DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

VOLUME II

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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

P R O C E E D I N G S

Call to Order

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

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

Conflict of Interest Statement

DR. CHAMBERLIN: Welcome.

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

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

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

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

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

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

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

Thank you.

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

DR. DOULL: John Doull, KU Medical Center.

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

DR. CHAMBERLIN: Nancy Chamberlin, Exec. Sec.

DR. BYRN: Steve Byrn, Purdue University.

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

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

DR. VENITZ: Jurgen Venitz, Virginia Commonwealth University.

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

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

Welcome, Introduction

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

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

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

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

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

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

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

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

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

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

Lastly, we are going to talk about failed bio studies in generic drugs. Again, this is a new regulation that we are looking to issue, and we are looking for input from the committee in the direction we should be going.

So, we should have a very good day and I appreciate all your input and thank you.

DR. BYRN: Thanks very much, Helen.

As was outlined, we are going to start with the first section, which is Updates on Guidances. The first speaker is Ajaz Hussain, who is going to give us an update on the Biopharmaceutics Classification System.

GUIDANCE UPDATES

Biopharmaceutics Classification System

DR. HUSSAIN: Good morning. I have a brief presentation which will sort of outline the approach we took in developing this guidance. I won't go into the details of the guidance per se, but more in terms of the philosophy and the approach we took in developing this guidance.

[Slide.]

If you start with the time line, the process of developing this guidance started early in the 1990s when Professor Gordon Amidon spent a year, a sabbatical at FDA, and I think that was the start of a research program that involved FDA, Medical Product Agency of Sweden, and several universities especially Michigan, Uppsala, and University of

Maryland.

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

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

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

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

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

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

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

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

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

[Slide.]

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

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

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

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

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

[Slide.]

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

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

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

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

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

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

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

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

[Slide.]

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

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

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

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

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

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

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

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

[Slide.]

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

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

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

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

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

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

[Slide.]

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

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

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

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

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

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

[Slide.]

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

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

"over-discriminating" for that purpose.

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

[Slide.]

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

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

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

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

[Slide.]

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

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

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

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

affect absorption, so that also needed to be addressed.

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

[Slide.]

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

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

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

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

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

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

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

So, small intestine is the primary area of absorption. Stomach is not a primary organ for absorption.

The other aspect for dissolution is

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

[Slide.]

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

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

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

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

[Slide.]

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

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

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

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

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

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

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

[Slide.]

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

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

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

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

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

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

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

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

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

[Slide.]

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

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

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

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

Thank you.

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

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

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

Any questions for Dr. Hussain?

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

Is that a problem?

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

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

DR. BYRN: Is a bit slow.

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

DR. BYRN: When was that USP statement made?

DR. HUSSAIN: I don't have ti.

DR. BYRN: A long time ago.

DR. HUSSAIN: A long time ago, yes.

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

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

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

DR. HUSSAIN: Right.

DR. ANDERSON: Thank you.

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

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

would be very rapid.

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

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

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

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

General Bioavailability/Bioequivalence

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

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

[Slide.]

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

[Slide.]

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

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

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

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

[Slide.]

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

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

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

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

[Slide.]

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

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

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

[Slide.]

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

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

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

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

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

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

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

[Slide.]

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

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

[Slide.]

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

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

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

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

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

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

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

That was the recommendation again that came from

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

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

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

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

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

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

What it is talking about is three different ways of exposure measures. One is called the early exposure, which is an area under the curve, truncated maybe up to the Tmax of the median reference product. The peak exposure would give the same as the Cmax, and the total exposure, meaning the area under the curve. So, these are the three different terms of exposure measures which is described in detail in the guidance.

[Slide.]

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

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

[Slide.]

For the immediate release products, the general

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

[Slide.]

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

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

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

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

[Slide.]

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

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

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

[Slide.]

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

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

[Slide.]

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

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

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

This particular system would be also applicable

for the approval of the biowaivers for the postapproval cases.

[Slide.]

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

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

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

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

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

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

[Slide.]

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

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

If all these four criterias are in existence,

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

[Slide.]

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

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

[Slide.]

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

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

[Slide.]

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

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

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

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

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

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

DR. BYRN: Questions for Vinod?

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

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

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

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

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

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

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

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

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

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

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

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

not the metabolite.

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

DR. SHAH: Yes.

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

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

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

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

DR. SHAH: Okay.

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

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

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

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

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

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

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

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

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

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

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

[Slide.]

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

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

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

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

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

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

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

So, that was the clarification.

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

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

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

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

DR. SHAH: Okay. Sorry.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

a drug substance from a dosage form.

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

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

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

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

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

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

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

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

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

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

Any other questions? Identify yourself, please.

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

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

DR. SHAH: I suggest you wait until the food

effect guidance comes out.

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

Now, the recommendation for enrollment of women and elderly?

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

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

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

DR. BYRN: Dr. Lesko.

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

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

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

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

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

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

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

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

DR. BYRN: Any other questions?

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

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

a food effect bioequivalence study?

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

MR. AGRAWAL: Immediate release.

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

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

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

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

DR. CONNER: Requested for the product.

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

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

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

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

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

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

[No response.]

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

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

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

Average, Population, and Individual Approaches to Establishing Bioequivalence

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

[Slide.]

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

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

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

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

[Slide.]

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

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

[Slide.]

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

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

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

[Slide.]

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

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

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

[Slide.]

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

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

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

[Slide.]

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

[Slide.]

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

[Slide.]

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

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

[Slide.]

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

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

[Slide.]

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

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

That is my update today. Thank you.

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

DR. LAMBORN: I was interested in your statement about where this use of the population bioequivalence stood. In the one slide it says that population bioequivalence is used in the in vitro testing of the nasal and oral

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

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

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

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

DR. CHEN: Correct.

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

DR. BYRN: Other questions for Dr. Chen?

[No response.]

DR. BYRN: Thank you very much.

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

[Recess.]

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

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

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

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

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

CLINICAL PHARMACOLOGY

Modeling and Simulation Introduction

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

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

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

[Slide.]

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

[Slide.]

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

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

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

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

[Slide.]

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

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

physician or decision-making on approval.

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

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

[Slide.]

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

Modeling and simulation, we envision in an

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

[Slide.]

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

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

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

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

[Slide.]

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

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

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

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

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

DR. BYRN: Thank you very much, Larry.

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

The Applications of Simulation in Drug Development

DR. HALE: Thank you.

[Slide.]

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

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

[Slide.]

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

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

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

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

of this grey zone.

[Slide.]

I would like to start with definitions. Basically, I am taking the point of view that modeling and simulation are the way that we have a technical expression or articulation of what we understand or what we think we understand.

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

[Slide.]

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

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

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

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

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

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

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

[Slide.]

Primary areas of use.

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

graphics you will see today.

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

[Slide.]

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

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

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

[Slide.]

One of my colleagues, Anne Hersey, gave me this

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

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

[Slide.]

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

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

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

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

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

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

[Slide.]

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

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

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

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

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

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

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

[Slide.]

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

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

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

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

[Slide.]

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

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

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

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

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

[Slide.]

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

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

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

whatever post-dose.

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

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

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

[Slide.]

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

In this case, this involved an approved drug. There is a PK/PD relationship that had been demonstrated in the literature, and it was also the case that people in the

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

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

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

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

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

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

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

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

[Slide.]

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

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

a rational person accept modeling and simulation?

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

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

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

Lastly, we could fail in interpretation.

[Slide.]

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

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

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

explicitly study them as factors in our simulation.

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

[Slide.]

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

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

[Slide.]

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

[Slide.]

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

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

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

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

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

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

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

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

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

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

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

[Slide.]

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

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

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

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

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

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

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

[Slide.]

To summarize here, why not simulate?

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

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

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

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

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

[Slide.]

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

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

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

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

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

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

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

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

[Slide.]

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

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

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

[Slide.]

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

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

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

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

[Slide.]

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

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

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

Thank you very much.

DR. BYRN: Thanks.

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

A Framework of Modeling and Simulation in Regulatory Decision

DR. LEE: Thank you, Steve.

[Slide.]

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

[Slide.]

I want to start out with a terminology slide. I

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

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

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

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

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

[Slide.]

So, the topic for my presentation today include

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

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

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

[Slide.]

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

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

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

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

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

[Slide.]

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

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

[Slide.]

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

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

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

[Slide.]

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

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

[Slide.]

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

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

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

[Slide.]

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

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

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

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

[Slide.]

We also have some new experience specifically in

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

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

[Slide.]

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

[Slide.]

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

[Slide.]

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

[Slide.]

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

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

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

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

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

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

[Slide.]

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

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

[Slide.]

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

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

[Slide.]

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

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

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

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

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

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

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

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

[Slide.]

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

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

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

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

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

[Slide.]

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

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

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

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

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

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

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

[Slide.]

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

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

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

[Slide.]

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

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

[Slide.]

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

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

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

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

[Slide.]

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

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

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

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

DR. BYRN: Thank you very much.

