sgg

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

OPEN MEETING

Friday, September 24, 1999

8:30 a.m.

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

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

PARTICIPANTS

Stephen R. Byrn, Ph.D., Acting Chairman
Kimberly Littleton Topper, Executive Secretary

Arthur Goldberg, Ph.D.
Robert A. Branch, M.D., F.R.C.P.
Stephen R. Byrn, Ph.D.
Mary J. Berg, Pharm.D.
John Doull, M.D., Ph.D.
Judy P. Boehlert, Ph.D.
Gloria L. Anderson, Ph.D., Consumer Representative
Dr. Anderson, Consultant

FDA

Roger Williams, M.D., Center for Drug Evaluation and Research
Larry Lesko, Ph.D., Office of Clinical Pharmacology and Biopharmaceutics

C O N T E N T S

P R O C E E D I N G S

DR. BYRN: I would like to welcome you to this second day of the Advisory Committee for Pharmaceutical Science meeting. Kimberly Topper will read the conflict of interest statement.

Conflict of Interest

MS. TOPPER: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made 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 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 participants present no potential for the 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 USC 208(b) each participant has been granted a waiver which permits them to participate in today's discussions.

A copy of this waiver statement may be obtained by submitted a written request to the agency's Freedom of

Information Office, Room 12A-30 of the Parklawn Building. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

DR. BYRN: Thank you, Kimberly. Let's introduce the people at the table, the committee members and others, starting with Judy Boehlert.

Introductions

DR. BOEHLERT: Good morning. I am Judy Boehlert and I am a consultant to the pharmaceutical industry.

DR. DOULL: I am John Doull, and I am from University of Kansas Medical Center.

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

DR. GOLDBERG: Good morning. I am Arthur Goldberg. I am a consultant to the pharmaceutical industry.

DR. BRANCH: I am Bob Branch, from the University of Pittsburgh.

DR. ANDERSON: Gloria Anderson, Department of

Chemistry, Morris Brown College, Atlanta, Georgia.

DR. LESKO: I am Larry Lesko, from the Office of Clinical Pharmacology and Biopharmaceutics at FDA.

DR. WILLIAMS: Roger Williams, in the Center for Drug Evaluation and Research at FDA.

DR. BYRN: This morning we are going to begin with clinical pharmacology policy topics, and Roger is going to introduce this section by discussing exposure-response introduction and overview.

Clinical Pharmacology Policy Topics

Exposure-Response Introduction/Overview

DR. WILLIAMS: Well, I will say good morning to the committee and welcome back. It seems like your number has dwindled a bit but I hope it wasn't due to any mishaps.

[Slide]

As I was thinking about how to introduce the topic this morning, I wanted to tie it to the discussion yesterday because I think in some ways they are very closely related and in some ways it is very different.

First of all, I would argue it is closely related in the sense that the discussion topics today, at least certainly the first one on exposure-response relationships, relate to market access. That was certainly a key question in the discussion yesterday, and I think you saw yesterday that because there were elements of increased regulatory

burden you heard from a lot of producers who were worrying about producer risk as opposed to consumer risk.

Now, I will argue today that perhaps the same question will arise in terms of market access but it really relates perhaps to a reverse, in terms of the political time, in the sense that some of the producers will be happy to see a better way of approaching market access in terms of safety and efficacy. I am not sure about that. I never want to predict what producer constituencies out there will say to me, but I think there is an element here of reduction in regulatory burden and a move towards more informative tests as opposed to large late-phase empirical studies that are very expensive and very cumbersome to perform.

There is another difference that I would like to draw the committee's attention to, which is the way this committee works. That is, we don't just bring a topic and get a decision. Frequently, on a topic we bring it time and time again to the committee and get a discussion. That, in my view, is a very healthy process. It is a public process; it is a process that involves transparency. I think yesterday you saw a conclusion of that process in some ways for the topic of individual bioequivalence. That is not to say we won't bring many points of it back to the committee but we certainly got to a branch point that will allow us to proceed.

