, what you were  
25 talking about when I first posed this question is something

1 that is even potentially more important, which is the joint  
2 involvement of the Agency with all the people involved to  
3 come up with a best way to do things, which may not be  
4 things that eventually come directly to be part of a  
5 regulatory package at all, and therefore, really wouldn't be  
6 part of a guidance.

7 DR. LESKO: Part of the attempt--and I guess I  
8 sort of took this approach with that population PK  
9 guidance--if you get a modeling and simulation study  
10 submitted to the Agency, you would hope that, as a sponsor,  
11 that that would be an acceptable exercise.

12 I can't tell you how many times we have had in the  
13 past population PK studies that were submitted with  
14 conclusions that were rejected because the study wasn't  
15 designed properly, analyzed properly, samples weren't  
16 collected at the right times, and it seems like a total  
17 waste of time if you don't have that assurance that this is  
18 currently what we are thinking.

19 These may be general attributes, but if they are  
20 considered as part of the modeling and simulation exercise,  
21 this is, in fact, what the statisticians or the clinicians  
22 or clinical pharmacology folks will hold as important.

23 That is kind of the motivation for it. It is not  
24 that the guidance presents--and I suspect there may be some  
25 fear of that--but it isn't that a guidance on the topic

1 would set an expectation that this becomes a part of each  
2 and every application. So, I think it is sort of  
3 delineating more what we think is the current knowledge base  
4 and the best practices.

5 DR. BYRN: Other comments?

6 I think we should come back to this, but if we  
7 would answer this yes, are there any comments anybody wants  
8 to put on the table about what the important information  
9 that the guidance should include?

10 I think Larry in a way outlined some of that in  
11 that it probably would be a general over-arching guidance.  
12 Do you want to outline some other thoughts you might have?

13 DR. LESKO: I would think there may be some  
14 discussion--well, first of all, I think there would be some  
15 examples that might be helpful. There could be, for  
16 example, an appendix to this thing that would give examples  
17 of applications that maybe go beyond internal decision-  
18 making, but more towards how it was valuable to resolve the  
19 regulatory question. So, that might be one part of it.

20 I think there is a process of model building and a  
21 process of simulating, and maybe this is what the experts  
22 have been talking about, the simulation plan, the  
23 assumptions are clearly stated, the results are reported in  
24 a certain way, and maybe it is just that structure that  
25 would be valuable in advancing this, that we are at least

1 all on the same page with regard to the process we are going  
2 to go through and apply good science to the modeling of the  
3 data to the simulation, and then have some agreement on what  
4 those characteristics are.

5 DR. BYRN: And then the Agency, when they got  
6 these, would have them in an order that they expected and  
7 could review them appropriately.

8 DR. LESKO: Yes, and I would think there would be  
9 again a buy-in or an agreement on what is necessary  
10 information to assess this modeling and simulation exercise,  
11 if there is, in fact, a desire by an applicant or sponsor to  
12 use this information in a prospective way.

13 DR. HALE: The state of the art of modeling and  
14 simulation in many clinical applications right now is such  
15 that I think many of us would welcome some guidelines that  
16 would help in terms of enabling, in other words, better  
17 consistency, better uniformity of what to expect.

18 In terms of requirements, I don't think we are  
19 there yet because there are so many things we haven't  
20 answered - how do we validate the models, how do we gain  
21 certainty. If it were viewed as a requirement, it would be  
22 very difficult, but it were viewed as something to enable a  
23 meaningful dialogue, a way that we could actually sit down  
24 and share a common language, and I would add to that some of  
25 us have been discussing whether we need an ongoing forum,

1 something like this Product Quality Research Institute you  
2 have on the agenda this afternoon, do we need something like  
3 that for modeling and simulation.

4 DR. BYRN: I wonder if it could even be in the  
5 Product Quality Research Institute as another group.

6 DR. LESKO: I told Mike when I talked about this,  
7 that was something I was going to look into.

8 DR. BYRN: Let's take a break of lunch, and then  
9 we will come back at 1:00 and have an open public hearing,  
10 and people will have an hour to think about this. Maybe we  
11 can make a little bit more of a list of things for the  
12 Agency and the committee to think of, although I think we  
13 have had very good discussion up to this point.

14 [Whereupon, at 12:00 p.m., the proceedings were  
15 recessed, to be resumed at 1:00 p.m.]





1 really to communicate the results and give the information  
2 to other disciplines.

3 I notice that there is different disciplines in  
4 these committee meetings. Can anyone address that? What is  
5 a medical officer or medical clinician, and what is a  
6 statistician actually looking for when they see a modeling  
7 and simulation program?

8 DR. BYRN: Kathleen.

9 DR. LAMBORN: I guess since one of the questions  
10 was the statistician, I think that the first thing I would  
11 look for would be the information that was mentioned by  
12 Diane and others this morning, which is that there was a  
13 research plan and a careful statement of what that plan was  
14 and what the methodology was, and I guess I am always  
15 particularly concerned about the assumptions and the basis  
16 for the assumptions, and anything that has been done to look  
17 at the impact of if the assumptions were not correct, how  
18 much that would change the outcome and whether such  
19 additional studies were looked at before the conclusions  
20 were reached.

21 That would be a start anyhow to what I want to  
22 know to know whether it was a valid study.

23 DR. LEE: So, what you are saying is the  
24 sensitivity of the result to a particular question, like a  
25 robustness.

1 DR. LAMBORN: Both the basis of the assumptions  
2 and the sensitivity of the assumptions, but certainly that  
3 there was a prior research plan, a prior research question,  
4 and how the results were followed up on that research  
5 question.

6 DR. VENITZ: As a clinician, I would say I want  
7 you to convince me that your model is plausible if it's a  
8 mechanistic model, or if it's an perogram [?] model, what  
9 kind of data you use to come up with your model per se.

10 The second question is in terms of your parameter  
11 estimates, how did you get your parameter estimates, what  
12 kind of studies did you use without getting caught up in the  
13 technical details.

14 DR. BYRN: Other comments?

15 DR. LaLONDE: I have maybe a request or a  
16 suggestion. I think it was Mike this morning that talked  
17 about one of the needs in this area is better information on  
18 diseases as we try to do clinical trial simulations to  
19 better understand all the different factors that may affect  
20 numerous different diseases, disease progression, placebo  
21 response, and I was wondering if, as part of your  
22 initiative, if the Agency was considering taking the lead in  
23 this area as information that may becoming available to the  
24 Agency from different sources, if possible, I don't know  
25 what the confidentiality issues are there, but if possible,

1 to have that information become part of the public domain  
2 somehow.

3           Unfortunately, the industry often will want to be  
4 secretive about this type of information, but I am wondering  
5 if once if it is submitted to the Agency, if after a  
6 certain number of months, for example, it could become  
7 available under the Freedom of Information Act or some other  
8 means.

9           DR. LEE: First, I agree that the progression  
10 model is very important because we have seen in the past  
11 that many simulations have failed just because it doesn't  
12 have a good disease progression model. Basically, it  
13 doesn't account for any change of disease stage as a  
14 function of time, so a placebo patient may have something  
15 changed, but it never accounts for that.

16           To answer that question whether we are doing  
17 something, internal disease progression model, I can think  
18 about two projects that we have ongoing at this time.

19           The first project is looking at QTc prolongation  
20 due to drug treatments. This has been a very hot topic in  
21 the past few years. Quite a few drugs were withdrawn from  
22 the market due to the QTc prolongations.

23           One of the problems with QTc prolongations was  
24 that the intrinsic daily variation of QTc in any normal,  
25 healthy subject, for example, any normal, healthy subject

1 may have a plus or minus 60 millisecond of change of QTc,  
2 but sometimes a drug may have only 10 milliseconds or 20  
3 millisecond, affect the QTc by only 10 or 20 milliseconds.

4           So, how do you identify such a small change or  
5 such a small effect with such a large inherent variability?  
6 So, that is what we are looking at, if we can model the  
7 daily variation of QTc, and this will be your physiological  
8 model, and on top of the physiological model, we can put a  
9 dry effect models.

10           We are looking at our NDA data. Also, we don't  
11 specify the drug name, but we are looking at NDA data. We  
12 also look at the literature data. We also work with IREF,  
13 which is the Ischemia Research Education Foundation, to get  
14 their information or their database to look at the models.

15           A second project--actually, we have three  
16 projects--a second project was also in cardiovascular area.  
17 It was headed by Dr. Ray Lipicki, and it was a collaboration  
18 with another foundation, that we are looking at I believe  
19 all the NDAs in the entire hypotensive areas, and look at  
20 the patient information and disease progression, and so on,  
21 and so forth.

22           That database, I believe will be open to the  
23 public, and can be used to build the disease progression  
24 models.

25           I think the third area is the diabetes disease,

1 because there are many interplayed factors that may affect  
2 disease progression, as well the surrogate and biomarker.  
3 For example, we can look at the glucose concentration post  
4 prandial or fasting group of concentration.

5 Right now the standard for the surrogate endpoints  
6 is hemoglobin A1C, but you have insulin that may interplay  
7 with the final effect. So, we are looking at a good disease  
8 progression model for diabetes, as well, and see if the  
9 glucose or postprandial glucose can be also a good surrogate  
10 endpoint for diabetes.

11 Because of the problem with hemoglobin A1C is you  
12 have to wait for 12 weeks before any significant effect can  
13 be measured, but postprandial glucose effect can be almost  
14 immediate. So, we also have a program to look at that.

15 DR. LaLONDE: I guess what I am just trying to  
16 avoid is having everybody have to do the same type of work  
17 independent of one another, and I think that is what is  
18 happening right now. So, I mean there are different  
19 options. Maybe a consortium of companies, they could pool  
20 this information together or a federal agency.

21 I know there are independent companies right now  
22 like Pharsight, who are purchasing these databases to  
23 basically use them as part of their efforts in disease  
24 modeling, so you can pay companies to get access to these  
25 data. That is one way. I am just wondering if in the role

1 of the FDA to basically look after the American public and  
2 the health of Americans, if there should be an effort to try  
3 to make this information more widely available more quickly.

4 DR. LEE: I think there is another initiative by  
5 Price Waterhouse Cooper, and actually by Mike Hale, as well,  
6 and this was a Pharma Simulation Board, and one of the  
7 objectives of the Simulation Board is to come up with a  
8 consortium just like you said, a collection of different  
9 models, disease progression model, and focally, everybody  
10 can share that information, because only by sharing that  
11 information we can move the research area quicker.

12 DR. BYRN: Kathleen.

13 DR. LAMBORN: I was thinking that perhaps this  
14 committee, if others agree, could formalize that suggestion  
15 by saying that anything that the FDA could do to encourage  
16 this activity based on the individual diseases, because  
17 often what will happen is that while the individual product  
18 is in development, they might not be able to share. Often  
19 there is the same comparator as the standard, and that can  
20 form a basis, but I think it would be appropriate, and I  
21 would like to put on the table a specific recommendation  
22 that this committee would encourage any efforts that the FDA  
23 could take to bring about this kind of activity.

24 DR. LaLONDE: Or other federal agencies if it was  
25 better done by the NIH or whatever.

1 DR. LAMBORN: Right, but the development of these  
2 in a collaborative fashion with all people who would have  
3 sources for data, that would be useful.

4 DR. LaLONDE: I very much support that.

5 DR. BYRN: Is there any additional discussion?  
6 Can we just take by acclamation that the committee  
7 encourages this, would like to go on record to encourage  
8 this? Okay. It looks unanimous.

9 Other points or comments? Let's just spend one  
10 more moment reading the section called Issues to be  
11 Considered. If the committee and all would just read those,  
12 and see if there is any area that they would like to comment  
13 on, and then at the end of that, I think we will conclude  
14 this discussion.

15 Yes, Kathleen.

16 DR. LAMBORN: Could I just ask, is there any item  
17 that was--we have talked around a lot of these--is there any  
18 particular component of this list of questions that you feel  
19 has not been addressed in case we missed something?

20 DR. LEE: I guess the committee has addressed  
21 almost all the questions. If you ask which item I want to  
22 hear more, I guess it would be Question No. 3, what is the  
23 attribute to a good model and simulation process.

24 DR. BYRN: So, maybe we could spend a moment.  
25 What do you have so far, Peter, as attributes from the notes



1 that you made prior to this, and then we will see if we can  
2 expand on those?