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

Before we do that, are there any questions that

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

[No response.]

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

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

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

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

[No response.]

Committee Discussion

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

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

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

DR. BYRN: Yes, go ahead.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. LaLONDE: I was wondering if maybe the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

the extrapolation of adult efficacy data to pediatric populations.

DR. BYRN: Yes.

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

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

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

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

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

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

development.

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

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

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

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

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

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

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

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

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

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

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

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

Dr. Mould.

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

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

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

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

our guesses.

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

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

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

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

data.

DR. BYRN: Dr. Doull.

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

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

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

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

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

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

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

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

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

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

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

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

DR. BYRN: Gloria.

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

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

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

market.

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

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

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

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

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

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

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

an analysis plan.

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

Other attributes?

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

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

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

DR. LAMBORN: Basically, the thing that you would

expect from any research project, whatever it is.

DR. BYRN: Larry.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. BYRN: Other comments?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

A F T E R N O O N S E S S I O N

[1:10 p.m.]

DR. BYRN: We will call this meeting to order, the afternoon session to order.

Open Public Hearing

DR. BYRN: The agenda calls for an open hearing, so we would like to call for comments from the audience. Please come to the microphone and identify yourself.

At this point, we don't have to limit discussion although we wouldn't like to have an hour discussion from a single person, so it is open for comment.

[No response.]

DR. BYRN: Hearing no comments, we will reopen to the committee to see if there are any further discussion points and what we will do is go over the four initial questions and then move to the other items.

Committee Discussion

DR. BYRN: Is there anything the committee would like to add on the four initial discussion points that we were discussing prior to lunch? Yes, Peter.

DR. LEE: When we are doing modeling and simulation in clinical pharmacology, I see one of the difficulties that we have is not actually on the technical part, which means building the model or coming out with a simulation program, I think one of the difficulties is

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

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

DR. BYRN: Kathleen.

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

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

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

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

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

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

DR. BYRN: Other comments?

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

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

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

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

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

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

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

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

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

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

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

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

I think the third area is the diabetes disease,

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

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

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

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

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

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

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

DR. BYRN: Kathleen.

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

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

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

DR. LaLONDE: I very much support that.

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

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

Yes, Kathleen.

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

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

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

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

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

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

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

I guess that is all I have.

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

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

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

DR. LEE: You mean external data?

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

DR. BYRN: Dr. Mould.

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

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

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

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

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

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

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

DR. BYRN: Kathleen.

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

DR. BYRN: Any other comments?

[No response.]

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

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

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

FDA Research Report

Product Quality Research Institute

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

[Slide.]

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

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

[Slide.]

The Office of Testing and Research in CDER, we

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

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

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

[Slide.]

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

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

[Slide.]

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

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

I think the key important areas for CDER's mission right now focus on nonclinical to clinical linkages, product quality, how to build quality, and then how to improve the methods that we use for product quality assessment. Clearly, database availability and monitoring has been a focus, but currently that focus has been limited to toxicological databases and hopefully, we would like to expand that further to include quality and other databases.

[Slide.]

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

[Slide.]

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

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

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

[Slide.]

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

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

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

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

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

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

[Slide.]

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

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

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

my morning presentation.

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

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

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

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

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

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

sorbitol per dose.

[Slide.]

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

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

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

[Slide.]

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

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

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

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

[Slide.]

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

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

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

[Slide.]

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

[Slide.]

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

[Slide.]

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

[Slide.]

You can also apply individual bioequivalence criteria, and in this case, the formulations fair to meet bioequivalence criteria regardless of how you do the analysis, whether you use constant scale approach or a reference scale approach, so they were bio-in-equal irrespective of the approach applied.

[Slide.]

Subject-by-formulation interaction was the topic that was discussed extensively at the last meeting. In this study, the AUCI reached a value of 0.15, which our guidance had suggested was a critical value.

Although it did reach the value of 0.15, it was not statistically significant because the confidence interval around the interaction included zero.

[Slide.]

Here is a stick blot showing the effect of two excipients on the area under the curve for this drug. If you look at sucrose, the between subject or inter-subject variability is quite significant, whereas, the variability tends to decrease when the excipient is sorbitol. Obviously, the two are in-equivalent, but at the same time you do see some tendency for differences between subject or inter-subject variability.

The inter-subject variability between the two formulations was insignificant.

[Slide.]

So, the conclusions we draw from this study is the significant risk of bio-in-equivalence between sucrose and sorbitol based syrups. We have practice in the sense generally when a request is submitted for biowaiver, this is generally granted because the amounts of excipient used are

within the inactive ingredient guide, so this is something we felt was a high risk, and this study resulted in strengthening the language that goes in the BABE guidance that you heard this morning. So, the research went to Policy quite quickly.

In addition to literature report, I mean obviously, when we focus on regulatory research, one study obviously is not the basis of a decision. You really need to be able to generalize your study findings to other situations, and so we did find similar trends.

For example, furosemide and atenolol, you have examples in the submissions, and so forth, that tablet formulation actually has higher bioavailability than the syrup formulation. So, again, syrup containing sorbitol.

[Slide.]

But I think we also wanted to generalize it further to test the hypothesis that highly permeable drugs would be less prone to this effect. This part of the study is just being completed. I don't have complete analysis of that, but the preliminary data that I have does suggest that the difference one would see between sucrose and sorbitol would be far less and we knew for theophylline, which is higher permeability than metoprolol, which we use as a boundary drug, and you can see here the difference between sorbitol and sucrose-based solutions for metoprolol, which

is a boundary, high-permeability drug, is best, slight differences there, but not likely to be a major difference. I will have to wait until the analysis is done.

[Slide.]

Here is an example of sort of a focused regulatory research that addresses the particular question, and then we can translate this information quickly to policy. It fills the gap that existed in the literature, and was used in that way.

[Slide.]

Let me change the focus now and move to Product Quality Research Institute. Many of you probably already know what this institute is. Product Quality Research Institute was developed by CDER in collaboration with several associations and organizations, trade associations.

It took a long time to develop this. I remember the first meeting we had for developing this was on January 11, 1966. I had four or six feet of snow here, but we did have that meeting, so that was on the sign that this institute had to work.

The institute is organized into several layers. You have a board of directors. Ken Heimlich serves as the chair of this board of directors. You have a steering committee, which have representation from all the founding members. What is not shown in the steering committee

membership are the new members that joined PQRI. The new members are USP, ISPE, and IPEC, so different associations are joining, so the steering committee is increasing.

Then, you have a series of four technical committees. You have Drug Product Technical Committee chaired by Sid Goldstein. Drug Substance Technical Committee chaired by our own chairperson, Steve Byrn here, and Biopharmaceutics Technical Committee, Elizabeth Lane, who is in the audience. I just saw her come in. The Science Management Committee, and the position of chair is vacant. Dave Savilla used to chair it, and had to move because of other obligations.

[Slide.]

I am going to briefly talk to you about the philosophy behind how we are approaching in terms of defining the research plan for this. I will just share with you here, under Drug Product Technical Committee, we have plans for three working groups. One is up and running. That deals with the uniformity issue, and I will talk to you about that.

The two other working groups under Drug Product are Manufacturing Changes, Container Closure or Packaging Changes. Under Drug Substance, you have Specification or Bulk Active Post-Approval Changes Working Group, Particle Size Working Group, and Impurities Working Group. Since

Steve is here, I will request him to share some more information on that committee.

Under Biopharmaceutics Technical Committee, we currently have only one project, and that is extension of BCA's Base Biowaivers. We originally had two other groups planned. One dealt with Nasal and Inhalation Products, the other one, DPK or dermatopharmacokinetics. Those for the time being have been taken off because I think we will bring those back after our discussions tomorrow and possibly some more discussions and see how that goes.

There is only group under Science Management that deals with process management. It is not active at this time.

[Slide.]

Just to give you a brief overview of PQRI, it is a virtual institute. I think we bring together expertise from industry, academia, and FDA to work on regulatory problems, and I think the founding members are listed here.

You have the AAPS, which has the responsibility of day-to-day management of the institute. Then, you have Consumer Health Product Association, Generic Pharmaceutical Industry Association. We left it there because I think that was a founding member, but I think the association has changed, as you heard yesterday.

Then, you have National Association of

Pharmaceutical Manufacturers and the National Pharmaceutical Alliance, the Parenteral Drug Association, the Pharmaceutical Research and Manufacturing Association, and obviously, FDA.

As I said earlier, I think there are three new members now - USP, ISP, and IPEC.

[Slide.]

PQRI essentially is designed to address scientific needs, regulatory scientific needs, and PQRI would entertain and conduct research to address scientific issues related to regulations, guidances, and so forth.

Once a project is completed by a working group under this institute, that information will be transported to the FDA via the Steering Committee. I think we have built-in safeguards, so that the conflict of interest, as well I think FDA participation in this institute is clearly above board and consistent with approaches FDA utilizes.

So, for example, in this case, if a vote is required on the research outcomes, FDA would recuse itself from voting on that.