Now, I would argue for this topic and some of the other topics today, particularly the first one, that it will be a discussion topic that we come back to the committee perhaps again and again before we reach a truly final conclusion. Again, I think that is very healthy, very valuable.

Another difference I would say is, as we begin to talk about this topic, we move away from a topic that is sort of quality and focused entirely in the Office of Pharmaceutical Science in the Center and start directing our attention towards the medical officers in the Center and the 15 drug review divisions. That linkage is a very important linkage. So, I could imagine that in future meetings it will be necessary to involve that constituency, if you will, in the Center more intimately in what we discuss here at this committee. Again, I think that will be very healthy, and positive and rewarding.

Finally, before I go into some of the more detailed information, I hope the committee understands that all of our discussions here, in one way or another, tend to get expressed to the public via guidances, and usually guidances for industry that provide a set of best practices, if you will, on how to meet our statutory and regulatory commitments. Again, I think that is very valuable. I think the clearer the agency can be about what it thinks is

important and how it intends to analyze data, the more valuable, the more helpful we, as an agency, can be working with industry.

[Slide]

So, with those brief words of introduction let me go on and I will show this picture. I don't know if Larry is going to show it as well, but this is a core group of boxes that really reflect -- people always wonder why I like boxes so much, well, it is not just because they are clear and square and colored sometimes, it is more because they reflect the way people work together. What you need to do when you look at these boxes is to think of groups of people who are interacting appropriately and intelligently to solve a problem, a regulatory problem. It helps you figure out what you are talking about, and who should be in the box and who should not be in the box to work on the problem, and how the box needs to link with other boxes. You can imagine, in a huge center with many, many things going on, those linkages are critical.

Larry has headed this box for the last four years, and assisting him has been Shiew-Mei Huang. Down at the bottom you see that they are working on guidances. I would argue that this has been an extraordinary effort, an effort that will have both national and global impact, and I really congratulate Larry and Shiew-Mei and all the people who have

worked with them over the years to focus on these boxes.

Now, there is a logic to these boxes that may not be immediately apparent, but some of them related to intrinsic and extrinsic factors -- renal impairment, hepatic impairment, in vivo metabolism, and drug-drug interactions. If you think about it, those are the intrinsic and extrinsic factors, some but not all of them, that are discussed in the ICH-E5 document. So, you might think of these as the guidances that provide a "how to" set of approaches to assess intrinsic and extrinsic factors.

But over more to the right you start seeing general guidances that speak to more general approaches in the use of exposure-response relationships. And, I think there are two there. One is already finalized, the population PK guidance, and then today, in the morning, Larry will be introducing the exposure-response or PK/PD guidance.

I think over on the right you see a summary document and then also an immediate release to modified release document. Its name may be changing but it is a very important document that I will speak about in a couple of slides.

[Slide]

Let's go on. This is my favorite slide. I move through favorite slides in the course of my tenure at the

agency, and this is my current one. We are now leaving this realm where exposure is created by the drug product and we can either talk about exposure in terms of dose or concentration-response relationship usually. Our discussion today will be in this realm, and this, of course, is a very interesting realm. It includes in the response, the Y axis, endpoints that can either be clinical benefit, surrogate endpoint or biomarkers -- lots going on there. I am delighted to see Greg Downing in the room, who is from NIH, who was instrumental in putting on that conference last year, in April. Then, of course, you get to the Y axis which focuses on dose, optimal dose, therapeutic window.

[Slide]

If you go to this slide, and I am now going to use a slide from Louis which I showed last night. Louis has a slightly different way of looking at this, which he describes in terms of the benefit of a drug in terms of the X axis and Y axis. Then you adjust your exposure based on intrinsic and extrinsic factors. I won't say much more about this, except I certainly encourage Louis to talk about this vision, if you will, in the course of the morning.