3 DR. LEE: I have I guess a lot of discussion on  
4 have a prior research plan or some kind of protocol for  
5 simulation. Everybody said that is important. We have to  
6 look at assumption when you build a model, and what is the  
7 basis for assumption, what are the data to support  
8 assumptions.

9 Analyses of model verifications, that is important  
10 to how do you know the model actually works. There was also  
11 talk about we cannot separate simulation from the model, so  
12 a lot of times we can use simulation to verify models.

13 We should have predetermined acceptance criterias.  
14 I guess the criteria may be different depending on the  
15 different regulatory applications. If it is exploratory, it  
16 can be less stringent than if you use the model and  
17 simulation to confirm certain things for regulatory  
18 decision, such as determining efficacy and safety in your  
19 subpopulation without any clinical data. That may require  
20 more stringent criteria for the model and simulation  
21 project.

22 I guess that is all I have.

23 DR. BYRN: Would people like to expand on those,  
24 or are they satisfied with those?

25 DR. VENITZ: I would add if you have any data, who

1 well does the model predict. The predictability of the  
2 model. If you have any data that you can compare to your  
3 model predictions, how well does it predict.

4 DR. LEE: You mean external data?

5 DR. VENITZ: Or internal data. Let's assume you  
6 generate your model from some dataset, how well does it  
7 predict that particular dataset. If you have external data,  
8 that would even be better, maybe some cross-validation  
9 studies.

10 DR. BYRN: Dr. Mould.

11 DR. MOULD: I was just sort of quoting something  
12 that Dr. Sheinin said at the last advisory committee  
13 meeting. I think this kind of summarizes to what do you  
14 want to know, how well do you want to know it, what kind of  
15 assumptions do you need to make, and that, to me, sort of  
16 summarizes everything.

17 But you might also want to add what are the  
18 consequences if I am wrong as a sort of a post-hoc step to a  
19 simulation, so that, you know, you have done what you could  
20 to assure that your simulation is as scientifically valid  
21 and accurate as possible given the information, but if you  
22 make a mistake or if you have made an incorrect assumption,  
23 it might be helpful to speculate about what the consequences  
24 of a mistake might be.

25 DR. BYRN: Any other comments? Yes, Dr. Hussain.

1 DR. HUSSAIN: I am going to speak from my neural  
2 network experience, I think. One of the aspects in modeling  
3 is I think the distribution of data in a sense of how rich  
4 your databases are that you use for developing model and how  
5 sparse the demographics might be, so I think distribution of  
6 your attributes within the dataset needs to be looked at.

7 DR. BYRN: So, that is another criteria to add.

8 DR. LEE: Any comments on using model to  
9 interpolate or extrapolate data? Would you always accept an  
10 interpolation based on the model all the time?

11 DR. VENITZ: I would say in general it is much  
12 easier to interpret it than it is extrapolating, and if you  
13 are extrapolating, I second what Dr. Mould was saying, you  
14 have to worry about the worst case, what happens if my  
15 extrapolation is wrong in order for me to decide whether I  
16 am willing to accept my model prediction.

17 DR. BYRN: Kathleen.

18 DR. LAMBORN: I was going to say very much the  
19 same thing.

20 DR. BYRN: Any other comments?

21 [No response.]

22 DR. BYRN: Let's just check one more time to make  
23 sure. Perakash Parab? Did Perakash Parab come into the room?  
24 That is tomorrow? Okay. We thought it was tomorrow, but we  
25 had it on the list today, so we just wanted to make sure.

1 I think that concludes our open hearing and our  
2 discussion of the clinical pharmacology issues.

3 Now, we will move to the next agenda item, which  
4 is an FDA Research Report on the Product Quality Research  
5 Institute. That will be done by Dr. Hussain.

6 FDA Research Report

7 Product Quality Research Institute

8 DR. HUSSAIN: Good afternoon. I just hope the  
9 computer will function.

10 [Slide.]

11 I wanted to provide an update to this committee.

12 There are several new members on this committee, and I would  
13 like to talk to you about two aspects. One is our  
14 Intramural Research, Office of Testing and Research  
15 Programs, and then the Product Quality Research Institute.

16 Yesterday, Helen Winkle mentioned that we are  
17 trying to improve the management and improve the programs in  
18 the Office of Testing and Research. At one of the next  
19 advisory committee meetings, I would like to come back to  
20 you with more detailed information on our re-engineering  
21 efforts and how we are trying to focus that, but right now,  
22 today, I will just give you an overview of what we are doing  
23 and what are the challenges.

24 [Slide.]

25 The Office of Testing and Research in CDER, we

1 have our ceiling, FTE ceiling going down. I think  
2 currently, it is, what, 95, Helen? Eighty-six. So, we have  
3 86 FTEs distributed in different disciplines.

4 We have three divisions, Division of Product  
5 Quality Research, Division of Applied Pharmacology Research,  
6 and Division of Pharmaceutical Analysis, and then we have  
7 the laboratory and staff functions. The laboratory is  
8 Laboratory for Clinical Pharmacology.

9 We have a Regulatory Research Staff Analysis  
10 function, which essentially creates our databases and  
11 focuses on structure activity and database type of  
12 activities there.

13 [Slide.]

14 The primary mission of this office is to advance  
15 the scientific basis of regulatory policy. Assure that  
16 regulatory policy and decision-making are based on best  
17 available science. Obviously, we also provide scientific  
18 and laboratory support for review, postmarketing  
19 surveillance, and compliance activities.

20 So, broadly, that is the mission, and then we try  
21 to achieve this mission through various programs, projects,  
22 and committees.

23 [Slide.]

24 The Office of Testing and Research embodies all  
25 key disciplines that are brought to bear upon review

1 decisions, so by nature, this is a multidisciplinary focus  
2 area, so I think we have an opportunity to build bridges  
3 across disciplines, and I think we try to do so more so than  
4 other parts of Center.

5 I think the key important areas for CDER's mission  
6 right now focus on nonclinical to clinical linkages, product  
7 quality, how to build quality, and then how to improve the  
8 methods that we use for product quality assessment.

9 Clearly, database availability and monitoring has been a  
10 focus, but currently that focus has been limited to  
11 toxicological databases and hopefully, we would like to  
12 expand that further to include quality and other databases.

13 [Slide.]

14 We also serve as consultant reviewers and provide  
15 other support functions to the review staff. Since I joined  
16 the Agency in 1995, I think I have seen the resources  
17 available to this office keep going down, and I think the  
18 future, I hope looks brighter, but I can't promise that, but  
19 what we have tried to do is with diminishing resources, we  
20 have developed more collaborations.

21 [Slide.]

22 PQRI is one I want to talk to you about, and Jim  
23 MacGregor will talk to you about using the advisory  
24 committee approach for building collaborations, and that  
25 presentation will be tomorrow.

1           Obviously, we work with other sister agencies and  
2 sister groups, such as NIH, and so forth. Academia and  
3 industry collaborations have always been there, and with  
4 industry, for example, we have a mechanism called  
5 Collaborative Research and Development Agreement, that  
6 provides a means for us to collaborate with a given company,  
7 for example.

8           We also collaborate with USP, and we have several  
9 collaborative links established with these organizations.

10          [Slide.]

11          I just want to summarize some topics. The  
12 regulatory contributions of this office to science base and  
13 policy- and decision-making, I am not going to go in detail,  
14 but I did provide you a list of publications from last  
15 fiscal year.

16          If you really look at that, I think with the  
17 resources we have, we did publish significantly, over 70  
18 publications and presentations, so the output has been quite  
19 good, and I think we will further focus this output to meet  
20 the needs of the Center, so you have that as a handout, and  
21 when you go home and look at that, you will see different  
22 areas of expertise that we have in our office.

23          The re-engineering efforts that we have ongoing  
24 right now primarily focus on management issues, developing a  
25 management system, but beyond management system I think we

1 are trying to enhance our ability to meet the needs of the  
2 Center more effectively and more efficiently, and introduce  
3 a concept of multidisciplinary teams. This is teams that  
4 will function and will have membership across our divisions.

5           One of the teams that we have in place now is a  
6 rapid response team, and this rapid response team brings to  
7 bear all the resources in OTR to address a high-priority  
8 issue, so all the resources are available to answer a  
9 question that comes from the review site at the earliest  
10 possible time frame.

11           Also, we are strengthening the linkages with the  
12 review function by establishing coordinating committees,  
13 which will monitor the research and will also provide a  
14 means for some sort of peer review also for the research  
15 unit.

16           [Slide.]

17           I would like to share with you one example of a  
18 regulatory research project. This project was discussed at  
19 the previous advisory committee, so I felt just to give you  
20 a flavor of what type of impact we have and what type of  
21 work we take on.

22           I will share with you a few slides on excipients  
23 and risk of bio-in-equivalence.

24           If you recall, this project was discussed at the  
25 last advisory committee meeting, and I did refer to this in



1 my morning presentation.

2           While we were developing the Biopharm  
3 Classification System, obviously, excipients were looked at  
4 very carefully, and we did find some high-risk practices  
5 that we felt needed to be addressed. The high-risk practice  
6 is related to use of sorbitol in oral syrups and oral  
7 liquids.

8           Sorbitol is a widely used excipient in oral and  
9 liquid dosage forms. It is related to mannose and is  
10 isomeric with mannitol, so mannitol and sorbitol essentially  
11 are similar molecules.

12           The component itself had low intestinal  
13 permeability. It is metabolized in the liver to fructose  
14 and glucose.

15           Reports of adverse reactions are largely due to  
16 its action as an osmotic laxative, and generally, we see  
17 this at doses 20 grams or more, but some individuals tend to  
18 be sensitive to this, and you could see adverse events as  
19 low as 5 grams.

20           Just for reference, 5.48 percent weight by volume  
21 aqueous solution is iso-osmotic with serum.

22           We have products on the market where the amount of  
23 sorbitol is quite significant. For example, there are a  
24 couple of products where one oral dose, which is two  
25 tablespoonfuls are 3 ml, can deliver up to 23 grams or

1 sorbitol per dose.

2 [Slide.]

3 So, the exposure or amount of sorbitol in  
4 commercial preparations, especially cough and cold  
5 preparations is quite significant, and we have known for  
6 some time that low permeability excipients can exert osmotic  
7 pressure in the GI tract, and partly because of that osmotic  
8 pressure, they can induce rapid intestinal transit.

9 Here is an example where you are comparing gastric  
10 emptying, small intestinal transit, and colon arrival time  
11 for different liquids - water, mannitol--I am just going to  
12 focus on water and mannitol.

13 If you look at mannitol, you see a significant  
14 reduction in the small intestinal transit time, whereas,  
15 sucrose and water do not provide that. So, this has been  
16 proposed as a reason for reduced bioavailability for some  
17 drugs.

18 [Slide.]

19 The literature data that supports that hypothesis  
20 is, for example, one study was done in 1995, it had 2.3  
21 grams of mannitol in the chewable tablet. That is a large  
22 tablet, chewable tablet, reduced bioavailability of  
23 cimetidine, which is a low-permeability drug.

24 For example, if you look at AUC, Cmax, and Tmax  
25 ratios compared to mannitol-containing tablets, chewable

1 tablet, with respect to sucrose, you see a reduction in AUC  
2 and Cmax and some extension in the Tmax.

3           However, we do have reports from the literature  
4 that large amounts of sorbitol generally have shown no or  
5 minimal effects on absorption of drugs, such as  
6 theophylline, which tend to be highly permeable drugs.

7           [Slide.]

8           So, based on available information, we did a  
9 study. We had information from published and in-house data  
10 suggesting that low permeability excipients, such as  
11 sorbitol or mannitol--other examples of low permeability  
12 excipients would be polyethylene glycol--in amounts used in  
13 typical syrup formulations can significantly reduce  
14 bioavailability of drugs that also exhibit low intestinal  
15 permeability.

16           I think the assumption or the hypothesis here is  
17 bioavailability of drugs that exhibit high intestinal  
18 permeability may be less likely to be affected by these  
19 excipients.

20           So, we conducted a bio study. It is a replicate  
21 design, bioequivalence study using ranitidine as a model low  
22 permeability drug, and we used simple solutions, one  
23 containing 5 grams of sorbitol and the other containing 5  
24 grams of sucrose, very simple formulations, and the  
25 formulations are shown here.