[Slide.]

Once the information is forwarded to the FDA, I think obviously, FDA has the sole authority for developing regulatory policy and guidance, so this information obviously is going to be recommendation, and since we are

participating on this institute, we hope to minimize any differences of opinion that can come about.

[Slide.]

Let me now give you a sense of how we approach in developing the research plan for this. I believe you are all familiar with the traditional approach that we have utilized for years in discovering and developing new drug materials, new drug products.

At the Agency, at the FDA, the primary focus tends to be from a safety and efficacy point of view, tends to focus on preclinical assessment, clinical Phase I, II, III evaluation, approval of the NBA, and then Phase IV commitment and monitoring adverse event reports. I think that is well recognized within the Agency.

I think supporting all those functions is product development activities, which start with pre-formulation. You use a formulation or you use a product to establish safety and efficacy profile, so when we say we approve a drug, we mean we are approving a drug product.

That material has to be scaled up and there are changes that occur to that material. The key questions we have asked ourselves are: how do you build quality in the products that are used in clinic? This is an extremely important question because if quality is not built it, then, you confound the safety and efficacy database with quality

problems. So, that is Question 1.

Question 2 is once you have the safety and efficacy database, how do you establish meaningful specifications, so that you could control or you could mange postapproval changes that result from, say, scale-up and other changes that occur. So, that is the debate sort of thing we have.

I will just share with you some slides from AAPS symposium that was set up as a debate, and I will explain that to you in a minute.

[Slide.]

We selected the Drug Product Technical Committee for this debate. Essentially, we have a regulatory hypothesis approach. This is how we started, and I think Steve will say a few words about how we have changed this approach later on.

If you look at what is the hypothesis under Drug Product Technical Committee, it simply states--and we discussed this on day one--"Adherence to Current Good Manufacturing Practices, which include validation, and appropriately established product specifications are sufficient to assure consistent quality and performance of drug products that are manufactured at different locations using alternate pharmaceutical unit operations, excipients, and container/closure systems." So, essentially all

aspects.

So, this is based on the changed model, that if specifications are appropriate, then, these changes should be managed via those specifications.

Clearly, the initial projects, focus has been on immediate release dosage form because of the long manufacturing history. If you recall, tablets and capsules have been manufactured in almost the same form for last 120 years, so we have 120 years of manufacturing history and development history with this.

[Slide.]

What are the outcomes are we expecting from this exercise? Clearly, we would like to reduce the time and cost of implementing manufacturing changes, and this would definitely benefit industry.

We would like to reduce the number of CMC and biopharm supplements. I think the number is a large number. I think the number can be 1,500 for new drugs and 3,000 for generic drugs. It is a very big load on review, and hopefully, we would like introduce the concept of one-time review by CDER.

CDER reviews it once, and then once specifications are deemed appropriate, then, changes could be managed with that, and when changes in the specifications are needed, then, CDER would get involved. Again, that is a dream, and

that is a hope.

Clearly, the other aspect is to facilitate introduction of new technology, and this is to help maintain the competitive edge of the U.S. industry.

I think we approach this by saying that if we ensure that quality is built in, then, this is all possible. So, part of the argument here is by doing this analysis, by doing this exercise, we will ensure quality is being built in.

[Slide.]

At the AAPS meeting in New Orleans, not this one previous to this, we set up a debate just to provide perspectives, so that we can find ways for moving forward.

The debate we set up was as follows. CGMPs, which include validation, and product specifications are not--underlined--not sufficient to assure consistent quality and performance of most immediate release drug products that are manufactured, and so forth, and so forth.

I argued at the symposium why FDA feels that these are not sufficient, and we used the SUPAC-IR as a model, and we asked Sid Goldstein, Arni Repta--Arni Repta used to chair the Biopharm Committee--and Steve--I misspelled Steve, sorry, Steve--Steve Byrn to argue why not. So, that was the argument, sort of debate we had, and I will share with you my part of the debate, my argument here.

[Slide.]

Clearly, we are trying to identify high risk and low risk. The first day we did have the discussion, and I think I want to share with you the perspective here again.

Release testing that is based on specifications, at the time of manufacture does not provide the information that assures shelf life.

So, stability commitment may identify stability problems at a later time when the product is already in use by the patients, and if it fails to meet the specifications once it is distributed, it has to be recalled, and recall takes time and may be incomplete, so that is the risk.

If we approve a product on the basis of specification, and the specifications do not assure shelf life, then, the issue becomes of a recall, and recall can never be complete or isn't generally not complete, and the patient already has a substandard product. So, that is the risk.

[Slide.]

If you really look at what are the major reasons for recall in 1999, if you look at the quality-related recalls, we recalled, voluntarily, companies recalled products, or we had initiated some recalls because of sub-potency, dissolution failures. The number two reason for recall tends to be dissolution failure for quite a few

years. Super-potency, stability data generated did not support expiry date, failure to meet established impurity or degradant limits.

So, these are the top five reasons for chemistry-related recalls.

[Slide.]

Clearly, one of the aspects for risk assessment here is we feel that a combination of long term and accelerated stability testing (and PAS) are currently the only means of assuring correct expiry date.

Principles of accelerated stability testing are fundamentally based on the arrhenius equation, and the arrhenius equation is based on simple reactions, solution reactions, and so forth.

Now, if you are trying to use that fundamental reaction theory to predict physical changes, polymorphic changes, and other physical, that may not be appropriate, so I think having dissolution failures as number two reason for recall is an indication that the stability testing, accelerated stability testing may not be predicting physical changes that occur in products.

[Slide.]

Clearly, this morning I shared with you the FDA perspective on biopharm, why in vitro dissolution specifications may not assure bioequivalence, so I am not

going to go over that again.

So, that was sort of the debate we had. So, in a sense, having that debate and having laid out what are the risks associated allows us to then focus on how to approach that. Clearly, from a chemistry perspective, the issue becomes if we move away from pool supplement, the step would be if companies commit to having sufficient stability data before they distribute, that might be a solution. So, to begin to identify solutions for moving forward by clearly identifying where we stand and what are the reasons for current policy the way it is.

[Slide.]

So let me focus on the drug product and then share with you some thoughts on the project on blend uniformity. Blend uniformity is considered as an in-process control test and it is definitely a development test, but what are the problems with this.

Current policies require demonstration of adequacy of mixing or in-process powder blend homogeneity for batches that we currently manufacture. However, blend uniformity testing using sampling thieves is the only accepted method. If you try to imagine a vessel almost this room size, I mean if you are making a huge product of that size, it is a huge vessel that you mix your powders in, and you have to go and take samples from different parts of the blender and use a

thief to do this, and demonstrate that the mixing has resulted in a homogeneous blend of powder to move forward to the next step in the manufacturing process.

For most powder blends, based on the industrial input and based on current understanding of blending operations, it is felt that blend testing for every production batch is not necessary and that unit dose sampling, the thief that we use, can pose significant problems. In fact, the sampling procedure itself can introduce artifact and actually tell you that it is not homogeneous when truly it is homogeneous.

At the same time you have to keep in mind when you mix powders, that is not when the mixing stops. Then, you transport that powder blend to a different machine. If you are encapsulating a capsule, then, you have to transport that powder to capsule-filling machine or tableting machine. All the procedures used to transport that material can induce mixing or can induce de-mixing, so mixing doesn't stop at the blender.

Clearly, the debate that we are facing now is the gap in the scientific understanding and regulatory policies are a source of continued debate and from an industry perspective, leads to undesirable regulatory action, warning letters, and so forth.

At the same time we feel that current policies may

be devoting industry and FDA time and resources to address a redundant question, so that is the problem that needs to be addressed.

[Slide.]

The Blend Uniformity Working Group has been functioning for a couple of months now, and they already have held a workshop, and from that workshop we have had public input in how to proceed. The approach that the group is going to take is to identify if or when blending uniformity tests are needed to assure product quality.

What this entails is a risk assessment, what are the high risk practices in blending operations right now? For example, if you have powders which have very different particle sizes or powders which have static charges, and so forth, and if you don't account for that, then, blending might be a problem.

At the same time, how do you select the right blender for a given powder material, and so forth? So, a risk assessment of what are the high risk practices would be a step one. Then, clearly, the second step is to seek to enhance confidence in end product content uniformity to assure batch-to-batch content uniformity without the need for this in-process blend uniformity test.

What a patient gets is the tablet or a capsule. That has to have the right dose and has to have uniform

distribution of the drug in that material, so that is the proper question.

Blend homogeneity testing is an important development function. That is how a company would establish an optimal blend time, an optimal mixer, and so forth, but from a regulatory perspective, if we can develop an approach which says that end product or core sampling, just material coming out of a tableting machine, if that is homogeneous throughout the production batch, that might be a better approach to working with the current problem that we have.

Clearly, in some cases we probably would need blend uniformity testing, and if that is the case, then, we would like to develop and validate more effective methods. Here, methods, such as near IR methods and other methods will be looked upon.