Over on the right you will see a whole bunch of guidances that have come out over the last decade regarding this general approach. This isn't even updated. They have been coming out so fast it is hard to keep it updated. But

there have been some very seminal documents and thinking that the agency has worked on over the last decade. I don't have to tell you that Carl, whom I am delighted to see in the audience, was a seminal thinker in this regard and particularly I always point back, and many of us do, to that 1991 conference on PK/PD that was one of the most successful conferences that AAPS ever put on. I think we are the spiritual heirs of that conference, and we continue to evolve the thinking in this regard in very important ways, both for the American consumer, the industry, pioneer industry and internal agency constituencies.

It is going to be a powerful set of documents when it is completed, and a powerful set of conceptual documents. I urge you to pay attention to what is going on over here because I think we are working it out. I see the end of the story coming, and that is not to say there is not a lot more work to do but a lot of times when you get the conceptual understanding work done, that really is the end of the story and then it is just putting the pieces of the puzzle in place.

[Slide]

I want to come back again to a Louisonian vision, and I will always acknowledge Louis as being very powerful in helping us think at the agency about some of these things. The Y axis is the response. The dose regimen is the

X axis, and the Z is you adjust the dose regimen based on intrinsic and extrinsic factors. I may not be saying it quite right. I am sure Louis can say it better; I know he can say it faster --

[Laughter]

-- anyway, I think it is a very powerful theme for us to work with. Now, this is the theme that is the debatable theme, the hot topic -- you know, when can we rely on surrogates? When can we rely on PK/PD models, etc., etc.? You are going to hear that in the course of the morning.

I am actually also very interested in this theme, and I want to come back to it at the end of my talk. Of course, this is a very powerful theme that talks about adjusting the dose based on a subpopulation factor. I think, in some ways, that theme relates closely to subject by the formulation interaction topic that we talked about yesterday.

I will say this, you all know that FDAMA Section 115 intruded the thought of confirmatory evidence to allow market access so that you could use one adequate and well-controlled study instead of more than one. You recall that the statute used the word in plural, "studies," when it said adequate and well-controlled studies and that was always interpreted to mean two or more.

This additional word allowed the possibility of

one. If you talk to Bob Temple, he would have said, "well, we always could do that, anyway, and have done it." But I think it put in a statutory framework a very clear mandate to the agency to allow market access using one adequate and well-controlled, confirmatory, empirical study plus perhaps additional information.

I have to confess, right now we have a problem with nomenclature. Confirmatory is the wrong word, and I say that maybe with my congressional masters breathing down my neck. And, I think we have to do a slight translation in terms of what we think the Congress meant, and a word emerged last night that we are using, "supportive." We will see how long that word lasts. I sort of like it but nomenclature is always evolving.

Now, in closing, I just want to say that somehow what we are going to talk about in the course of this morning is this, and it is going to be exciting and it is going to be challenging but we are moving from two or more to one, and I would even argue that there is the concept of none.

Now, in saying none, I want to come back to the X axis because a lot of times I think the X axis challenge can allow none if you have a good understanding of PK/PD responses. When I say none I am talking here about line extensions or new routes of administration. That is a very

powerful thing for industry to be able to have market access with no clinical trials if you have a good understanding of PK/PD. Of course, we have done that in the past. So, I think this is an interesting area focus, and if I want to be slightly provocative, if you want to go to a line extension and you just want to reiterate people, that is a prescribability question. But if you want to switch people from an immediate release, say, to a modified release, I might say that that is a switching question.

Now, with that provocative statement, which you can ponder as to just what the heck is Roger saying here, I will leave you for further discussion and turn it over to Larry.

DR. BYRN: Questions of clarification for Roger?

[No response]

Larry is going to go ahead now and present an overview of the purpose and goal.

Purpose/Goal

DR. LESKO: Good morning, everybody. Thanks, Steve.