1 [Slide.]

2 You have 150 mg of the drug, which is low  
3 permeability. You have sucrose, which exhibits high  
4 permeability, 5 grams, sorbitol, low permeability, and water  
5 is obviously a highly permeable compound.

6 [Slide.]

7 So, if you look at the results, the mean results  
8 are shown here. It was a replicate design, and so this is  
9 the mean of N equals 40. You see a dramatic effect or  
10 dramatic difference between sucrose solution with the  
11 sorbitol solution. You can also look at individual  
12 replicates, and the data is fairly consistent.

13 [Slide.]

14 If you apply the average criteria for  
15 bioequivalence, using sucrose as a reference material, you  
16 see approximately 50 percent reduction in Cmax and AUC. So,  
17 obviously, these are not bioequivalent, but the effect is  
18 quite dramatic.

19 [Slide.]

20 You can also apply individual bioequivalence  
21 criteria, and in this case, the formulations fair to meet  
22 bioequivalence criteria regardless of how you do the  
23 analysis, whether you use constant scale approach or a  
24 reference scale approach, so they were bio-in-equal  
25 irrespective of the approach applied.

1 [Slide.]

2 Subject-by-formulation interaction was the topic  
3 that was discussed extensively at the last meeting. In this  
4 study, the AUCI reached a value of 0.15, which our guidance  
5 had suggested was a critical value.

6 Although it did reach the value of 0.15, it was  
7 not statistically significant because the confidence  
8 interval around the interaction included zero.

9 [Slide.]

10 Here is a stick blot showing the effect of two  
11 excipients on the area under the curve for this drug. If  
12 you look at sucrose, the between subject or inter-subject  
13 variability is quite significant, whereas, the variability  
14 tends to decrease when the excipient is sorbitol.  
15 Obviously, the two are in-equivalent, but at the same time  
16 you do see some tendency for differences between subject or  
17 inter-subject variability.

18 The inter-subject variability between the two  
19 formulations was insignificant.

20 [Slide.]

21 So, the conclusions we draw from this study is the  
22 significant risk of bio-in-equivalence between sucrose and  
23 sorbitol based syrups. We have practice in the sense  
24 generally when a request is submitted for biowaiver, this is  
25 generally granted because the amounts of excipient used are

1 within the inactive ingredient guide, so this is something  
2 we felt was a high risk, and this study resulted in  
3 strengthening the language that goes in the BABE guidance  
4 that you heard this morning. So, the research went to  
5 Policy quite quickly.

6 In addition to literature report, I mean  
7 obviously, when we focus on regulatory research, one study  
8 obviously is not the basis of a decision. You really need  
9 to be able to generalize your study findings to other  
10 situations, and so we did find similar trends.

11 For example, furosemide and atenolol, you have  
12 examples in the submissions, and so forth, that tablet  
13 formulation actually has higher bioavailability than the  
14 syrup formulation. So, again, syrup containing sorbitol.

15 [Slide.]

16 But I think we also wanted to generalize it  
17 further to test the hypothesis that highly permeable drugs  
18 would be less prone to this effect. This part of the study  
19 is just being completed. I don't have complete analysis of  
20 that, but the preliminary data that I have does suggest that  
21 the difference one would see between sucrose and sorbitol  
22 would be far less and we knew for theophylline, which is  
23 higher permeability than metoprolol, which we use as a  
24 boundary drug, and you can see here the difference between  
25 sorbitol and sucrose-based solutions for metoprolol, which

1 is a boundary, high-permeability drug, is best, slight  
2 differences there, but not likely to be a major difference.  
3 I will have to wait until the analysis is done.

4 [Slide.]

5 Here is an example of sort of a focused regulatory  
6 research that addresses the particular question, and then we  
7 can translate this information quickly to policy. It fills  
8 the gap that existed in the literature, and was used in that  
9 way.

10 [Slide.]

11 Let me change the focus now and move to Product  
12 Quality Research Institute. Many of you probably already  
13 know what this institute is. Product Quality Research  
14 Institute was developed by CDER in collaboration with  
15 several associations and organizations, trade associations.

16 It took a long time to develop this. I remember  
17 the first meeting we had for developing this was on January  
18 11, 1966. I had four or six feet of snow here, but we did  
19 have that meeting, so that was on the sign that this  
20 institute had to work.

21 The institute is organized into several layers.  
22 You have a board of directors. Ken Heimlich serves as the  
23 chair of this board of directors. You have a steering  
24 committee, which have representation from all the founding  
25 members. What is not shown in the steering committee

1 membership are the new members that joined PQRI. The new  
2 members are USP, ISPE, and IPEC, so different associations  
3 are joining, so the steering committee is increasing.

4           Then, you have a series of four technical  
5 committees. You have Drug Product Technical Committee  
6 chaired by Sid Goldstein. Drug Substance Technical  
7 Committee chaired by our own chairperson, Steve Byrn here,  
8 and Biopharmaceutics Technical Committee, Elizabeth Lane,  
9 who is in the audience. I just saw her come in. The  
10 Science Management Committee, and the position of chair is  
11 vacant. Dave Savilla used to chair it, and had to move  
12 because of other obligations.

13           [Slide.]

14           I am going to briefly talk to you about the  
15 philosophy behind how we are approaching in terms of  
16 defining the research plan for this. I will just share with  
17 you here, under Drug Product Technical Committee, we have  
18 plans for three working groups. One is up and running.  
19 That deals with the uniformity issue, and I will talk to you  
20 about that.

21           The two other working groups under Drug Product  
22 are Manufacturing Changes, Container Closure or Packaging  
23 Changes. Under Drug Substance, you have Specification or  
24 Bulk Active Post-Approval Changes Working Group, Particle  
25 Size Working Group, and Impurities Working Group. Since



1 Steve is here, I will request him to share some more  
2 information on that committee.

3 Under Biopharmaceutics Technical Committee, we  
4 currently have only one project, and that is extension of  
5 BCA's Base Biowaivers. We originally had two other groups  
6 planned. One dealt with Nasal and Inhalation Products, the  
7 other one, DPK or dermatopharmacokinetics. Those for the  
8 time being have been taken off because I think we will bring  
9 those back after our discussions tomorrow and possibly some  
10 more discussions and see how that goes.

11 There is only group under Science Management that  
12 deals with process management. It is not active at this  
13 time.

14 [Slide.]

15 Just to give you a brief overview of PQRI, it is a  
16 virtual institute. I think we bring together expertise from  
17 industry, academia, and FDA to work on regulatory problems,  
18 and I think the founding members are listed here.

19 You have the AAPS, which has the responsibility of  
20 day-to-day management of the institute. Then, you have  
21 Consumer Health Product Association, Generic Pharmaceutical  
22 Industry Association. We left it there because I think that  
23 was a founding member, but I think the association has  
24 changed, as you heard yesterday.

25 Then, you have National Association of

1 Pharmaceutical Manufacturers and the National Pharmaceutical  
2 Alliance, the Parenteral Drug Association, the  
3 Pharmaceutical Research and Manufacturing Association, and  
4 obviously, FDA.

5 As I said earlier, I think there are three new  
6 members now - USP, ISP, and IPEC.

7 [Slide.]

8 PQRI essentially is designed to address scientific  
9 needs, regulatory scientific needs, and PQRI would entertain  
10 and conduct research to address scientific issues related to  
11 regulations, guidances, and so forth.

12 Once a project is completed by a working group  
13 under this institute, that information will be transported  
14 to the FDA via the Steering Committee. I think we have  
15 built-in safeguards, so that the conflict of interest, as  
16 well I think FDA participation in this institute is clearly  
17 above board and consistent with approaches FDA utilizes.

18 So, for example, in this case, if a vote is  
19 required on the research outcomes, FDA would recuse itself  
20 from voting on that.

21 [Slide.]

22 Once the information is forwarded to the FDA, I  
23 think obviously, FDA has the sole authority for developing  
24 regulatory policy and guidance, so this information  
25 obviously is going to be recommendation, and since we are

1 participating on this institute, we hope to minimize any  
2 differences of opinion that can come about.

3 [Slide.]

4 Let me now give you a sense of how we approach in  
5 developing the research plan for this. I believe you are  
6 all familiar with the traditional approach that we have  
7 utilized for years in discovering and developing new drug  
8 materials, new drug products.

9 At the Agency, at the FDA, the primary focus tends  
10 to be from a safety and efficacy point of view, tends to  
11 focus on preclinical assessment, clinical Phase I, II, III  
12 evaluation, approval of the NBA, and then Phase IV  
13 commitment and monitoring adverse event reports. I think  
14 that is well recognized within the Agency.

15 I think supporting all those functions is product  
16 development activities, which start with pre-formulation.  
17 You use a formulation or you use a product to establish  
18 safety and efficacy profile, so when we say we approve a  
19 drug, we mean we are approving a drug product.

20 That material has to be scaled up and there are  
21 changes that occur to that material. The key questions we  
22 have asked ourselves are: how do you build quality in the  
23 products that are used in clinic? This is an extremely  
24 important question because if quality is not built in, then,  
25 you confound the safety and efficacy database with quality

1 problems. So, that is Question 1.

2 Question 2 is once you have the safety and  
3 efficacy database, how do you establish meaningful  
4 specifications, so that you could control or you could manage  
5 postapproval changes that result from, say, scale-up and  
6 other changes that occur. So, that is the debate sort of  
7 thing we have.

8 I will just share with you some slides from AAPS  
9 symposium that was set up as a debate, and I will explain  
10 that to you in a minute.

11 [Slide.]

12 We selected the Drug Product Technical Committee  
13 for this debate. Essentially, we have a regulatory  
14 hypothesis approach. This is how we started, and I think  
15 Steve will say a few words about how we have changed this  
16 approach later on.

17 If you look at what is the hypothesis under Drug  
18 Product Technical Committee, it simply states--and we  
19 discussed this on day one--"Adherence to Current Good  
20 Manufacturing Practices, which include validation, and  
21 appropriately established product specifications are  
22 sufficient to assure consistent quality and performance of  
23 drug products that are manufactured at different locations  
24 using alternate pharmaceutical unit operations, excipients,  
25 and container/closure systems." So, essentially all

1 aspects.

2           So, this is based on the changed model, that if  
3 specifications are appropriate, then, these changes should  
4 be managed via those specifications.

5           Clearly, the initial projects, focus has been on  
6 immediate release dosage form because of the long  
7 manufacturing history. If you recall, tablets and capsules  
8 have been manufactured in almost the same form for last 120  
9 years, so we have 120 years of manufacturing history and  
10 development history with this.

11           [Slide.]

12           What are the outcomes are we expecting from this  
13 exercise? Clearly, we would like to reduce the time and  
14 cost of implementing manufacturing changes, and this would  
15 definitely benefit industry.

16           We would like to reduce the number of CMC and  
17 biopharm supplements. I think the number is a large number.  
18 I think the number can be 1,500 for new drugs and 3,000 for  
19 generic drugs. It is a very big load on review, and  
20 hopefully, we would like introduce the concept of one-time  
21 review by CDER.

22           CDER reviews it once, and then once specifications  
23 are deemed appropriate, then, changes could be managed with  
24 that, and when changes in the specifications are needed,  
25 then, CDER would get involved. Again, that is a dream, and

1 that is a hope.

2           Clearly, the other aspect is to facilitate  
3 introduction of new technology, and this is to help maintain  
4 the competitive edge of the U.S. industry.

5           I think we approach this by saying that if we  
6 ensure that quality is built in, then, this is all possible.  
7 So, part of the argument here is by doing this analysis, by  
8 doing this exercise, we will ensure quality is being built  
9 in.

10           [Slide.]

11           At the AAPS meeting in New Orleans, not this one  
12 previous to this, we set up a debate just to provide  
13 perspectives, so that we can find ways for moving forward.

14           The debate we set up was as follows. CGMPs, which  
15 include validation, and product specifications are not--  
16 underlined--not sufficient to assure consistent quality and  
17 performance of most immediate release drug products that are  
18 manufactured, and so forth, and so forth.

19           I argued at the symposium why FDA feels that these  
20 are not sufficient, and we used the SUPAC-IR as a model, and  
21 we asked Sid Goldstein, Arni Repta--Arni Repta used to chair  
22 the Biopharm Committee--and Steve--I misspelled Steve,  
23 sorry, Steve--Steve Byrn to argue why not. So, that was the  
24 argument, sort of debate we had, and I will share with you  
25 my part of the debate, my argument here.