The outcome we are hoping from this work is that we would have science-based recommendations for development of new guidance documents that will identify when and how powder blend uniformity should be tested, and the hope is that this guidance can save, not only development time and resources, but also reduce the number of unfavorable regulatory actions and save time for both FDA and the industry.

It is a bit ironic. I just want to step back and share some of my thoughts here. Blending is probably one of

the oldest unit operations that you can think of, and we have been making tablets and capsules for 120 years. I don't know how long have you been blending powders.

It is ironic from my perspective that I think we are having this debate. We started PQRI with the most simplest, the oldest unit operation to deal with, so I don't know what that says about the science of building products here. So, anyway, let me move on.

[Slide.]

Biopharmaceutics Technical Committee, the chairperson is Elizabeth Lane. The basic premise or the basic umbrella hypothesis that this committee has adopted it that in vitro drug release and other appropriate physical and chemical product tests can be developed to assure equivalent rate and extent of drug absorption from pharmaceutical equivalent dosage forms.

Clearly, I think the desire here is to move towards more in vitro based methods for assessing bioequivalence, and the first product selected is extension of the biopharm classification-based biowaivers for Class II and Class III drugs.

The chairperson here is Jim [Polli] from the University of Maryland, so that group also has been formed and they have started already working on developing a research plan.

Interestingly enough, in the first working group meeting, they felt that it made it easier to move in Class II direction, not Class III, although I would have expected that they would moved for Class III drugs, we will have to wait and see how that group develops the program.

[Slide.]

Drug Substance Technical Committee, I will just briefly mention this and then let Steve share some of his thoughts here. This committee is going to focus on a similar umbrella hypothesis and will deal with changes to bulk active materials.

Clearly, the desire here is to develop meaningful specifications for drug substances, so that we can control manufacturing changes for the drug substance itself. The point I would like to make here is I think this has been a long process, and we, by design, adopted a hypothesis approach which will essentially create he debate and through the debate will come data and information to make some decisions.

I think there has been some reservation with the hypothesis approach meaning that I think the hypothesis is so structured that it is favoring FDA current policy. That means you essentially can reject this hypothesis. I think Steve has some suggestions of moving away from the hypothesis-based approach to a more descriptive approach,

and I will let him share that.

[Slide.]

Let me just share with you some thoughts on the Science Management Technical Committee. This committee was put together with a goal to develop strategies that maximize efficiency of the processes that produce an optimally performing drug product that meets public health objectives for identity, strength, quality, purity, and potency.

It was thought that we will start with process mapping, how does a company develop product and how does the company interact with FDA, and can we optimize those interactions between FDA and companies, so that reviews could be done quickly, as well as that information could be used in development to improve efficiency, and do this for both CMC and biopharm.

As I said, that Dave Savilla is leaving this committee. The committee has not been active, and we hope o reactivate this committee soon.

[Slide.]

With that, I will just share with you we have more detailed description of the research projects and other information on PQRI, and we have a web site, is www.pqri.org.

With that, I will stop and let Steve share some of his thoughts.

DR. BYRN: Thanks very much, Ajaz.

I will just give you a quick additional update on the Drug Substance Technical Committee. As you saw, the hypothesis basically stated that if you followed GMPs and you critically compared three parameters, which would be physical properties, specifications, and impurities, that the hypothesis is that those activities alone would be enough to ensure equivalence in a drug substance made by different routes at different sites, and so on.

Now, of course, this issue is related to the site-specific stability issue and really to a long-standing issue in Drug Substance, which is that--and this was extensively discussed at the BACPAC, AAPS, FDA symposium that was held in Arlington about three years ago--the widely held belief that even though two bottles of drug substance are assured or said to be the same by analytical chemists, they don't perform the same in the formulation, and they don't make the same drug product with the same dissolution tests and stability.

So, in this case, the hypothesis is running against what is commonly held in the field, and we have been going through a lot of iterations of how to deal with this. What we decided to do was to constitute, divide it into three parts, so we are going to divide it into a part involving physical properties, a part involving

specifications, and a part involving impurities, and then those three working groups will redefine their area and their hypotheses, to more carefully examine this broad issue.

Obviously, this is related to BACPAC-2 and BACPAC-1. The current BACPAC-1 guidance is out for discussion. BACPAC-2, I believe has not yet been issued, but maybe is somewhat imminent I think it is fair to say. I said "somewhat imminent." Is that fair, Helen?

This is another critical aspect. In the long run, we think that this will be a very worthwhile activity because this whole issue, what we are really trying to do fundamentally is understand what the problem really is and why there is this apparent gap between the science of understanding the sameness, if you will, of drug substance and the performance of those materials that are thought to be the same once they are taken into formulation and in dissolution and stability.

So, the working committees have all been assigned by our group, and those working committees we are hoping to constitute formally in January with a training session, and then their job will be to define the projects further in these three areas.

I don't know whether Ajaz wants to add anything more, but that is sort of an update on where we are.

Now we are ready for committee discussion on this matter, so it is open for discussion, either part of Ajaz's talk, either the PQRI or the Office of Testing and Research discussion. Any committee questions?

Committee Discussion

DR. RODRIGUEZ-HORNEDO: Not a question, but I want to support the initiative. I think it is an extraordinary effort in bringing industry and academia and other groups together to work on very relevant problems.

I suspect that the challenge lies in raising money for some of this work, so is there a binding on which projects get supported or is not a problem, you have more money than projects?

DR. HUSSAIN: No, money aspects of PQRI are handled by non-FDA, so I would rather not comment on money aspects.

DR. BYRN: But there is a major effort on the board of directors that Ajaz listed, there is a major effort to raise funds from the private sector to support the program.

DR. ANDERSON: You mentioned something about sampling techniques for the powders, I believe, and then you mentioned something about infrared analysis. Could you comment on that, because you kind of lost me?

DR. HUSSAIN: The current method is using sampling

thief. You insert a thief and then collect a small sample, and the sample has to be approximately the same size of the dosage unit. It cannot be more than three times. That is what is required.

But there are new technologies coming about where we actually could do homogeneity assessment with, say, having near IR probes built into the blender where you could look at the blend homogeneity based on some of the new technologies. That is what I was referring to.

DR. ANDERSON: Okay.

DR. BYRN: Any more questions from the committee?

[No response.]

DR. BYRN: We will open this discussion to the audience. Would anybody like to ask a question or make a comment?

[No response.]

DR. BYRN: Hearing no question, we are scheduled to take a break. I think we will go ahead and take a 15-minute break until 2:30 and then we will start the Failed Bio Studies discussion.

[Recess.]

DR. BYRN: We will go to the last session of today. It is a session on ANDA bioequivalence studies that fail to meet FDA's current bioequivalence criteria.

To initiate the discussion, Dale Conner, Pharm D.,

will make a presentation. Thanks very much, Dale.

GENERIC ISSUES

Failed Bio Studies

DR. CONNER: I am here to talk today about something that is of great, I guess, interest and concern to us in the Office of Generic Drugs and in OPS. Strangely enough, when I discuss this with people who are not part of the industry or the FDA, they often express a great deal of surprise at what I am about to say. You will see what I mean in a second.

We obviously in Generic Drugs, deal with ANDAs, Abbreviated New Drug Applications. As you know, there is a limited set of one or more studies, bioequivalence studies, that we use to approve these generic products.

[Slide.]

To review, for those of you who may not have looked at this in a little while, most of the studies that we look at, or at least up until recently have been looking at, are generally two-day, crossover studies, single dose for the most part, although we have in a limited subset of products, we have done multiple-dose studies, normally under fasting conditions, and most importantly, our BE criteria is 90 percent confidence intervals calculated based on the variability of the study, must fall between 80 and 125 percent, or if you would like to express it in fractions,

0.8 to 1.25. We do that on both area under the curve and Cmax.

To date, also, the fed bioequivalence studies, performed in a similar manner, are done as a point estimate between those same numbers, 80 to 125. As an aside, because I was asked about it outside this morning, I will reiterate that at the moment, that criteria of point estimate between 80 to 125 has not been changed. That guidance that was discussed this morning merely changes the design of the study from a three-way study to a two-arm study. That is really the only change to date that is out and official in a guidance.

Now, we are working on things and we have proposals to change that, but until the food guidance comes out, as far as I know, it will stay at point estimate between 80 to 125.

[Slide.]

As another review, I have put down various scenarios of results that one could get from a bioequivalence trial. Before I go into this, I have drawn them, you know, for the sake of simplicity, as a bar, and the width of this bar is supposed to represent the width of the 90 percent confidence interval results from a study, but it is important to remember that the results truly are not a bar that runs very evenly across.

It is more of a bell-shaped curve with most of the subjects in the studies centered around the center, and as you get out to the edges, you get much less of the subjects with those values, so keep that in mind that it is not an even distribution like I have drawn it here, but for simplicity sake I have depicted it this way because it is easier to look at.