[Slide]

Unlike yesterday, this morning we are not bringing specific issues to the committee for deliberation or for voting. The purpose of this morning is to bring before the committee really for the first time our current thinking on

the topic of exposure response.

As Roger mentioned, the idea here is to share some information today with the committee, lay some groundwork for probably future discussions with the committee on perhaps more specific issues but, beyond that, the purpose today is to get your general impressions of the document that we included in your background, which is this red book, and I think it is Tab A, and get general impressions of the document. Can you imagine it being of value to the industry and to the regulatory authorities? As you think about the document, are there things that are poorly stated? Unclear? Are there omissions? Or, are there things that you feel are positive about what we are trying to do?

[Slide]

What we are talking about today is exposure response, Pk/PD, and this represents a general model for our discussion. It is general and it is relatively simplistic but I think it gives a concept of where we are coming from today.

We are talking about PK/PD and in the input-output relationship of therapeutics the PK process is over here. To the left we have the input. We can refer to it as exposure to a drug or the dose of a drug. This is a broad sort of term. The drug, after it gets into systemic circulation, interacts with the receptor and that elicits a

pharmacodynamic effect. That effect, in turn, could be related to the therapeutic effect, perhaps some safety effects, adverse effects, ultimately to the clinical outcome, therapeutic response or output of the drug.

So, we are focusing on the PK/PD part of this model of drug action or, in broad terms, the exposure-response relationship.

[Slide]

Roger sort of alluded to a little bit of a history, and I think it is important as it relates to this background document. The document, in many ways, coalesces a lot of effort that has gone into conceptually framing PK/PD.

These are some of the FDA co-sponsored conferences over the years, and you can see there are many organizations that we have worked with over the years -- AAPS, ASCPT, ACCP and so on. This was that Arlington conference in 1991 that really began a public discussion of the topic. There was a second conference that was similar in 1998, here in the Washington area. Then most recently, in 1999, in April, the NIH put on a program related to a specific part of PK/PD, the biomarker and surrogate endpoint aspects of it. It is these types of meetings that have funneled into what I think is reflected in that background document.

[Slide]

The common theme of all of these meetings --

particularly from an industry standpoint, the number of new chemical entities with potential importance is increasing exponentially. I think everyone attributes that to the advances in technology that have occurred over the last five years or so.

There is also a sense from these meetings that there is a need to demonstrate efficacy and safety and acceptable risk benefit, and that is a challenge in this day and age, and people are concerned about the time, cost, and not only that but the value of the information that comes out of the process, both for drug development and for regulatory decision making.

Then, finally, there is a hypothesis and advancement that certain aspects of clinical pharmacology, particularly PK/PD, can perhaps accelerate the drug development process and provide more informative information and greater insights into the input-output relationship.

[Slide]

Along with the coalescing of thinking over the last ten years or so through the public workshops and symposia, regulatory authorities have been active in the area with various guidances -- several guidances that are out there under the International Conference for Harmonization. They provide general perspectives on dose response or concentration response. They are key documents

in the evolution of our backgrounder. The first is the so-called ICH-E4 document. That was in your background package, and also the E5 document, Ethnic Factors in the Acceptability of Foreign Data, that positioned PK/PD data as a way to bridge efficacy from one region of the world to another.

[Slide]

From the FDA standpoint, there are two guidances that relate to our topic today. The first is a key guidance, providing clinical evidence of effectiveness for drug and biological products. This guidance has many references to the value of PK/PD, and points out many opportunities for firms to advance regulatory decision-making by using PK/PD in terms of alternatives to repeating the efficacy trials that may have been conducted.

I put the population PK/PD guidance up here because it sent into a lot of the current thinking that we had on modeling in general and in simulation. I think it is a companion document to the backgrounder that we distributed.

[Slide]

More recently, in the last year or two, we have had some FDA guidances that have made specific statements about the application of PK/PD. For example, in the impaired renal function guidance we talk about the use of PK/PD to

set boundaries for therapeutic equivalence so that that can facilitate a label statement on the need to adjust the dose or not adjust the dose based on the knowledge of exposure response.