1 [Slide.]

2 Clearly, we are trying to identify high risk and  
3 low risk. The first day we did have the discussion, and I  
4 think I want to share with you the perspective here again.

5 Release testing that is based on specifications,  
6 at the time of manufacture does not provide the information  
7 that assures shelf life.

8 So, stability commitment may identify stability  
9 problems at a later time when the product is already in use  
10 by the patients, and if it fails to meet the specifications  
11 once it is distributed, it has to be recalled, and recall  
12 takes time and may be incomplete, so that is the risk.

13 If we approve a product on the basis of  
14 specification, and the specifications do not assure shelf  
15 life, then, the issue becomes of a recall, and recall can  
16 never be complete or isn't generally not complete, and the  
17 patient already has a substandard product. So, that is the  
18 risk.

19 [Slide.]

20 If you really look at what are the major reasons  
21 for recall in 1999, if you look at the quality-related  
22 recalls, we recalled, voluntarily, companies recalled  
23 products, or we had initiated some recalls because of sub-  
24 potency, dissolution failures. The number two reason for  
25 recall tends to be dissolution failure for quite a few

1 years. Super-potency, stability data generated did not  
2 support expiry date, failure to meet established impurity or  
3 degradant limits.

4 So, these are the top five reasons for chemistry-  
5 related recalls.

6 [Slide.]

7 Clearly, one of the aspects for risk assessment  
8 here is we feel that a combination of long term and  
9 accelerated stability testing (and PAS) are currently the  
10 only means of assuring correct expiry date.

11 Principles of accelerated stability testing are  
12 fundamentally based on the arrhenius equation, and the  
13 arrhenius equation is based on simple reactions, solution  
14 reactions, and so forth.

15 Now, if you are trying to use that fundamental  
16 reaction theory to predict physical changes, polymorphic  
17 changes, and other physical, that may not be appropriate, so  
18 I think having dissolution failures as number two reason for  
19 recall is an indication that the stability testing,  
20 accelerated stability testing may not be predicting physical  
21 changes that occur in products.

22 [Slide.]

23 Clearly, this morning I shared with you the FDA  
24 perspective on biopharm, why in vitro dissolution  
25 specifications may not assure bioequivalence, so I am not



1 going to go over that again.

2           So, that was sort of the debate we had. So, in a  
3 sense, having that debate and having laid out what are the  
4 risks associated allows us to then focus on how to approach  
5 that. Clearly, from a chemistry perspective, the issue  
6 becomes if we move away from pool supplement, the step would  
7 be if companies commit to having sufficient stability data  
8 before they distribute, that might be a solution. So, to  
9 begin to identify solutions for moving forward by clearly  
10 identifying where we stand and what are the reasons for  
11 current policy the way it is.

12           [Slide.]

13           So let me focus on the drug product and then share  
14 with you some thoughts on the project on blend uniformity.  
15 Blend uniformity is considered as an in-process control test  
16 and it is definitely a development test, but what are the  
17 problems with this.

18           Current policies require demonstration of adequacy  
19 of mixing or in-process powder blend homogeneity for batches  
20 that we currently manufacture. However, blend uniformity  
21 testing using sampling thieves is the only accepted method.  
22 If you try to imagine a vessel almost this room size, I mean  
23 if you are making a huge product of that size, it is a huge  
24 vessel that you mix your powders in, and you have to go and  
25 take samples from different parts of the blender and use a

1 thief to do this, and demonstrate that the mixing has  
2 resulted in a homogeneous blend of powder to move forward to  
3 the next step in the manufacturing process.

4           For most powder blends, based on the industrial  
5 input and based on current understanding of blending  
6 operations, it is felt that blend testing for every  
7 production batch is not necessary and that unit dose  
8 sampling, the thief that we use, can pose significant  
9 problems. In fact, the sampling procedure itself can  
10 introduce artifact and actually tell you that it is not  
11 homogeneous when truly it is homogeneous.

12           At the same time you have to keep in mind when you  
13 mix powders, that is not when the mixing stops. Then, you  
14 transport that powder blend to a different machine. If you  
15 are encapsulating a capsule, then, you have to transport  
16 that powder to capsule-filling machine or tableting machine.  
17 All the procedures used to transport that material can  
18 induce mixing or can induce de-mixing, so mixing doesn't  
19 stop at the blender.

20           Clearly, the debate that we are facing now is the  
21 gap in the scientific understanding and regulatory policies  
22 are a source of continued debate and from an industry  
23 perspective, leads to undesirable regulatory action, warning  
24 letters, and so forth.

25           At the same time we feel that current policies may

1 be devoting industry and FDA time and resources to address a  
2 redundant question, so that is the problem that needs to be  
3 addressed.

4 [Slide.]

5 The Blend Uniformity Working Group has been  
6 functioning for a couple of months now, and they already  
7 have held a workshop, and from that workshop we have had  
8 public input in how to proceed. The approach that the group  
9 is going to take is to identify if or when blending  
10 uniformity tests are needed to assure product quality.

11 What this entails is a risk assessment, what are  
12 the high risk practices in blending operations right now?  
13 For example, if you have powders which have very different  
14 particle sizes or powders which have static charges, and so  
15 forth, and if you don't account for that, then, blending  
16 might be a problem.

17 At the same time, how do you select the right  
18 blender for a given powder material, and so forth? So, a  
19 risk assessment of what are the high risk practices would be  
20 a step one. Then, clearly, the second step is to seek to  
21 enhance confidence in end product content uniformity to  
22 assure batch-to-batch content uniformity without the need  
23 for this in-process blend uniformity test.

24 What a patient gets is the tablet or a capsule.  
25 That has to have the right dose and has to have uniform

1 distribution of the drug in that material, so that is the  
2 proper question.

3 Blend homogeneity testing is an important  
4 development function. That is how a company would establish  
5 an optimal blend time, an optimal mixer, and so forth, but  
6 from a regulatory perspective, if we can develop an approach  
7 which says that end product or core sampling, just material  
8 coming out of a tableting machine, if that is homogeneous  
9 throughout the production batch, that might be a better  
10 approach to working with the current problem that we have.

11 Clearly, in some cases we probably would need  
12 blend uniformity testing, and if that is the case, then, we  
13 would like to develop and validate more effective methods.  
14 Here, methods, such as near IR methods and other methods  
15 will be looked upon.

16 The outcome we are hoping from this work is that  
17 we would have science-based recommendations for development  
18 of new guidance documents that will identify when and how  
19 powder blend uniformity should be tested, and the hope is  
20 that this guidance can save, not only development time and  
21 resources, but also reduce the number of unfavorable  
22 regulatory actions and save time for both FDA and the  
23 industry.

24 It is a bit ironic. I just want to step back and  
25 share some of my thoughts here. Blending is probably one of

1 the oldest unit operations that you can think of, and we  
2 have been making tablets and capsules for 120 years. I  
3 don't know how long have you been blending powders.

4 It is ironic from my perspective that I think we  
5 are having this debate. We started PQRI with the most  
6 simplest, the oldest unit operation to deal with, so I don't  
7 know what that says about the science of building products  
8 here. So, anyway, let me move on.

9 [Slide.]

10 Biopharmaceutics Technical Committee, the  
11 chairperson is Elizabeth Lane. The basic premise or the  
12 basic umbrella hypothesis that this committee has adopted is  
13 that in vitro drug release and other appropriate physical  
14 and chemical product tests can be developed to assure  
15 equivalent rate and extent of drug absorption from  
16 pharmaceutical equivalent dosage forms.

17 Clearly, I think the desire here is to move  
18 towards more in vitro based methods for assessing  
19 bioequivalence, and the first product selected is extension  
20 of the biopharm classification-based biowaivers for Class II  
21 and Class III drugs.

22 The chairperson here is Jim [Polli] from the  
23 University of Maryland, so that group also has been formed  
24 and they have started already working on developing a  
25 research plan.

1           Interestingly enough, in the first working group  
2 meeting, they felt that it made it easier to move in Class  
3 II direction, not Class III, although I would have expected  
4 that they would moved for Class III drugs, we will have to  
5 wait and see how that group develops the program.

6           [Slide.]

7           Drug Substance Technical Committee, I will just  
8 briefly mention this and then let Steve share some of his  
9 thoughts here. This committee is going to focus on a  
10 similar umbrella hypothesis and will deal with changes to  
11 bulk active materials.

12           Clearly, the desire here is to develop meaningful  
13 specifications for drug substances, so that we can control  
14 manufacturing changes for the drug substance itself. The  
15 point I would like to make here is I think this has been a  
16 long process, and we, by design, adopted a hypothesis  
17 approach which will essentially create he debate and through  
18 the debate will come data and information to make some  
19 decisions.

20           I think there has been some reservation with the  
21 hypothesis approach meaning that I think the hypothesis is  
22 so structured that it is favoring FDA current policy. That  
23 means you essentially can reject this hypothesis. I think  
24 Steve has some suggestions of moving away from the  
25 hypothesis-based approach to a more descriptive approach,

1 and I will let him share that.

2 [Slide.]

3 Let me just share with you some thoughts on the  
4 Science Management Technical Committee. This committee was  
5 put together with a goal to develop strategies that maximize  
6 efficiency of the processes that produce an optimally  
7 performing drug product that meets public health objectives  
8 for identity, strength, quality, purity, and potency.

9 It was thought that we will start with process  
10 mapping, how does a company develop product and how does the  
11 company interact with FDA, and can we optimize those  
12 interactions between FDA and companies, so that reviews  
13 could be done quickly, as well as that information could be  
14 used in development to improve efficiency, and do this for  
15 both CMC and biopharm.

16 As I said, that Dave Savilla is leaving this  
17 committee. The committee has not been active, and we hope o  
18 reactivate this committee soon.

19 [Slide.]

20 With that, I will just share with you we have more  
21 detailed description of the research projects and other  
22 information on PQRI, and we have a web site, is  
23 [www.pqri.org](http://www.pqri.org).

24 With that, I will stop and let Steve share some of  
25 his thoughts.

1 DR. BYRN: Thanks very much, Ajaz.

2 I will just give you a quick additional update on  
3 the Drug Substance Technical Committee. As you saw, the  
4 hypothesis basically stated that if you followed GMPs and  
5 you critically compared three parameters, which would be  
6 physical properties, specifications, and impurities, that  
7 the hypothesis is that those activities alone would be  
8 enough to ensure equivalence in a drug substance made by  
9 different routes at different sites, and so on.

10 Now, of course, this issue is related to the site-  
11 specific stability issue and really to a long-standing issue  
12 in Drug Substance, which is that--and this was extensively  
13 discussed at the BACPAC, AAPS, FDA symposium that was held  
14 in Arlington about three years ago--the widely held belief  
15 that even though two bottles of drug substance are assured  
16 or said to be the same by analytical chemists, they don't  
17 perform the same in the formulation, and they don't make the  
18 same drug product with the same dissolution tests and  
19 stability.

20 So, in this case, the hypothesis is running  
21 against what is commonly held in the field, and we have been  
22 going through a lot of iterations of how to deal with this.  
23 What we decided to do was to constitute, divide it into  
24 three parts, so we are going to divide it into a part  
25 involving physical properties, a part involving



1 specifications, and a part involving impurities, and then  
2 those three working groups will redefine their area and  
3 their hypotheses, to more carefully examine this broad  
4 issue.

5           Obviously, this is related to BACPAC-2 and BACPAC-  
6 1. The current BACPAC-1 guidance is out for discussion.  
7 BACPAC-2, I believe has not yet been issued, but maybe is  
8 somewhat imminent I think it is fair to say. I said  
9 "somewhat imminent." Is that fair, Helen?

10           This is another critical aspect. In the long run,  
11 we think that this will be a very worthwhile activity  
12 because this whole issue, what we are really trying to do  
13 fundamentally is understand what the problem really is and  
14 why there is this apparent gap between the science of  
15 understanding the sameness, if you will, of drug substance  
16 and the performance of those materials that are thought to  
17 be the same once they are taken into formulation and in  
18 dissolution and stability.