On the top, you can see the blue bar, which is what most generic sponsors hope to achieve when they do their studies and when they formulate, which is very nice passing results, and you will see on the x axis, we have the test to reference ratio, expressed as a percent, and the two dotted lines are the confidence interval limits at 80 and 125 just for reference.

So, it is centered around 1 or 100 percent, which is an idea result, which means most of the subjects T-R ratios are around 1, which is exactly what the sponsor is looking for because it says that we are very, very close to the performance of the reference drug, and the variability is quite modest, therefore, the confidence intervals aren't really wide.

Now, we have a second case. The blue one is the only one of my slides or depiction that actually passes or is thought to pass, but we have different scenarios of failure, I guess, if you will.

The second one is simply, you know, it is again the point estimate is centered around 1, so if we looked at means only, we would be very happy, however, this study has high variability, so because of that variability, we end up with a very wide confidence interval.

That confidence interval, because of its width, also leads to a failure because it fails, in the way I have drawn it, on the low side. It goes below 80, therefore, even though the point estimate or mean of the data is about as good as you can expect it to be, the product still fails because the variability is so high that the confidence interval is wide and fails.

I suppose the sponsor could come back in and repeat the study with a test with much greater power or with many more subjects, and that would effectively shorten this confidence interval and may actually get this one to pass. But this illustrates how highly variable drugs often need more subjects in their study to be able to hope to pass.

Some other usual ways of failing to demonstrate bioequivalence--and these are pretty much the same case with the same variability--one is a failure on the low side, one is a failure on the high side. Those have roughly equivalent, if you will pardon the expression, equivalent variability to the first case which passed, but they are simply off the center.

The formulation has shown itself to be not all that close. The test is not all that close to the reference. Therefore, even though they have quite reasonable or low variability, they still manage to fail simply because there is a distance between the two formulations.

So, these failed, not because of variability issues, but because there is probably a somewhat significant difference between the two formulations.

The one second from the bottom, which is right here, I show kind of a further extreme. This fails. You will notice the previous two failed simply because they were close to the end, the point estimate yet was still inside.

The one second from the bottom is a bit more extreme case. You see that the actual point estimate or center part, which I have tried to draw a line, hopefully, you can see it, is also outside. So, even though a portion of the confidence interval or the data is inside the acceptance criteria, most of it, including the point estimate, is out.

It starts to get to a point where the probability is that simply powering up a study, you know, using lots of subjects may not help this product. I mean it is at such a state that although it is certainly possible, the likelihood is simply during a huge study is probably not going to pass

this one.

Finally, we get to a very extreme case, the entire confidence interval or data outside the acceptance criteria. This is one of the few cases where people, rightly or wrongly, have called this "bio-in-equivalent," and a lot of people throw around the term "bio-in-equivalent" in kind of a cavalier fashion, but in reality, the tests that we do really do one of two things.

Either they confirm that something is bioequivalent or they fail to confirm it is bioequivalent. Only in an extreme case do we actually, accurately call this bio-in-equivalent, which is quite a different statement from the first.

In this one, there is probably no conceivable way you could do this study and get it to pass. It is so different that it is probably truly not equivalent in any sense, and there is no type of conceivable study design or power that could ever fix that, and I am not saying fix it, but at least do a study that might demonstrate bioequivalence.

[Slide.]

So, what do I mean when we say "failed"? Different people with different viewpoints, I suppose for a sponsor, anytime they don't get the results that they would like to have and supports the eventual marketing of their

product, they consider that a failure, and I suppose in their way of looking at it, it is, but I define a failure as simply the results of a study failed to support, for an ANDA, bioequivalence, and therefore, approval of that product.

To repeat what I just said on the last slide, simply failing to show bioequivalence does not necessarily infer that it is bio-in-equivalent. There are a whole variety of reasons why one doesn't meet the confidence interval requirements or the bioequivalence requirements, and I will list a few of them later.

Sponsors, for the reasons I will go into, often choose not to submit failed studies in ANDAs, and I will beyond to say it is more than often, it is most of the time they choose not to submit these studies.

When they get a failed result or a result that doesn't meet their expectations, they either repeat the study or reformulate and then do a study on that new formulation. Oftentimes or most of the time, the FDA is blissfully ignorant of the existence of these studies, and I will give you some examples of how that can be not optimal for our decision-making.

[Slide.]

Why do sponsors or people feel that they don't really need to submit these studies to ANDAs? You have to

go back for the justification or the understanding of this to the regulations.

I have paraphrased or almost directly quoted the ANDA information. In the law, which I have the citation down below, it says, "For NDAs all human investigations made to show whether or not such drug is safe for use and whether such drug is effective must be submitted." So, it really doesn't give the NDA sponsor much choice.

If you have done or commissioned or know about a study that fulfills these requirements, you must submit it in your NDA, and for those of you who either look at NDAs or submit them, you know how large they are. One of the reasons they are so large is because you just have to submit every single study you have ever done.

Not all of them directly support the approval, some of them have been done for very different reasons, but all of them must be submitted, and certainly for safety reasons and sometimes efficacy, there are good reasons for that.

Now, we turn to the ANDA sections of the same law, and for some reason which we, based on the amount of time that has elapsed, don't really know why this occurred, but the similar language to the NDA language was not included in the ANDA section, so if you look, you will not find that statement up there in the section that deals with ANDAs and

the requirements for ANDA submission.

Even the people that were around at the time don't seem to remember why that was omitted, whether it was simply an oversight or it was done with a specific reason in mind, but suffice to say that it is not there.

Therefore, the interpretation of many has been that we don't have to do it, if the law leaves that out, it must mean we don't have to do it. So, the interpretation for a great many years has been that sponsors of ANDAs do not have to submit studies that failed.

[Slide.]

Some other important considerations or discussions, and this is just to provide more information. I got these facts from some of our lawyers, who put these out as things to think about.

There are a couple of other parts of the law and pronouncements from FDA that kind of affect this. The first one I have listed there is a requirement in 505(j) that an application may not contain untrue statements of material fact. So, things that are material facts can't be misstated, and this I think to everyone makes sense. You can't purposely make misstatements in your application. I don't think that is a very controversial rule.

The second thing is that selective reporting of data may constitute untrue statements of material fact, and

the example that I cited up there is actually about stability testing where a firm was doing stability testing on their product, and some of the stability tests didn't actually get very favorable results.

They were able to keep doing the stability testing until they got the results they wanted, and they simply submitted the best ones.

Based on this particular case, it was stated that this is not acceptable behavior and that it is truly selective reporting to make a case that may not be true.

So, if you put these two things together, one of the thoughts is that failure to report failed studies may be considered selective reporting, because you have a body of data, you are only submitting a portion of it.

Again, just food for thought, something to think about.

[Slide.]

Why do studies fail? I came up with probably the short list. Those of you who do these studies or are in the industry maybe can come up with even more. But first and foremost, is an under-powered study. I kind of referred to that in my graph of results. Simply when you make a statistical analysis or study plan, you try and estimate the variability and therefore, the number of subjects you need to do your study, and sometimes the estimate is wrong, or

you might have made a correct estimate and you get an unusual number of dropouts. So, by the time you have finished your study, the study was well performed, you have a product that you really believe in, yet, you have come up short as far as the number of subjects you need for that study, and you come up with an under-powered study.

One of the two things that controls the width of that confidence interval are how many subjects you use, and the other is obviously the variability of the products. I mean that is an obvious one, and I think probably people who have done the studies have all come up against this at one time or another.

Some sponsors seem determined to be ahead of the curve and use some type of unusual study designs, and it backfires on them. We have seen that occasionally. They really believe they have a better way of doing things than everyone else, and it is perfectly legitimate to come in and make that argument to the FDA if you think, you know, even if it is in a guidance, you can come in and make an argument that you know a better way and discuss it with the FDA, but sometimes people just go ahead without discussing it and it really backfires. They don't get the results they want, or the results that they get are very hard to interpret based on an unusual study design.

You can fail because of outliers, and I will go

into a little bit more depth about what we consider--and I specifically refer to it as an "outlier" response, and I will explain that in a minute.

When you are doing only 24 subjects or perhaps a little more than that, it doesn't take too many odd results to get it to fail. I have spoken to a great many sponsors who believe that 23 of their subjects told them the truth and exactly what they wanted to hear, and just one subject whose data kind of misbehaved actually caused the whole stud to fail. So, we get into a lot of discussions on that.

Certainly, assay issues of various kinds. Strangely enough, some sponsors still try and validate their assay after they have used it, which seems to me it kind of makes sense you would want to determine that your assay works before you actually did the study and spent the money, but some people only remember to do it afterwards.

Other issues where samples are lost, you end up with missing data that is hard to incorporate. There may be questions. I have dealt with one sponsor who had a study which failed on one data point, a single data point. If we dropped the data point, the study passed, if we included it, it failed. It was a very unusual looking data point, but they had absolutely no documentation there was anything amiss with it, you know, nothing in the lab books, nothing that said, oh, I dropped the sample or I dropped drug into

the sample, or anything like that, no documentation at all that it was a lab error. So, we had no choice but to not drop it.