We have done the same thing in the in vivo metabolism drug interaction studies, again alluding to the possibility of using PK/PD to impact label statements following approval of that product.

[Slide]

Some of the drivers for this backgrounder, and also for the evidence of effectiveness guidance that I previously mentioned, from May, 1998, were the requirements of the FDA Modernization Act of 1997, specifically Section 115(a) which amended 505(b) of the FDA&C Act. The key of this was that the agency may consider data from adequate and well-controlled clinical investigations and confirmatory evidence to constitute evidence of effectiveness. This particular guidance laid out the circumstances under which a single efficacy trial may be acceptable. It also mentioned the fact that these conditions include the use of multiple endpoints, involving different events within a single Phase III study.

[Slide]

Further legal and regulatory developments have facilitated the advancement of exposure response. In the

accelerated approval regulations we have a mechanism to approve the antiretroviral drugs using, in essence, a surrogate marker. And, the conditions under application of surrogate marker in this case is the great therapeutic need, the prior knowledge of the disease, physiology, mechanism of action, and a biomarker that is considered reasonably likely to predict clinical benefit.

In a more recent guidance related to accelerated approval of antiretroviral drugs, August, 1999, one of the study design options for gaining market access is a dose comparison study that includes treatments design to show an exposure-response slope. So, I think you can see the advancement, if you will, of exposure-response concepts within the regulatory decision process.

[Slide]

Similarly, there have been advancements in the area of pediatrics, and the regulations and the guidances that are out there, particularly the efficacy guidance, has indicated when pediatric approvals and pediatric labeling can be granted when we have a similar course of disease and effects of drug in pediatrics to adults. There are some conditions listed here when that is concluded.

The key point here in the pediatric use is the similar exposure-response relationship. What that leads to is the utility of PK and/or PK/PD bridging studies without

repeating the adequate and well-controlled clinical efficacy trials in that pediatric population. So, again, this represents an advancement in the use of this information.

[Slide]

Finally, in the efficacy guidance there are a number of sections that deal with market access based on the so-called bridging studies. The bridging study refers to the use of PK and PK/PD studies. The requirement or the condition for this to occur is when one has an understanding of exposure response, and a few examples are listed here. Some key examples are when we are looking to approve a modified release dosage form from a previously approved IR dosage form, or when there is an approval of a new dose or dosing regimen. Those are two examples of where PK and PK/PD come into play. Again, it is being used as a substitute for the traditional adequate and well-controlled clinical efficacy studies.

[Slide]

As you can see, the groundwork was laid with some prior activities for the application of PK/PD. We were interested in elaborating on that progress that had been made so far, with the possibility of developing a guidance on PK/PD that would delve into more specific information regarding its use, regarding its application and, in some ways, coalescing what we currently know to be the best

practices in both study design, modeling and interpretation of data.

It was with that motivation that we formed a working group in 1998 under our Medical Policy Coordinating Committee, and we started out with two co-chairs, Terry Blaschke who was on sabbatical at FDA, and Raymond Miller from OCPB. Terry finished up his term at FDA. Raymond has actually left FDA to go to industry. So, we have been continuing this effort with myself, Peter Lee from our office, and Roger from OPS.

As the committee realizes, we have a good guidance practice process to develop guidances, and we started this process with a public workshop. It was an FDA-PhRMA workshop in June of 1998, and we also had at that time our first expert panel meeting.

What we focused on in that workshop are best practices in PK/PD, the use of surrogates, the application in regulatory decision-making and in drug development.

[Slide]

This slide shows the members of the PK/PD working group, many of whom participated in that first expert panel meeting and PhRMA workshop. I would mention that the members of the working group here, and I apologize if I have missed anybody -- many of these are from the Office of Clinical Pharmacology and Biopharmaceutics. We also have

representation from the medical side of the Center, Office of Generic Drugs, Biostatistics, and Center for Biologics. So, it is really cross-Center, interdisciplinary.