19           So, the working committees have all been assigned  
20 by our group, and those working committees we are hoping to  
21 constitute formally in January with a training session, and  
22 then their job will be to define the projects further in  
23 these three areas.

24           I don't know whether Ajaz wants to add anything  
25 more, but that is sort of an update on where we are.

1           Now we are ready for committee discussion on this  
2 matter, so it is open for discussion, either part of Ajaz's  
3 talk, either the PQRI or the Office of Testing and Research  
4 discussion. Any committee questions?

5                           Committee Discussion

6           DR. RODRIGUEZ-HORNEDO: Not a question, but I want  
7 to support the initiative. I think it is an extraordinary  
8 effort in bringing industry and academia and other groups  
9 together to work on very relevant problems.

10           I suspect that the challenge lies in raising money  
11 for some of this work, so is there a binding on which  
12 projects get supported or is not a problem, you have more  
13 money than projects?

14           DR. HUSSAIN: No, money aspects of PQRI are  
15 handled by non-FDA, so I would rather not comment on money  
16 aspects.

17           DR. BYRN: But there is a major effort on the  
18 board of directors that Ajaz listed, there is a major effort  
19 to raise funds from the private sector to support the  
20 program.

21           DR. ANDERSON: You mentioned something about  
22 sampling techniques for the powders, I believe, and then you  
23 mentioned something about infrared analysis. Could you  
24 comment on that, because you kind of lost me?

25           DR. HUSSAIN: The current method is using sampling

1 thief. You insert a thief and then collect a small sample,  
2 and the sample has to be approximately the same size of the  
3 dosage unit. It cannot be more than three times. That is  
4 what is required.

5 But there are new technologies coming about where  
6 we actually could do homogeneity assessment with, say,  
7 having near IR probes built into the blender where you could  
8 look at the blend homogeneity based on some of the new  
9 technologies. That is what I was referring to.

10 DR. ANDERSON: Okay.

11 DR. BYRN: Any more questions from the committee?

12 [No response.]

13 DR. BYRN: We will open this discussion to the  
14 audience. Would anybody like to ask a question or make a  
15 comment?

16 [No response.]

17 DR. BYRN: Hearing no question, we are scheduled  
18 to take a break. I think we will go ahead and take a 15-  
19 minute break until 2:30 and then we will start the Failed  
20 Bio Studies discussion.

21 [Recess.]

22 DR. BYRN: We will go to the last session of  
23 today. It is a session on ANDA bioequivalence studies that  
24 fail to meet FDA's current bioequivalence criteria.

25 To initiate the discussion, Dale Conner, Pharm D.,

1 will make a presentation. Thanks very much, Dale.

2 GENERIC ISSUES

3 Failed Bio Studies

4 DR. CONNER: I am here to talk today about  
5 something that is of great, I guess, interest and concern to  
6 us in the Office of Generic Drugs and in OPS. Strangely  
7 enough, when I discuss this with people who are not part of  
8 the industry or the FDA, they often express a great deal of  
9 surprise at what I am about to say. You will see what I  
10 mean in a second.

11 We obviously in Generic Drugs, deal with ANDAs,  
12 Abbreviated New Drug Applications. As you know, there is a  
13 limited set of one or more studies, bioequivalence studies,  
14 that we use to approve these generic products.

15 [Slide.]

16 To review, for those of you who may not have  
17 looked at this in a little while, most of the studies that  
18 we look at, or at least up until recently have been looking  
19 at, are generally two-day, crossover studies, single dose  
20 for the most part, although we have in a limited subset of  
21 products, we have done multiple-dose studies, normally under  
22 fasting conditions, and most importantly, our BE criteria is  
23 90 percent confidence intervals calculated based on the  
24 variability of the study, must fall between 80 and 125  
25 percent, or if you would like to express it in fractions,

1 0.8 to 1.25. We do that on both area under the curve and  
2 Cmax.

3 To date, also, the fed bioequivalence studies,  
4 performed in a similar manner, are done as a point estimate  
5 between those same numbers, 80 to 125. As an aside, because  
6 I was asked about it outside this morning, I will reiterate  
7 that at the moment, that criteria of point estimate between  
8 80 to 125 has not been changed. That guidance that was  
9 discussed this morning merely changes the design of the  
10 study from a three-way study to a two-arm study. That is  
11 really the only change to date that is out and official in a  
12 guidance.

13 Now, we are working on things and we have  
14 proposals to change that, but until the food guidance comes  
15 out, as far as I know, it will stay at point estimate  
16 between 80 to 125.

17 [Slide.]

18 As another review, I have put down various  
19 scenarios of results that one could get from a  
20 bioequivalence trial. Before I go into this, I have drawn  
21 them, you know, for the sake of simplicity, as a bar, and  
22 the width of this bar is supposed to represent the width of  
23 the 90 percent confidence interval results from a study, but  
24 it is important to remember that the results truly are not a  
25 bar that runs very evenly across.

1           It is more of a bell-shaped curve with most of the  
2 subjects in the studies centered around the center, and as  
3 you get out to the edges, you get much less of the subjects  
4 with those values, so keep that in mind that it is not an  
5 even distribution like I have drawn it here, but for  
6 simplicity sake I have depicted it this way because it is  
7 easier to look at.

8           On the top, you can see the blue bar, which is  
9 what most generic sponsors hope to achieve when they do  
10 their studies and when they formulate, which is very nice  
11 passing results, and you will see on the x axis, we have the  
12 test to reference ratio, expressed as a percent, and the two  
13 dotted lines are the confidence interval limits at 80 and  
14 125 just for reference.

15           So, it is centered around 1 or 100 percent, which  
16 is an idea result, which means most of the subjects T-R  
17 ratios are around 1, which is exactly what the sponsor is  
18 looking for because it says that we are very, very close to  
19 the performance of the reference drug, and the variability  
20 is quite modest, therefore, the confidence intervals aren't  
21 really wide.

22           Now, we have a second case. The blue one is the  
23 only one of my slides or depiction that actually passes or  
24 is thought to pass, but we have different scenarios of  
25 failure, I guess, if you will.

1           The second one is simply, you know, it is again  
2 the point estimate is centered around 1, so if we looked at  
3 means only, we would be very happy, however, this study has  
4 high variability, so because of that variability, we end up  
5 with a very wide confidence interval.

6           That confidence interval, because of its width,  
7 also leads to a failure because it fails, in the way I have  
8 drawn it, on the low side. It goes below 80, therefore,  
9 even though the point estimate or mean of the data is about  
10 as good as you can expect it to be, the product still fails  
11 because the variability is so high that the confidence  
12 interval is wide and fails.

13           I suppose the sponsor could come back in and  
14 repeat the study with a test with much greater power or with  
15 many more subjects, and that would effectively shorten this  
16 confidence interval and may actually get this one to pass.  
17 But this illustrates how highly variable drugs often need  
18 more subjects in their study to be able to hope to pass.

19           Some other usual ways of failing to demonstrate  
20 bioequivalence--and these are pretty much the same case with  
21 the same variability--one is a failure on the low side, one  
22 is a failure on the high side. Those have roughly  
23 equivalent, if you will pardon the expression, equivalent  
24 variability to the first case which passed, but they are  
25 simply off the center.

1           The formulation has shown itself to be not all  
2 that close. The test is not all that close to the  
3 reference. Therefore, even though they have quite  
4 reasonable or low variability, they still manage to fail  
5 simply because there is a distance between the two  
6 formulations.

7           So, these failed, not because of variability  
8 issues, but because there is probably a somewhat significant  
9 difference between the two formulations.

10           The one second from the bottom, which is right  
11 here, I show kind of a further extreme. This fails. You  
12 will notice the previous two failed simply because they were  
13 close to the end, the point estimate yet was still inside.

14           The one second from the bottom is a bit more  
15 extreme case. You see that the actual point estimate or  
16 center part, which I have tried to draw a line, hopefully,  
17 you can see it, is also outside. So, even though a portion  
18 of the confidence interval or the data is inside the  
19 acceptance criteria, most of it, including the point  
20 estimate, is out.

21           It starts to get to a point where the probability  
22 is that simply powering up a study, you know, using lots of  
23 subjects may not help this product. I mean it is at such a  
24 state that although it is certainly possible, the likelihood  
25 is simply during a huge study is probably not going to pass



this one.

2           Finally, we get to a very extreme case, the entire  
3 confidence interval or data outside the acceptance criteria.  
4 This is one of the few cases where people, rightly or  
5 wrongly, have called this "bio-in-equivalent," and a lot of  
6 people throw around the term "bio-in-equivalent" in kind of  
7 a cavalier fashion, but in reality, the tests that we do  
8 really do one of two things.

9           Either they confirm that something is  
10 bioequivalent or they fail to confirm it is bioequivalent.  
11 Only in an extreme case do we actually, accurately call this  
12 bio-in-equivalent, which is quite a different statement from  
13 the first.

14           In this one, there is probably no conceivable way  
15 you could do this study and get it to pass. It is so  
16 different that it is probably truly not equivalent in any  
17 sense, and there is no type of conceivable study design or  
18 power that could ever fix that, and I am not saying fix it,  
19 but at least do a study that might demonstrate  
20 bioequivalence.

21           [Slide.]

22           So, what do I mean when we say "failed"?  
23 Different people with different viewpoints, I suppose for a  
24 sponsor, anytime they don't get the results that they would  
25 like to have and supports the eventual marketing of their

1 product, they consider that a failure, and I suppose in  
2 their way of looking at it, it is, but I define a failure as  
3 simply the results of a study failed to support, for an  
4 ANDA, bioequivalence, and therefore, approval of that  
5 product.

6           To repeat what I just said on the last slide,  
7 simply failing to show bioequivalence does not necessarily  
8 infer that it is bio-in-equivalent. There are a whole  
9 variety of reasons why one doesn't meet the confidence  
10 interval requirements or the bioequivalence requirements,  
11 and I will list a few of them later.

12           Sponsors, for the reasons I will go into, often  
13 choose not to submit failed studies in ANDAs, and I will  
14 beyond to say it is more than often, it is most of the time  
15 they choose not to submit these studies.

16           When they get a failed result or a result that  
17 doesn't meet their expectations, they either repeat the  
18 study or reformulate and then do a study on that new  
19 formulation. Oftentimes or most of the time, the FDA is  
20 blissfully ignorant of the existence of these studies, and I  
21 will give you some examples of how that can be not optimal  
22 for our decision-making.

23           [Slide.]

24           Why do sponsors or people feel that they don't  
25 really need to submit these studies to ANDAs? You have to

1 go back for the justification or the understanding of this  
2 to the regulations.

3 I have paraphrased or almost directly quoted the  
4 ANDA information. In the law, which I have the citation  
5 down below, it says, "For NDAs all human investigations made  
6 to show whether or not such drug is safe for use and whether  
7 such drug is effective must be submitted." So, it really  
8 doesn't give the NDA sponsor much choice.

9 If you have done or commissioned or know about a  
10 study that fulfills these requirements, you must submit it  
11 in your NDA, and for those of you who either look at NDAs or  
12 submit them, you know how large they are. One of the  
13 reasons they are so large is because you just have to submit  
14 every single study you have ever done.

15 Not all of them directly support the approval,  
16 some of them have been done for very different reasons, but  
17 all of them must be submitted, and certainly for safety  
18 reasons and sometimes efficacy, there are good reasons for  
19 that.

20 Now, we turn to the ANDA sections of the same law,  
21 and for some reason which we, based on the amount of time  
22 that has elapsed, don't really know why this occurred, but  
23 the similar language to the NDA language was not included in  
24 the ANDA section, so if you look, you will not find that  
25 statement up there in the section that deals with ANDAs and

1 the requirements for ANDA submission.

2 Even the people that were around at the time don't  
3 seem to remember why that was omitted, whether it was simply  
4 an oversight or it was done with a specific reason in mind,  
5 but suffice to say that it is not there.

6 Therefore, the interpretation of many has been  
7 that we don't have to do it, if the law leaves that out, it  
8 must mean we don't have to do it. So, the interpretation  
9 for a great many years has been that sponsors of ANDAs do  
10 not have to submit studies that failed.

11 [Slide.]

12 Some other important considerations or  
13 discussions, and this is just to provide more information.  
14 I got these facts from some of our lawyers, who put these  
15 out as things to think about.