So, even in some borderline cases, even a single sample is enough to throw a study into the failure.

Also, strangely enough, wrong reference, we have encountered that once or twice. We had a case recently where a firm was pursuing registration in two countries, the United States and a foreign country. They brought large quantities of the reference brand name drug in each of those countries, and they had kind of a snafu in their shipping department, and for both studies they shipped out the foreign reference. So, they did two studies on that reference, and didn't use the U.S. reference.

They came in and said, well, you know, we think it is the same thing, could we just use that study anyway, and, you know, sorry, it has to be the U.S. reference. You would think that this wouldn't happen, but it has happened, so people have actually used the wrong reference.

[Slide.]

Are there other things that give people trouble? Baseline-corrected versus non-corrected. Some endogenous substances that are given, hormones or potassium, really can make a big difference whether you baseline-correct or don't correct the data. I think baseline correction is a very

controversial issue, and with a lot of drugs there is really no right answer. You know, people could argue yes, we should take away that baseline which is there anyway in the subject, or we just use all the data. So, that is kind of controversial, but it often makes a big difference in whether a study fails or passes.

You can do incorrect statistical analysis. You would think that what we do up to now is fairly simple, especially for a statistician, but some people kind of screw it up now and then and use the wrong model or the wrong analysis, and they either think they passed, when they really failed, or vice versa.

Compliance issues, not terribly germane to this because usually, it is a study that we think has passed, and inspectors go out and find some major flaws with the study, and we have to throw it out because the flaws that they find actually invalidate the study, so that is I guess a way to fail the study or at least negate the effects of the study.

Last but not least is the formulation just may not be bioequivalent, and, you know, in a way you have got a failure as a result, but to me as a regulator, it has told me what I want to know. I mean if the product really is so far away that it cannot be considered therapeutically equivalent, I really would like to know.

I mean I consider that a successful test if it

tells me that even though, as a sponsor, you may all not like it.

[Slide.]

I have a couple of examples, hopefully, this will illustrate.

The first one, I have disguised the names of these drugs, so we won't embarrass any sponsors or actually give away proprietary information.

The first example I have we will call Drug X. It is an oral liquid. This is a liquid dosage form that is mixed with a beverage prior to administration, and when it is mixed, it forms a complex dosage form. It is not in solution.

So, we asked for bioequivalence studies on that product. Now, we had one sponsor who used a beverage of their choosing, and they did the required bioequivalence studies. They were found to be bioequivalent and eventually approved.

In the meantime, while we were reviewing the ANDA before the decision was made, they performed another study in another beverage. Now, this beverage happened to be one that was specifically recommended in the labeling, the first beverage was not, but it was a beverage that was commonly used with this drug, so we didn't think much of it at the time.

They did this in this other beverage that was one of the beverages that was recommended, and lo and behold, they got very surprising results in that it was not the least bit bioequivalent in this other study, in one of the labeled conditions of use, labeled beverages. In fact, it came very close to being bio-in-equivalent although not quite.

So, faced with this dilemma about should I submit this to the FDA or should I not, they chose the usual course, which was, well, we don't have to submit failed studies, so, of course, they didn't submit it.

We went on, even though the results of this were back in more than enough time to submit it prior to the approval, they decided it wasn't necessary. So, we went on and approved the product.

Now, clearly, this is a very good example of why we really need these studies, because this is one of the studies that would have drastically affected our approval decision. I mean this was a labeled condition of use specified in the labeling.

If we had seen this, we in all likelihood would not have approved this product.

[Slide.]

My second example is a solid--I will call it Drug Y--solid oral modified release dosage form. We received an

ANDA. It had a study or studies which appeared to be passing studies. We were proceeding with our review. Because of our normal procedures, we sent out an inspection on these studies and while the inspectors were there, they happened to discover that the firm had done another study on the same drug. That study, when they looked at it, that study had failed.

So, they brought that to our attention. We had a lot of discussions with the sponsor about what the implications of this other study were. Come to find out, they had actually performed a third study. I have depicted the results 1, 2, 3 here. The third study was kind of their justification for why they thought the first study that they submitted was the appropriate one, and the second one was not.

So, we will say the first study against Lot A of the brand product, which is the first they did, failed, and as you can see it failed on Cmax 105 to 130. That is the first study they did, and, of course, they dutifully tried to investigate why this had occurred, because they really believed that their product development had been on target and that they had a bioequivalent product.

They picked another lot, and we will call it Lot B, of the brand, and did another study, again with their same test against that product, and that one passed very

nicely. Then, in the process of trying to justify what the problem was, they did a third study, somewhat smaller than a regular bioequivalent study, but still I think meaningful.

In this one, they tested Lot A versus Lot B of the brand, and that failed, with the results shown, 111 to 131. Their contention was, look, you know, we have done the best we can to target our formulation to be equivalent to this product, but, look, different lots of the innovator are now bioequivalent to each other.

That wasn't the only part of their argument, but that was a major point in their argument that, look, you have a problem with this innovator. The formulation they are putting out is extremely variable, and not all of them are bioequivalent to each other. So, how can you hold a generic to a higher standard than you would separate acceptable marketed lots of the innovator.

It turned out to be some sort of a problem with the RLD.

[Slide.]

I have shown you types of studies that we don't usually see. This is actually a failed study that we actually see more often than not. That is outlier issues. A lot of people get confused or people that have done other types of studies, saying, well, I have outlier data, I can use statistics to drop it because there is something wrong

with that person or that data, and generally, we are very resistant to dropping data based on outliers because in the one case, if a person is qualified as a normal subject to be in the study, and you simply don't like the way they respond, and we will assume that it is a good response for that subject, is not a reason to drop it. That is actually more of a reason to include it. That was a valid result for subjects, and the fact that that subject happens to lie out on one edge or the other, as far as its response, is really much more reason to include it than drop it.

However, there is another case where something happened, some technical flaw in the study where one of the periods for that subject did not give you in any way reasonable results. It might be much larger than anyone else, it might be next to no drug present. So the belief of the sponsor is if I studied this person 10 more times, I wouldn't get this result, this was something anomalous and this person is not an odd person, but just gave me an anomalous result.

What we do in those cases is generally ask the sponsor to study the drug, study that subject again with a couple of the original people from the original study as controls and see can you repeat this, you know, do they give you the same odd-looking result, or does now the subject look much like everyone else.

The whole point of that is to simply provide justification for dropping that subject in the original study. Unless anyone is worried, we don't take that new data and substitute it back into the old study. It is simply by saying yes, that was a bad study for that subject, and some technical flaw caused that subject to give you very bizarre results, and if you did it 10 more times, it wouldn't happen.

So, it is kind of a way to allow the sponsor to submit data that was truly anomalous response, and not simply the study subject was kind of an outlier physiologically. I have an example here of that.

[Slide.]

So, the questions for discussion for the committee, because we have been considering this and discussing it a lot internally, and started to discuss it in public is: Should sponsors of ANDAs submit the results of all bioequivalent studies performed on the to-be-marketed ANDA formulation?

Now, it is probably not reasonable or even necessary that a sponsor submit their early developmental type of work on developmental formulations, but I think our current belief is that the formulation that a sponsor actually intends to put on the market, if they have done other additional studies, we would certainly like to look at

that to make a judgment of whether it impacts our approval decision or not.

The second one, some people in the generic industry have expressed to me that it is kind of a burden to expect sponsors to submit full, complete audited reports with all of the data like they would with their so-called pivotal study, and that they aren't as opposed to doing more summary type of information, just to say we have done a study, these are the results. We had enough details to be able to judge whether it is important or not, but perhaps not all the raw data, not all the chromatograms and things, and not the full QC that you usually would do.

So, some sponsors have expressed that they think that would be reasonable to just get complete summary information rather than a full report, and that that wouldn't be quite so burdensome to them.

The final question: What should the FDA do with this information? Should we do a complete and in-depth review on these failed studies, or would simply a brief, but very careful examination of the study to see if, you know, in those rare cases where it would affect our decision, whether there is anything else that would make us doubt the equivalence and approvability of this product.

So, those are our questions.

DR. BYRN: So, now we will have questions for our

speaker and then discussion among themselves.

DR. VENITZ: Dale, on one of your slides you used the term RLD, what does that stand for?

DR. CONNER: Reference listed drug. It is the drug that is designated in the Orange Book as the reference that all generic or ANDA sponsors have to compare themselves against. Most often it is the brand name although not 100 percent.

DR. LAMBORN: I had a question about your first example of failed, the instance where the sponsor did a study with a beverage that was actually listed in the labeling and failed, I would have thought that not telling you about that, under this general guideline of selecting reporting, since that was specifically in the labeling, would have already been covered as distinct from the majority of the cases.