16 There are a couple of other parts of the law and  
17 pronouncements from FDA that kind of affect this. The first  
18 one I have listed there is a requirement in 505(j) that an  
19 application may not contain untrue statements of material  
20 fact. So, things that are material facts can't be  
21 misstated, and this I think to everyone makes sense. You  
22 can't purposely make misstatements in your application. I  
23 don't think that is a very controversial rule.

24 The second thing is that selective reporting of  
25 data may constitute untrue statements of material fact, and

1 the example that I cited up there is actually about  
2 stability testing where a firm was doing stability testing  
3 on their product, and some of the stability tests didn't  
4 actually get very favorable results.

5           They were able to keep doing the stability testing  
6 until they got the results they wanted, and they simply  
7 submitted the best ones.

8           Based on this particular case, it was stated that  
9 this is not acceptable behavior and that it is truly  
10 selective reporting to make a case that may not be true.

11           So, if you put these two things together, one of  
12 the thoughts is that failure to report failed studies may be  
13 considered selective reporting, because you have a body of  
14 data, you are only submitting a portion of it.

15           Again, just food for thought, something to think  
16 about.

17           [Slide.]

18           Why do studies fail? I came up with probably the  
19 short list. Those of you who do these studies or are in the  
20 industry maybe can come up with even more. But first and  
21 foremost, is an under-powered study. I kind of referred to  
22 that in my graph of results. Simply when you make a  
23 statistical analysis or study plan, you try and estimate the  
24 variability and therefore, the number of subjects you need  
25 to do your study, and sometimes the estimate is wrong, or

1 you might have made a correct estimate and you get an  
2 unusual number of dropouts. So, by the time you have  
3 finished your study, the study was well performed, you have  
4 a product that you really believe in, yet, you have come up  
5 short as far as the number of subjects you need for that  
6 study, and you come up with an under-powered study.

7           One of the two things that controls the width of  
8 that confidence interval are how many subjects you use, and  
9 the other is obviously the variability of the products. I  
10 mean that is an obvious one, and I think probably people who  
11 have done the studies have all come up against this at one  
12 time or another.

13           Some sponsors seem determined to be ahead of the  
14 curve and use some type of unusual study designs, and it  
15 backfires on them. We have seen that occasionally. They  
16 really believe they have a better way of doing things than  
17 everyone else, and it is perfectly legitimate to come in and  
18 make that argument to the FDA if you think, you know, even  
19 if it is in a guidance, you can come in and make an argument  
20 that you know a better way and discuss it with the FDA, but  
21 sometimes people just go ahead without discussing it and it  
22 really backfires. They don't get the results they want, or  
23 the results that they get are very hard to interpret based  
24 on an unusual study design.

25           You can fail because of outliers, and I will go

1 into a little bit more depth about what we consider--and I  
2 specifically refer to it as an "outlier" response, and I  
3 will explain that in a minute.

4           When you are doing only 24 subjects or perhaps a  
5 little more than that, it doesn't take too many odd results  
6 to get it to fail. I have spoken to a great many sponsors  
7 who believe that 23 of their subjects told them the truth  
8 and exactly what they wanted to hear, and just one subject  
9 whose data kind of misbehaved actually caused the whole stud  
10 to fail. So, we get into a lot of discussions on that.

11           Certainly, assay issues of various kinds.  
12 Strangely enough, some sponsors still try and validate their  
13 assay after they have used it, which seems to me it kind of  
14 makes sense you would want to determine that your assay  
15 works before you actually did the study and spent the money,  
16 but some people only remember to do it afterwards.

17           Other issues where samples are lost, you end up  
18 with missing data that is hard to incorporate. There may be  
19 questions. I have dealt with one sponsor who had a study  
20 which failed on one data point, a single data point. If we  
21 dropped the data point, the study passed, if we included it,  
22 it failed. It was a very unusual looking data point, but  
23 they had absolutely no documentation there was anything  
24 amiss with it, you know, nothing in the lab books, nothing  
25 that said, oh, I dropped the sample or I dropped drug into

1 the sample, or anything like that, no documentation at all  
2 that it was a lab error. So, we had no choice but to not  
3 drop it.

4 So, even in some borderline cases, even a single  
5 sample is enough to throw a study into the failure.

6 Also, strangely enough, wrong reference, we have  
7 encountered that once or twice. We had a case recently  
8 where a firm was pursuing registration in two countries, the  
9 United States and a foreign country. They brought large  
10 quantities of the reference brand name drug in each of those  
11 countries, and they had kind of a snafu in their shipping  
12 department, and for both studies they shipped out the  
13 foreign reference. So, they did two studies on that  
14 reference, and didn't use the U.S. reference.

15 They came in and said, well, you know, we think it  
16 is the same thing, could we just use that study anyway, and,  
17 you know, sorry, it has to be the U.S. reference. You would  
18 think that this wouldn't happen, but it has happened, so  
19 people have actually used the wrong reference.

20 [Slide.]

21 Are there other things that give people trouble?  
22 Baseline-corrected versus non-corrected. Some endogenous  
23 substances that are given, hormones or potassium, really can  
24 make a big difference whether you baseline-correct or don't  
25 correct the data. I think baseline correction is a very



1 controversial issue, and with a lot of drugs there is really  
2 no right answer. You know, people could argue yes, we  
3 should take away that baseline which is there anyway in the  
4 subject, or we just use all the data. So, that is kind of  
5 controversial, but it often makes a big difference in  
6 whether a study fails or passes.

7           You can do incorrect statistical analysis. You  
8 would think that what we do up to now is fairly simple,  
9 especially for a statistician, but some people kind of screw  
10 it up now and then and use the wrong model or the wrong  
11 analysis, and they either think they passed, when they  
12 really failed, or vice versa.

13           Compliance issues, not terribly germane to this  
14 because usually, it is a study that we think has passed, and  
15 inspectors go out and find some major flaws with the study,  
16 and we have to throw it out because the flaws that they find  
17 actually invalidate the study, so that is I guess a way to  
18 fail the study or at least negate the effects of the study.

19           Last but not least is the formulation just may not  
20 be bioequivalent, and, you know, in a way you have got a  
21 failure as a result, but to me as a regulator, it has told  
22 me what I want to know. I mean if the product really is so  
23 far away that it cannot be considered therapeutically  
24 equivalent, I really would like to know.

25           I mean I consider that a successful test if it

1 tells me that even though, as a sponsor, you may all not  
2 like it.

3 [Slide.]

4 I have a couple of examples, hopefully, this will  
5 illustrate.

6 The first one, I have disguised the names of these  
7 drugs, so we won't embarrass any sponsors or actually give  
8 away proprietary information.

9 The first example I have we will call Drug X. It  
10 is an oral liquid. This is a liquid dosage form that is  
11 mixed with a beverage prior to administration, and when it  
12 is mixed, it forms a complex dosage form. It is not in  
13 solution.

14 So, we asked for bioequivalence studies on that  
15 product. Now, we had one sponsor who used a beverage of  
16 their choosing, and they did the required bioequivalence  
17 studies. They were found to be bioequivalent and eventually  
18 approved.

19 In the meantime, while we were reviewing the ANDA  
20 before the decision was made, they performed another study  
21 in another beverage. Now, this beverage happened to be one  
22 that was specifically recommended in the labeling, the first  
23 beverage was not, but it was a beverage that was commonly  
24 used with this drug, so we didn't think much of it at the  
25 time.

1           They did this in this other beverage that was one  
2 of the beverages that was recommended, and lo and behold,  
3 they got very surprising results in that it was not the  
4 least bit bioequivalent in this other study, in one of the  
5 labeled conditions of use, labeled beverages. In fact, it  
6 came very close to being bio-in-equivalent although not  
7 quite.

8           So, faced with this dilemma about should I submit  
9 this to the FDA or should I not, they chose the usual  
10 course, which was, well, we don't have to submit failed  
11 studies, so, of course, they didn't submit it.

12           We went on, even though the results of this were  
13 back in more than enough time to submit it prior to the  
14 approval, they decided it wasn't necessary. So, we went on  
15 and approved the product.

16           Now, clearly, this is a very good example of why  
17 we really need these studies, because this is one of the  
18 studies that would have drastically affected our approval  
19 decision. I mean this was a labeled condition of use  
20 specified in the labeling.

21           If we had seen this, we in all likelihood would  
22 not have approved this product.

23           [Slide.]

24           My second example is a solid--I will call it Drug  
25 Y--solid oral modified release dosage form. We received an

1 ANDA. It had a study or studies which appeared to be  
2 passing studies. We were proceeding with our review.  
3 Because of our normal procedures, we sent out an inspection  
4 on these studies and while the inspectors were there, they  
5 happened to discover that the firm had done another study on  
6 the same drug. That study, when they looked at it, that  
7 study had failed.

8           So, they brought that to our attention. We had a  
9 lot of discussions with the sponsor about what the  
10 implications of this other study were. Come to find out,  
11 they had actually performed a third study. I have depicted  
12 the results 1, 2, 3 here. The third study was kind of their  
13 justification for why they thought the first study that they  
14 submitted was the appropriate one, and the second one was  
15 not.

16           So, we will say the first study against Lot A of  
17 the brand product, which is the first they did, failed, and  
18 as you can see it failed on Cmax 105 to 130. That is the  
19 first study they did, and, of course, they dutifully tried  
20 to investigate why this had occurred, because they really  
21 believed that their product development had been on target  
22 and that they had a bioequivalent product.

23           They picked another lot, and we will call it Lot  
24 B, of the brand, and did another study, again with their  
25 same test against that product, and that one passed very

1 nicely. Then, in the process of trying to justify what the  
2 problem was, they did a third study, somewhat smaller than a  
3 regular bioequivalent study, but still I think meaningful.

4 In this one, they tested Lot A versus Lot B of the  
5 brand, and that failed, with the results shown, 111 to 131.  
6 Their contention was, look, you know, we have done the best  
7 we can to target our formulation to be equivalent to this  
8 product, but, look, different lots of the innovator are now  
9 bioequivalent to each other.

10 That wasn't the only part of their argument, but  
11 that was a major point in their argument that, look, you  
12 have a problem with this innovator. The formulation they  
13 are putting out is extremely variable, and not all of them  
14 are bioequivalent to each other. So, how can you hold a  
15 generic to a higher standard than you would separate  
16 acceptable marketed lots of the innovator.

17 It turned out to be some sort of a problem with  
18 the RLD.

19 [Slide.]

20 I have shown you types of studies that we don't  
21 usually see. This is actually a failed study that we  
22 actually see more often than not. That is outlier issues.  
23 A lot of people get confused or people that have done other  
24 types of studies, saying, well, I have outlier data, I can  
25 use statistics to drop it because there is something wrong

1 with that person or that data, and generally, we are very  
2 resistant to dropping data based on outliers because in the  
3 one case, if a person is qualified as a normal subject to be  
4 in the study, and you simply don't like the way they  
5 respond, and we will assume that it is a good response for  
6 that subject, is not a reason to drop it. That is actually  
7 more of a reason to include it. That was a valid result for  
8 subjects, and the fact that that subject happens to lie out  
9 on one edge or the other, as far as its response, is really  
10 much more reason to include it than drop it.

11           However, there is another case where something  
12 happened, some technical flaw in the study where one of the  
13 periods for that subject did not give you in any way  
14 reasonable results. It might be much larger than anyone  
15 else, it might be next to no drug present. So the belief of  
16 the sponsor is if I studied this person 10 more times, I  
17 wouldn't get this result, this was something anomalous and  
18 this person is not an odd person, but just gave me an  
19 anomalous result.

20           What we do in those cases is generally ask the  
21 sponsor to study the drug, study that subject again with a  
22 couple of the original people from the original study as  
23 controls and see can you repeat this, you know, do they give  
24 you the same odd-looking result, or does now the subject  
25 look much like everyone else.

1           The whole point of that is to simply provide  
2 justification for dropping that subject in the original  
3 study. Unless anyone is worried, we don't take that new  
4 data and substitute it back into the old study. It is  
5 simply by saying yes, that was a bad study for that subject,  
6 and some technical flaw caused that subject to give you very  
7 bizarre results, and if you did it 10 more times, it  
8 wouldn't happen.

9           So, it is kind of a way to allow the sponsor to  
10 submit data that was truly anomalous response, and not  
11 simply the study subject was kind of an outlier  
12 physiologically. I have an example here of that.