DR. CONNER: I am not sure I want to get too far into that, but I mean that I guess various legal people would have an opinion one way or the other whether that was covered or not. Again, I think it is a matter of interpretation. One of our desires I think is to kind of close the level of interpretation to make things more clear to sponsors and everyone else, you know, what they should submit and what they should not.

DR. LAMBORN: And the statement about selective

reporting constituting untrue statements, that is just somebody's clause, that someone said maybe this is something that could apply?

DR. CONNER: Yes, that is just one legal opinion and you could probably get others, as well. I mean it is one way of thinking about putting those two previous statements together. We are not pronouncing it to say that it is a definite fact, but it is one way to interpret the previous things that I have said.

By any means, it is not the only way to interpret it.

DR. BOEHLERT: With regard to NDA failed studies, do they submit the complete report or just summaries?

DR. CONNER: My experience from being a reviewer of the Pharmacokinetic Section of an NDA, is most of the time if it is done in U.S. studies, it is pretty much complete. I have also seen variations, for example, when sponsors are submitting, say, early pharmacokinetic studies or early food BA studies to Japan, for Japanese registration, I have seen them in summary form.

Now, is important to note, though, that even if we request summaries, if the reviewer or the Review Division decides that that is an important study that we really need to see, we reserve the option of asking for the whole thing, so it is merely with the expectation that most of the time

we are not really going to see any significant problem with that summary. In a minority of the time, we will see something that could be very significant, and then we will go back to the sponsor and ask for the complete information.

It allows us to be selective and simply get the full report on only the things that we have looked at and consider important and significant.

DR. ANDERSON: On page 2 of this document that I have here, you state that sponsor often choose not to submit failed studies in ANDAs. You added to that during your presentation "most of the time."

DR. CONNER: Yes.

DR. ANDERSON: If they don't submit them, how do you know that they failed or they have them?

DR. CONNER: That is a very good question.

[Laughter.]

DR. CONNER: It goes to the part of, you know, some sponsors--for example, one of the sponsors in the first example, when we discussed later the results of the study and were in discussions with them, they said, well, we didn't submit it because you didn't ask us for it. The response I guess back is how could we ask you for it if we didn't know it existed.

So, it is question, I mean as part of the deliberations and discussions, one of it is, well, how many

studies are we really talking about here, you know, is it 20 percent, is it 10 percent, is it a very small number, you know, and I don't think that I have the exact numbers on it as a percent.

I am sure that the people who really know this are CROs, who do these type of studies for a lot of different sponsors. It may not even be a single sponsor knows exactly what the percentage is unless they have a lot of products and do a lot of this type of work, but I think CROs, that do literally hundreds and hundreds of these studies, probably have a good idea.

In fact, to give you kind of some preliminary information, Larry Lesko, who I am not sure if he is still here, prior to coming to the FDA, he worked for a few years in a CRO, and he estimates that of the studies that he did in that CRO, that probably 20 percent or so failed, perhaps 25 percent, and, of course, not all of them are on the final formulation, so it is probably a smaller percent or the ones we are actually discussing here.

It is hard for me to estimate exactly what we are looking at here, but maybe some sponsors or CROs would have a better idea.

DR. ANDERSON: I am not disagreeing with you in terms of a need to have the information, because in the next statement here, you say, "Sometimes these contain important

information," et cetera, et cetera, and I agree with that.

As an experimentalist myself, if something goes wrong in an experiment, I need to know why it went wrong, so I can correct it in the future, and it seems to me like it is not playing fair when you pretend that something didn't go wrong, and you go ahead and send it, but then I understand why these things happen.

I would say that I think it is important for anyone who is trying to make a judgment about something to have all of the information, and the person who has information that may not be quite as positive, if that makes sense, as one would like it, maybe could have an explanation for it, and then it would be up to the reviewer to determine whether or not the explanation makes sense.

DR. CONNER: I think you are perfectly correct. I would expect and encourage sponsors, when they submit this type of information, to give their spin on it or their interpretation of why this wasn't an important finding, you know, the flaws, you know, the reasons they think it failed. I mean obviously, they do that anything because when a study fails for a sponsor, they have to make the decision, well, was there a technical flaw in the study and should I stick with this formulation, and just do another study, or does this really tell that I should reformulate, should I keep trying to push this one through, which now I have a study

that tells me it might not be as good as I think it is, or should I go back and reformulate, and that is kind of an expensive and time-consuming process to reformulate a product when you are that far along, but also, these studies are very expensive, too.

It is something I think that most sponsors, you know, the decision when they get this type of result, they have to make that internally anyway.

DR. ANDERSON: I understand that, but it may fail once it gets to the public, and that is even more expensive.

DR. CONNER: Yes.

DR. ANDERSON: And perhaps they ought to also look at the fact that I believe that if we are talking about generic drugs, they don't have to do all the research and starting out from scratch, making the compound, and all of that, a very expensive part, but perhaps the most important thing here is that it may be disastrous if a failure occurs once you have approved it without knowing that the failure has occurred ahead of time, and it occurs once it is out in the public.

DR. BYRN: I wanted to ask, following on the discussion from the BACPAC discussion really where it is pretty widely held, I think, generally held, that drug substances they are saying don't manufacture into the same product necessarily, I don't know how often this happens,

but if the dissolution test is not very discriminating, you have that scenario, and then, say, a submitter does three bioequivalence tests, of which only one passes, and they submit that, under that scenario, there would be significant variability basically in the product, and that would seem to be something that the Agency should know about.

Are there cases like that, do we think it goes to that extent or not, or do we know?

DR. CONNER: As we said before, I am kind of limited in my knowledge of this. I have heard through some rumors, some very informal discussions over cocktails at meetings and things, that people do studies that don't pass.

You have to remember, though, although I am sure there have been sponsors that have kind of plunged ahead and done three studies, even four studies on the same formulation, but most--there are a number of generic sponsors in the room right now--but most of these studies are very expensive and most of these companies, you know, they aren't the multibillion dollar companies that produce brand drugs, so I mean most of the companies can't afford to just keep plugging away, you know, a quarter of a million to a half a million dollars a shot, you know, beating their head against the wall to try and get a product through.

It becomes you either give up or reformulate. I don't expect that most of the time we will see more than one

extra study, although, as I said, I am kind of ignorant on the exact numbers and how many times people try on the same formulation.

DR. LAMBORN: In that sense, it seems to me that this becomes less of an issue because on the one hand, if, in fact, they don't do many more studies, and if all you have asked for is, as they have suggested, a summary, then, there does not become a substantial additional burden on their part to provide the information.

If there is the occasional case when, in fact, there really is something substantively wrong, then, you will have the information to be aware of it, so I guess I am now moving from questions to votes, and I will reiterate something I have said at numerous other times when this has come before this committee, and I think we have had the sense before also that whatever we can do to support the regulation that would require that for the proposed marketed formulation, that there must be some record and that it could be in the form of a summary that should come to the Agency on all the studies that were done, and that would allow you to limit the burden for those instances where it is just part of the process, but would assure that you have some chance to identify in advance, prior to marketing, instances where there might be substantial risk to the consumer.

So, I would like to put that forth as a statement from the committee.

DR. VENITZ: I have two questions for you. The first one in your Example 1, did you have any recourse after you approved that product, or you basically shrugged it off?

DR. CONNER: Yes, when we finally discovered that, we took regulatory action.

DR. VENITZ: The second question. Let's assume that the committee comes out in favor of requiring submission either in the summary form, how are you going to enforce it because the law apparently doesn't require it?

DR. CONNER: Well, there is a variety of avenues that we are exploring. Obviously, one of them is to amend the law or the regulations, to incorporate language or to add language of the kind that is in the NDA section. There are perhaps some others, too, but that is probably the most solid way.

DR. LAMBORN: Would it be helpful in this case for us to give you a more formal vote?

DR. BYRN: What I thought is we might have comments from the audience and then the committee have some more discussion.

Are there comments from the audience, questions or comments from the audience? Just as before, please identify yourself.

MR. SHARGEL: I am Leon Shargel. I am with the National Association of Pharmaceutical Manufacturers. At the National Association of Pharmaceutical Manufacturers, I represent the interests of generic drug manufacturers and drug substances.

I would first like to thank Dr. Conner for mentioning in his title, that when we talk about filed bioequivalent studies, that these are studies that fail to meet bioequivalence goalposts or regulations.

Very often we are concerned that from the image point of view, that failed studies often mean the generic did not do the appropriate studies, and as mentioned, if you do good science, and we don't get the numbers that wanted, it is still good numbers, it just tells us that we have the wrong formulation of perhaps we sampled wrong or we have something else.

So, I do thank Dr. Conner for pointing this out. I just want to also point this part out. I also have some comments about the idea whether all studies should submit--and maybe I will go through some of these questions--in the NDA development, there is very little experience in human studies with a new drug entity.

You get that as you go through the various stages from the IND eventually to market approval. By the time the patent is at expiration date, there is a lot of experience

on the safety and efficacy of the product, otherwise, it would have been off the market prior to a generic coming through.

The pivotal bioequivalence study is usually made on the to be marketed batch that is going through CMC review and through Dr. Conner's Division of Bioequivalence, and that should be the focus for the basis of the quality of the product that we are asking for approval.

Very often we do do early studies. We may look at a formulation because we don't have the information from the brand or the reference listed drug, so we may do a pilot study to look at subject variability, intra- and inter-subject variability, or just in terms of sampling time or some other thing.

So, there may be a number of studies in the development of the final formulation and indeed, when you do what you think is a final formulation, as I said, it may not pass the bioequivalence requirements because we may have sampled wrong, the outlier, some other things, not enough subjects, didn't have the power, it could be a variety of other aspects.

Now, when these studies are done, it has been my experience that the sponsor does not write up a full-blown report on studies that they are not going to submit, so they would not have a full-blown study, why write up a whole

report on a small study or such when the importance of the study that is going to be marketed, the final formulation, is where the focus is.

Now we get to the point of what we are giving to the FDA, and the question is how much will this detract the reviewer from focusing on the formulation that we are saying we would like to market this formulation, we have had two formulations that we did in a pilot study, one that we thought would work, but now we realize that the formulation was releasing too quickly, too slowly, whatever the problem was, we have now corrected that problem, and here is the study that we are submitting, and that is where we want to focus.

We really don't want to lose review time and other things. The data is on file, I mean with the company. Certainly, in pre-approval inspections, as pointed out, A field inspector, an FDA field inspector will look at the industry, will say, okay, you have done other studies, and this can be certainly questioned and should be answered honestly, yes, we did three studies, and here is what we have.

But I have concerns as how much time will it take away from review time, where is the focus on that, and that is the way we feel.

Now, the last question is what should FDA do with

the data, and I would never tell FDA what to do with the data, so I will leave it alone, and I thank you very much.

DR. BYRN: Thank you.

DR. VENITZ: Would you be opposed to submitting all the clinical data on the to-be-marketed formulation, even if it is more than one study, or you are just opposed to the preliminary pilot studies with a variety of formulations?

MR. SHARGEL: I am not sure I want to submit all studies. I would not be opposed to summaries of this is what we have as prior art, that we have done two or three studies, and such, and maybe a quickie little summary saying, well, we did a formulation in 12 people to see whether we have inter-subject differences or inter-subject whatever it was we wanted to look at to get a better idea of the plasma level profile description of the kinetics before we did the bigger study, and then we realized we sampled wrong, but, you know, with maybe a comment that it was done, and if FDA really feels the urge or need for the data, certainly, it would be available.

DR. BYRN: Thank you.

Other questions, other comments from the audience? Yes, sir.

MR. TANTILLO: My name is Nick Tantillo with ESI Lederle.

The first question I guess that Dr. Conner posed was should sponsors submit the results of all BE studies performed on the to-be-marketed ANDA formulation, and as I guess the previous speaker had mentioned, that sometimes pilot studies are done, ultimately leading to a pivotal study. Sometimes that pivotal study may not demonstrate bioequivalence.

In that case, a firm can either repeat the study or do more studies, or, in effect, make a decision to reformulate or change the manufacturing procedure, in which case that formulation, that product is no longer to-be-marketed formulation, and now becomes something other than the to-be-marketed.

I guess I just wanted to ask the committee if you were considering the submission of all studies or really to clarify the point of the to-be-market formulation, which would be the formulation that is the subject of the application for clarification.

DR. BYRN: So, we can discuss that question.

DR. CONNER: I think our view, at least at the current moment, is we are interested in that formulation that is intended to be marketed. I mean if it is very early and very different formulations, although, of course, having that information would be very educational for us, I don't think it is necessary or compelling that we get that

information.

The other thing that I have a little worry about in the back of my mind is I think we have decided we want the to-be-marketed formulation, but the definition of the to-be-marketed formulation has to be clear.

For example, if a sponsor does a full biostudy and then changes the color of a tablet, nothing else, or some very superficial change, or the imprinting or something, is that the final formulation? I would say if the change is so tiny as to be nonsignificant, a change under, say, SUPAC, I would say I want to see that study.

If it is a more significant change, again, by some rules, such as SUPAC, perhaps that is a different formulation. It remains to be worked out what is the final formulation and how far do I need to be away from that before I am not interested in seeing that information anymore. So, it is something we have to iron out, I think, and perhaps with industry input about what exactly is the final formulation. So, we have to get that definition correct.

DR. BYRN: Any other comments from the floor?

[No response.]

DR. BYRN: Let's have another discussion of the committee or continue our discussion. Kathleen.

DR. LAMBORN: I think my proposal as the potential statement from the committee still stands. I think that that would be worthwhile, and I think it is consistent with what we heard from the audience because we are talking, with a clarifying of what is meant to be "to-be-marketed," it would resolve a lot of the questions about a lot of the things that would not be directly focused, and again I think we are talking about a summary rather than the same level of report that would be required for the pivotal, just enough information for the Agency to have a sense of, well, yes, they did a study, and they had too few patients in it, or they did a study, and the variance was higher than they expected, so they redid it.

Then, we have very limited information in the first one, and then we had the pivotal one which matched, or we did, you know, five studies and then we repeated exactly the same study a sixth time, and it finally passed, but maybe the Agency would then want to say, well, maybe we should see a little bit more about the others, because if it took you six tries with the exact same formulation, and the exact same study, was there something in there that we have to worry about.

So, I think we are talking about trying to limit the amount of extra work, but just give enough to highlight potential sources of a problem.

DR. BYRN: Other comments from the committee?

DR. BOEHLERT: I would just add I think it is going to be important for us to clarify, as Dale just spoke to, at this point, on what is the final formulation. It is not out of the realm of possibility that a dye change can change the performance of the product. There are interactions known in the literature between dyes and active ingredients. So, I think we are going to need to clarify what is indeed the final formulation, but cosmetic changes certainly should be included.

DR. BYRN: I guess there would be no way to put in there one say is to define it with SUPAC, another way would be to put a statement in there something like all BE studies that have any bearing on product variability would be reported to the Agency. That is probably too vague, but I am concerned.

Even the innovator may not know the effect of slight changes in the formulation on product variability, because they may have made it the same way all the time, and so we could have a situation where you start changing and adjusting just a little bit, and you get a very variable product, and there is no way to know that unless you report essentially all the experiments that showed how variable it was. Maybe that is not a real problem, but if there was a case like that, it would certainly be of concern, because

you would have a product that was pretty variable out on the market.

So, I don't know how to word it such that you could get--you would like the Agency to be able to review all that data, so that they were aware of it and could make some decision in their deliberation.

DR. CONNER: Some evidence, limited evidence but still good evidence about variability comes through biostudies.

DR. BYRN: Right.

DR. CONNER: Both the history of the innovator, as well as the information that generic sponsors put in on both their own product and the reference listed drug or the brand name. That gives you a lot of sense of total variability. With two-way crossovers, you can't really tease out intra-subject variability too well. That really takes a replicate design or some other type of design to do that.

One of the criteria in effect is based around variability. If you have an extremely variable product or two products, then, it is much more difficult to pass, or much more likely to fail. It requires greater power to determine bioequivalence in that case.

Also, I would like to go back to what Leon said two speakers ago. It is fine. I have heard the industry say this before, well, you know, we have them on file, and

you can just come and ask for them, but again we get back into that catch-22 of how can we ask for them if we don't know they exist.

In my experience, I have never been an inspector, but my experience with inspectors is we generally tell them what to go out and look for, and they look at the things we tell them to, and only in rare cases do they happen to stumble over something, but if they don't know something exists, the chances are they probably won't find it.

This particular study Drug X, you know, based on some discussions with the sponsor of that application, you know, after this all came out is they said, oh, yes, it was in file cabinet somewhere, you know, it was in somebody's office who had left the company. That was where the records were archived. An inspector, unless they were rifling through everyone's file cabinets in the company, would never have found that even by chance probably.

You know, the sponsor, for a variety of reasons, finally submitted it to us based on some requests from foreign regulatory agencies, I believe, and they discovered it again and decided to do the right thing and submit it. That is how we found out about it.

But even some of the people at that company didn't know that that study existed.

DR. BYRN: I think we have a proposal or general

consensus, which you do you want to reword that or just re-summarize it? Go ahead.

DR. LAMBORN: I can give it a try. I guess that I am suggesting that the committee state its support for whatever has to be done by the FDA to ensure that sponsors submit the results of all BE studies performed on the to-be-marketed and the formulation in the form of a complete summary, and that the FDA should do a brief, but careful examination to identify potential problems worthy of requesting additional information.

DR. BYRN: Okay. Any other comments?

[No response.]

DR. BYRN: I think we will just have a show of hands for a vote.

All in favor?

[Show of hands.]

DR. BYRN: Okay. It is unanimous.

I don't think we have anything else to discuss today, so I would like to thank all the members of the committee and the audience for their assistance.

Thank you very much.

[Whereupon, at 3:45 p.m., the meeting adjourned.]

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