13           [Slide.]

14           So, the questions for discussion for the  
15 committee, because we have been considering this and  
16 discussing it a lot internally, and started to discuss it in  
17 public is: Should sponsors of ANDAs submit the results of  
18 all bioequivalent studies performed on the to-be-marketed  
19 ANDA formulation?

20           Now, it is probably not reasonable or even  
21 necessary that a sponsor submit their early developmental  
22 type of work on developmental formulations, but I think our  
23 current belief is that the formulation that a sponsor  
24 actually intends to put on the market, if they have done  
25 other additional studies, we would certainly like to look at

1 that to make a judgment of whether it impacts our approval  
2 decision or not.

3           The second one, some people in the generic  
4 industry have expressed to me that it is kind of a burden to  
5 expect sponsors to submit full, complete audited reports  
6 with all of the data like they would with their so-called  
7 pivotal study, and that they aren't as opposed to doing more  
8 summary type of information, just to say we have done a  
9 study, these are the results. We had enough details to be  
10 able to judge whether it is important or not, but perhaps  
11 not all the raw data, not all the chromatograms and things,  
12 and not the full QC that you usually would do.

13           So, some sponsors have expressed that they think  
14 that would be reasonable to just get complete summary  
15 information rather than a full report, and that that  
16 wouldn't be quite so burdensome to them.

17           The final question: What should the FDA do with  
18 this information? Should we do a complete and in-depth  
19 review on these failed studies, or would simply a brief, but  
20 very careful examination of the study to see if, you know,  
21 in those rare cases where it would affect our decision,  
22 whether there is anything else that would make us doubt the  
23 equivalence and approvability of this product.

24           So, those are our questions.

25           DR. BYRN: So, now we will have questions for our



1 speaker and then discussion among themselves.

2 DR. VENITZ: Dale, on one of your slides you used  
3 the term RLD, what does that stand for?

4 DR. CONNER: Reference listed drug. It is the  
5 drug that is designated in the Orange Book as the reference  
6 that all generic or ANDA sponsors have to compare themselves  
7 against. Most often it is the brand name although not 100  
8 percent.

9 DR. LAMBORN: I had a question about your first  
10 example of failed, the instance where the sponsor did a  
11 study with a beverage that was actually listed in the  
12 labeling and failed, I would have thought that not telling  
13 you about that, under this general guideline of selecting  
14 reporting, since that was specifically in the labeling,  
15 would have already been covered as distinct from the  
16 majority of the cases.

17 DR. CONNER: I am not sure I want to get too far  
18 into that, but I mean that I guess various legal people  
19 would have an opinion one way or the other whether that was  
20 covered or not. Again, I think it is a matter of  
21 interpretation. One of our desires I think is to kind of  
22 close the level of interpretation to make things more clear  
23 to sponsors and everyone else, you know, what they should  
24 submit and what they should not.

25 DR. LAMBORN: And the statement about selective

1 reporting constituting untrue statements, that is just  
2 somebody's clause, that someone said maybe this is something  
3 that could apply?

4 DR. CONNER: Yes, that is just one legal opinion  
5 and you could probably get others, as well. I mean it is  
6 one way of thinking about putting those two previous  
7 statements together. We are not pronouncing it to say that  
8 it is a definite fact, but it is one way to interpret the  
9 previous things that I have said.

10 By any means, it is not the only way to interpret  
11 it.

12 DR. BOEHLERT: With regard to NDA failed studies,  
13 do they submit the complete report or just summaries?

14 DR. CONNER: My experience from being a reviewer  
15 of the Pharmacokinetic Section of an NDA, is most of the  
16 time if it is done in U.S. studies, it is pretty much  
17 complete. I have also seen variations, for example, when  
18 sponsors are submitting, say, early pharmacokinetic studies  
19 or early food BA studies to Japan, for Japanese  
20 registration, I have seen them in summary form.

21 Now, is important to note, though, that even if we  
22 request summaries, if the reviewer or the Review Division  
23 decides that that is an important study that we really need  
24 to see, we reserve the option of asking for the whole thing,  
25 so it is merely with the expectation that most of the time

1 we are not really going to see any significant problem with  
2 that summary. In a minority of the time, we will see  
3 something that could be very significant, and then we will  
4 go back to the sponsor and ask for the complete information.

5 It allows us to be selective and simply get the  
6 full report on only the things that we have looked at and  
7 consider important and significant.

8 DR. ANDERSON: On page 2 of this document that I  
9 have here, you state that sponsor often choose not to submit  
10 failed studies in ANDAs. You added to that during your  
11 presentation "most of the time."

12 DR. CONNER: Yes.

13 DR. ANDERSON: If they don't submit them, how do  
14 you know that they failed or they have them?

15 DR. CONNER: That is a very good question.

16 [Laughter.]

17 DR. CONNER: It goes to the part of, you know,  
18 some sponsors--for example, one of the sponsors in the first  
19 example, when we discussed later the results of the study  
20 and were in discussions with them, they said, well, we  
21 didn't submit it because you didn't ask us for it. The  
22 response I guess back is how could we ask you for it if we  
23 didn't know it existed.

24 So, it is question, I mean as part of the  
25 deliberations and discussions, one of it is, well, how many

1 studies are we really talking about here, you know, is it 20  
2 percent, is it 10 percent, is it a very small number, you  
3 know, and I don't think that I have the exact numbers on it  
4 as a percent.

5 I am sure that the people who really know this are  
6 CROs, who do these type of studies for a lot of different  
7 sponsors. It may not even be a single sponsor knows exactly  
8 what the percentage is unless they have a lot of products  
9 and do a lot of this type of work, but I think CROs, that do  
10 literally hundreds and hundreds of these studies, probably  
11 have a good idea.

12 In fact, to give you kind of some preliminary  
13 information, Larry Lesko, who I am not sure if he is still  
14 here, prior to coming to the FDA, he worked for a few years  
15 in a CRO, and he estimates that of the studies that he did  
16 in that CRO, that probably 20 percent or so failed, perhaps  
17 25 percent, and, of course, not all of them are on the final  
18 formulation, so it is probably a smaller percent or the ones  
19 we are actually discussing here.

20 It is hard for me to estimate exactly what we are  
21 looking at here, but maybe some sponsors or CROs would have  
22 a better idea.

23 DR. ANDERSON: I am not disagreeing with you in  
24 terms of a need to have the information, because in the next  
25 statement here, you say, "Sometimes these contain important

1 information," et cetera, et cetera, and I agree with that.

2           As an experimentalist myself, if something goes  
3 wrong in an experiment, I need to know why it went wrong, so  
4 I can correct it in the future, and it seems to me like it  
5 is not playing fair when you pretend that something didn't  
6 go wrong, and you go ahead and send it, but then I  
7 understand why these things happen.

8           I would say that I think it is important for  
9 anyone who is trying to make a judgment about something to  
10 have all of the information, and the person who has  
11 information that may not be quite as positive, if that makes  
12 sense, as one would like it, maybe could have an explanation  
13 for it, and then it would be up to the reviewer to determine  
14 whether or not the explanation makes sense.

15           DR. CONNER: I think you are perfectly correct. I  
16 would expect and encourage sponsors, when they submit this  
17 type of information, to give their spin on it or their  
18 interpretation of why this wasn't an important finding, you  
19 know, the flaws, you know, the reasons they think it failed.  
20 I mean obviously, they do that anything because when a study  
21 fails for a sponsor, they have to make the decision, well,  
22 was there a technical flaw in the study and should I stick  
23 with this formulation, and just do another study, or does  
24 this really tell that I should reformulate, should I keep  
25 trying to push this one through, which now I have a study

1 that tells me it might not be as good as I think it is, or  
2 should I go back and reformulate, and that is kind of an  
3 expensive and time-consuming process to reformulate a  
4 product when you are that far along, but also, these studies  
5 are very expensive, too.

6 It is something I think that most sponsors, you  
7 know, the decision when they get this type of result, they  
8 have to make that internally anyway.

9 DR. ANDERSON: I understand that, but it may fail  
10 once it gets to the public, and that is even more expensive.

11 DR. CONNER: Yes.

12 DR. ANDERSON: And perhaps they ought to also look  
13 at the fact that I believe that if we are talking about  
14 generic drugs, they don't have to do all the research and  
15 starting out from scratch, making the compound, and all of  
16 that, a very expensive part, but perhaps the most important  
17 thing here is that it may be disastrous if a failure occurs  
18 once you have approved it without knowing that the failure  
19 has occurred ahead of time, and it occurs once it is out in  
20 the public.

21 DR. BYRN: I wanted to ask, following on the  
22 discussion from the BACPAC discussion really where it is  
23 pretty widely held, I think, generally held, that drug  
24 substances they are saying don't manufacture into the same  
25 product necessarily, I don't know how often this happens,

1 but if the dissolution test is not very discriminating, you  
2 have that scenario, and then, say, a submitter does three  
3 bioequivalence tests, of which only one passes, and they  
4 submit that, under that scenario, there would be significant  
5 variability basically in the product, and that would seem to  
6 be something that the Agency should know about.

7 Are there cases like that, do we think it goes to  
8 that extent or not, or do we know?

9 DR. CONNER: As we said before, I am kind of  
10 limited in my knowledge of this. I have heard through some  
11 rumors, some very informal discussions over cocktails at  
12 meetings and things, that people do studies that don't pass.

13 You have to remember, though, although I am sure  
14 there have been sponsors that have kind of plunged ahead and  
15 done three studies, even four studies on the same  
16 formulation, but most--there are a number of generic  
17 sponsors in the room right now--but most of these studies  
18 are very expensive and most of these companies, you know,  
19 they aren't the multibillion dollar companies that produce  
20 brand drugs, so I mean most of the companies can't afford to  
21 just keep plugging away, you know, a quarter of a million to  
22 a half a million dollars a shot, you know, beating their  
23 head against the wall to try and get a product through.

24 It becomes you either give up or reformulate. I  
25 don't expect that most of the time we will see more than one

1 extra study, although, as I said, I am kind of ignorant on  
2 the exact numbers and how many times people try on the same  
3 formulation.

4 DR. LAMBORN: In that sense, it seems to me that  
5 this becomes less of an issue because on the one hand, if,  
6 in fact, they don't do many more studies, and if all you  
7 have asked for is, as they have suggested, a summary, then,  
8 there does not become a substantial additional burden on  
9 their part to provide the information.

10 If there is the occasional case when, in fact,  
11 there really is something substantively wrong, then, you  
12 will have the information to be aware of it, so I guess I am  
13 now moving from questions to votes, and I will reiterate  
14 something I have said at numerous other times when this has  
15 come before this committee, and I think we have had the  
16 sense before also that whatever we can do to support the  
17 regulation that would require that for the proposed marketed  
18 formulation, that there must be some record and that it  
19 could be in the form of a summary that should come to the  
20 Agency on all the studies that were done, and that would  
21 allow you to limit the burden for those instances where it  
22 is just part of the process, but would assure that you have  
23 some chance to identify in advance, prior to marketing,  
24 instances where there might be substantial risk to the  
25 consumer.



1           So, I would like to put that forth as a statement  
2 from the committee.

3           DR. VENITZ: I have two questions for you. The  
4 first one in your Example 1, did you have any recourse after  
5 you approved that product, or you basically shrugged it off?

6           DR. CONNER: Yes, when we finally discovered that,  
7 we took regulatory action.

8           DR. VENITZ: The second question. Let's assume  
9 that the committee comes out in favor of requiring  
10 submission either in the summary form, how are you going to  
11 enforce it because the law apparently doesn't require it?

12           DR. CONNER: Well, there is a variety of avenues  
13 that we are exploring. Obviously, one of them is to amend  
14 the law or the regulations, to incorporate language or to  
15 add language of the kind that is in the NDA section. There  
16 are perhaps some others, too, but that is probably the most  
17 solid way.

18           DR. LAMBORN: Would it be helpful in this case for  
19 us to give you a more formal vote?

20           DR. BYRN: What I thought is we might have  
21 comments from the audience and then the committee have some  
22 more discussion.

23           Are there comments from the audience, questions or  
24 comments from the audience? Just as before, please identify  
25 yourself.

1           MR. SHARGEL: I am Leon Shargel. I am with the  
2 National Association of Pharmaceutical Manufacturers. At  
3 the National Association of Pharmaceutical Manufacturers, I  
4 represent the interests of generic drug manufacturers and  
5 drug substances.

6           I would first like to thank Dr. Conner for  
7 mentioning in his title, that when we talk about filed  
8 bioequivalent studies, that these are studies that fail to  
9 meet bioequivalence goalposts or regulations.

10           Very often we are concerned that from the image  
11 point of view, that failed studies often mean the generic  
12 did not do the appropriate studies, and as mentioned, if you  
13 do good science, and we don't get the numbers that wanted,  
14 it is still good numbers, it just tells us that we have the  
15 wrong formulation of perhaps we sampled wrong or we have  
16 something else.

17           So, I do thank Dr. Conner for pointing this out.  
18 I just want to also point this part out. I also have some  
19 comments about the idea whether all studies should submit--  
20 and maybe I will go through some of these questions--in the  
21 NDA development, there is very little experience in human  
22 studies with a new drug entity.

23           You get that as you go through the various stages  
24 from the IND eventually to market approval. By the time the  
25 patent is at expiration date, there is a lot of experience

1 on the safety and efficacy of the product, otherwise, it  
2 would have been off the market prior to a generic coming  
3 through.

4           The pivotal bioequivalence study is usually made  
5 on the to be marketed batch that is going through CMC review  
6 and through Dr. Conner's Division of Bioequivalence, and  
7 that should be the focus for the basis of the quality of the  
8 product that we are asking for approval.

9           Very often we do do early studies. We may look at  
10 a formulation because we don't have the information from the  
11 brand or the reference listed drug, so we may do a pilot  
12 study to look at subject variability, intra- and inter-  
13 subject variability, or just in terms of sampling time or  
14 some other thing.

15           So, there may be a number of studies in the  
16 development of the final formulation and indeed, when you do  
17 what you think is a final formulation, as I said, it may not  
18 pass the bioequivalence requirements because we may have  
19 sampled wrong, the outlier, some other things, not enough  
20 subjects, didn't have the power, it could be a variety of  
21 other aspects.

22           Now, when these studies are done, it has been my  
23 experience that the sponsor does not write up a full-blown  
24 report on studies that they are not going to submit, so they  
25 would not have a full-blown study, why write up a whole

1 report on a small study or such when the importance of the  
2 study that is going to be marketed, the final formulation,  
3 is where the focus is.

4           Now we get to the point of what we are giving to  
5 the FDA, and the question is how much will this detract the  
6 reviewer from focusing on the formulation that we are saying  
7 we would like to market this formulation, we have had two  
8 formulations that we did in a pilot study, one that we  
9 thought would work, but now we realize that the formulation  
10 was releasing too quickly, too slowly, whatever the problem  
11 was, we have now corrected that problem, and here is the  
12 study that we are submitting, and that is where we want to  
13 focus.

14           We really don't want to lose review time and other  
15 things. The data is on file, I mean with the company.  
16 Certainly, in pre-approval inspections, as pointed out, A  
17 field inspector, an FDA field inspector will look at the  
18 industry, will say, okay, you have done other studies, and  
19 this can be certainly questioned and should be answered  
20 honestly, yes, we did three studies, and here is what we  
21 have.

22           But I have concerns as how much time will it take  
23 away from review time, where is the focus on that, and that  
24 is the way we feel.

25           Now, the last question is what should FDA do with

1 the data, and I would never tell FDA what to do with the  
2 data, so I will leave it alone, and I thank you very much.

3 DR. BYRN: Thank you.

4 DR. VENITZ: Would you be opposed to submitting  
5 all the clinical data on the to-be-marketed formulation,  
6 even if it is more than one study, or you are just opposed  
7 to the preliminary pilot studies with a variety of  
8 formulations?

9 MR. SHARGEL: I am not sure I want to submit all  
10 studies. I would not be opposed to summaries of this is  
11 what we have as prior art, that we have done two or three  
12 studies, and such, and maybe a quickie little summary  
13 saying, well, we did a formulation in 12 people to see  
14 whether we have inter-subject differences or inter-subject  
15 whatever it was we wanted to look at to get a better idea of  
16 the plasma level profile description of the kinetics before  
17 we did the bigger study, and then we realized we sampled  
18 wrong, but, you know, with maybe a comment that it was done,  
19 and if FDA really feels the urge or need for the data,  
20 certainly, it would be available.

21 DR. BYRN: Thank you.

22 Other questions, other comments from the audience?

23 Yes, sir.

24 MR. TANTILLO: My name is Nick Tantillo with ESI  
25 Lederle.

1           The first question I guess that Dr. Conner posed  
2 was should sponsors submit the results of all BE studies  
3 performed on the to-be-marketed ANDA formulation, and as I  
4 guess the previous speaker had mentioned, that sometimes  
5 pilot studies are done, ultimately leading to a pivotal  
6 study. Sometimes that pivotal study may not demonstrate  
7 bioequivalence.

8           In that case, a firm can either repeat the study  
9 or do more studies, or, in effect, make a decision to  
10 reformulate or change the manufacturing procedure, in which  
11 case that formulation, that product is no longer to-be-  
12 marketed formulation, and now becomes something other than  
13 the to-be-marketed.

14           I guess I just wanted to ask the committee if you  
15 were considering the submission of all studies or really to  
16 clarify the point of the to-be-market formulation, which  
17 would be the formulation that is the subject of the  
18 application for clarification.

19           DR. BYRN: So, we can discuss that question.

20           DR. CONNER: I think our view, at least at the  
21 current moment, is we are interested in that formulation  
22 that is intended to be marketed. I mean if it is very early  
23 and very different formulations, although, of course, having  
24 that information would be very educational for us, I don't  
25 think it is necessary or compelling that we get that

1 information.

2           The other thing that I have a little worry about  
3 in the back of my mind is I think we have decided we want  
4 the to-be-marketed formulation, but the definition of the  
5 to-be-marketed formulation has to be clear.

6           For example, if a sponsor does a full biostudy and  
7 then changes the color of a tablet, nothing else, or some  
8 very superficial change, or the imprinting or something, is  
9 that the final formulation? I would say if the change is so  
10 tiny as to be nonsignificant, a change under, say, SUPAC, I  
11 would say I want to see that study.

12           If it is a more significant change, again, by some  
13 rules, such as SUPAC, perhaps that is a different  
14 formulation. It remains to be worked out what is the final  
15 formulation and how far do I need to be away from that  
16 before I am not interested in seeing that information  
17 anymore. So, it is something we have to iron out, I think,  
18 and perhaps with industry input about what exactly is the  
19 final formulation. So, we have to get that definition  
20 correct.

21           DR. BYRN: Any other comments from the floor?

22           [No response.]

23           DR. BYRN: Let's have another discussion of the  
24 committee or continue our discussion. Kathleen.

25                           Committee Discussion

1 DR. LAMBORN: I think my proposal as the potential  
2 statement from the committee still stands. I think that  
3 that would be worthwhile, and I think it is consistent with  
4 what we heard from the audience because we are talking, with  
5 a clarifying of what is meant to be "to-be-marketed," it  
6 would resolve a lot of the questions about a lot of the  
7 things that would not be directly focused, and again I think  
8 we are talking about a summary rather than the same level of  
9 report that would be required for the pivotal, just enough  
10 information for the Agency to have a sense of, well, yes,  
11 they did a study, and they had too few patients in it, or  
12 they did a study, and the variance was higher than they  
13 expected, so they redid it.

14 Then, we have very limited information in the  
15 first one, and then we had the pivotal one which matched, or  
16 we did, you know, five studies and then we repeated exactly  
17 the same study a sixth time, and it finally passed, but  
18 maybe the Agency would then want to say, well, maybe we  
19 should see a little bit more about the others, because if it  
20 took you six tries with the exact same formulation, and the  
21 exact same study, was there something in there that we have  
22 to worry about.

23 So, I think we are talking about trying to limit  
24 the amount of extra work, but just give enough to highlight  
25 potential sources of a problem.



1 DR. BYRN: Other comments from the committee?

2 DR. BOEHLERT: I would just add I think it is  
3 going to be important for us to clarify, as Dale just spoke  
4 to, at this point, on what is the final formulation. It is  
5 not out of the realm of possibility that a dye change can  
6 change the performance of the product. There are  
7 interactions known in the literature between dyes and active  
8 ingredients. So, I think we are going to need to clarify  
9 what is indeed the final formulation, but cosmetic changes  
10 certainly should be included.

11 DR. BYRN: I guess there would be no way to put in  
12 there one say is to define it with SUPAC, another way would  
13 be to put a statement in there something like all BE studies  
14 that have any bearing on product variability would be  
15 reported to the Agency. That is probably too vague, but I  
16 am concerned.

17 Even the innovator may not know the effect of  
18 slight changes in the formulation on product variability,  
19 because they may have made it the same way all the time, and  
20 so we could have a situation where you start changing and  
21 adjusting just a little bit, and you get a very variable  
22 product, and there is no way to know that unless you report  
23 essentially all the experiments that showed how variable it  
24 was. Maybe that is not a real problem, but if there was a  
25 case like that, it would certainly be of concern, because

1 you would have a product that was pretty variable out on the  
2 market.

3           So, I don't know how to word it such that you  
4 could get--you would like the Agency to be able to review  
5 all that data, so that they were aware of it and could make  
6 some decision in their deliberation.

7           DR. CONNER: Some evidence, limited evidence but  
8 still good evidence about variability comes through  
9 biostudies.

10           DR. BYRN: Right.

11           DR. CONNER: Both the history of the innovator, as  
12 well as the information that generic sponsors put in on both  
13 their own product and the reference listed drug or the brand  
14 name. That gives you a lot of sense of total variability.  
15 With two-way crossovers, you can't really tease out intra-  
16 subject variability too well. That really takes a replicate  
17 design or some other type of design to do that.

18           One of the criteria in effect is based around  
19 variability. If you have an extremely variable product or  
20 two products, then, it is much more difficult to pass, or  
21 much more likely to fail. It requires greater power to  
22 determine bioequivalence in that case.

23           Also, I would like to go back to what Leon said  
24 two speakers ago. It is fine. I have heard the industry  
25 say this before, well, you know, we have them on file, and

1 you can just come and ask for them, but again we get back  
2 into that catch-22 of how can we ask for them if we don't  
3 know they exist.

4 In my experience, I have never been an inspector,  
5 but my experience with inspectors is we generally tell them  
6 what to go out and look for, and they look at the things we  
7 tell them to, and only in rare cases do they happen to  
8 stumble over something, but if they don't know something  
9 exists, the chances are they probably won't find it.

10 This particular study Drug X, you know, based on  
11 some discussions with the sponsor of that application, you  
12 know, after this all came out is they said, oh, yes, it was  
13 in file cabinet somewhere, you know, it was in somebody's  
14 office who had left the company. That was where the records  
15 were archived. An inspector, unless they were rifling  
16 through everyone's file cabinets in the company, would never  
17 have found that even by chance probably.

18 You know, the sponsor, for a variety of reasons,  
19 finally submitted it to us based on some requests from  
20 foreign regulatory agencies, I believe, and they discovered  
21 it again and decided to do the right thing and submit it.  
22 That is how we found out about it.

23 But even some of the people at that company didn't  
24 know that that study existed.

25 DR. BYRN: I think we have a proposal or general

1 consensus, which you do you want to reword that or just re-  
2 summarize it? Go ahead.

3 DR. LAMBORN: I can give it a try. I guess that I  
4 am suggesting that the committee state its support for  
5 whatever has to be done by the FDA to ensure that sponsors  
6 submit the results of all BE studies performed on the to-be-  
7 marketed and the formulation in the form of a complete  
8 summary, and that the FDA should do a brief, but careful  
9 examination to identify potential problems worthy of  
10 requesting additional information.

11 DR. BYRN: Okay. Any other comments?

12 [No response.]

13 DR. BYRN: I think we will just have a show of  
14 hands for a vote.

15 All in favor?

16 [Show of hands.]

17 DR. BYRN: Okay. It is unanimous.

18 I don't think we have anything else to discuss  
19 today, so I would like to thank all the members of the  
20 committee and the audience for their assistance.

21 Thank you very much.

22 [Whereupon, at 3:45 p.m., the meeting adjourned.]

23 - - -