[Slide]

One of the first things the working group did and presented at that PhRMA workshop was the current situation with PK/PD in our applications. What we did was survey section 6 of NDAs for the time period of '95, '96, '97 to get a status report on the frequency with which PK/PD is being used as part of submissions. This is the data from that survey.

There were roughly 316 NDAs or supplemental NDAs in the database, and a number of those applications with PK/PD respectively were 24 in '95, 12 in '96 and 32 in '97. You can see the percentage of applications that contain this type of information.

We did this survey to really get a benchmark to compare future trends in the application of this information, both in drug development and in submissions, and it is hard to say what this means in an absolute way but our intent is to continue looking at this information to see if there is a trend upwards as the science, both of modeling and biomarkers, evolves.

[Slide]

When we do have these applications with PK/PD,

most of them will contain one study per NDA. A few contain more than that but, by and large, we are limited to one or two studies.

[Slide]

Getting back to the consensus of that first FDA PhRMA workshop which began really channeling into our thinking on this backgrounder, the recommendations were to communicate very clearly the regulatory receptiveness for this type of information so that an argument could be made for its inclusion in drug development, not only for decisions made by the sponsor but also some value downstream when it comes into the agency.

There was expression of concern about the definitions and nomenclature, and the NIH conference in April went a long ways to sorting that out. There was a request to include examples and use of PK/PD in regulatory decisions to the extent possible in the backgrounder; to expand upon the ICH guidances, fill in the gaps where information was not there or was unclear; to stress the importance of the careful selection of the PD measure and parameter to make it useful in terms of decision-making; stress the main features of the model building process; discuss the current thinking on the extent of validation of models; and, finally, what are the submission requirements and format for PK/PD studies into the NDAs. So, these were

the recommendations then of that first workshop that we conducted in 1998.

[Slide]

A third expert panel occurred last night. After I am finished Don will report on the proceedings of last night's expert panel. I wanted to share with you here the members of the expert panel from academia, industry and, of course, we had a number of people from FDA present as well. So, I will hold off on that and let Don talk about last night's meeting.

[Slide]

As I mentioned, the PhRMA-FDA workshop was our first step into the public discussion area. Last September, in 1998, when we had a workshop on clinical pharmacology we also, in association with that workshop, had our second expert panel meeting. The members were similar to those on the panel that we had last night. However, three members of that second panel, Jaap Mandema, Terry and Steve, were not present last evening.

[Slide]

That second panel meeting last September advanced these ideas which, again, are building blocks for this backgrounder in our package today. The recommendation was to broaden the concept of PK/PD and PK/PD links, that is, to think of it conceptually in terms of input and output, where

input is the exposure measures, parameters of the pharmacokinetics and output is the response measures, parameters and pharmacodynamics. There was renewed emphasis on the need for careful definitions and nomenclature, recognizing that cross-disciplinary communication is important in this area of PK/PD, and again the emphasis on use and examples and value came out of that second meeting.

[Slide]

We had a lot of discussion in that second meeting on study design considerations, discussing it in terms of exploratory and confirmatory studies. There was a lot of deference to the ICH-E4 and FDA evidence guidances in terms of potential study design considerations. We talked about data analysis methods, models, assumptions, validation, simulation and inferences. This panel sort of concluded that we don't have any major technical hurdles out there if conceptually we can agree on how to structure the study design, the data analysis and then the interpretation.

[Slide]

A key part of that second expert panel was a delineation of potential regulatory applications of PK/PD, and we talked about implications in two areas. The first was labeling and supporting approval; the other was supporting market access. Some of the examples that were evidence in that meeting and also in our backgrounder now is the ability

to extrapolate from an existing database that has demonstrated evidence of efficacy and that extrapolation, with the appropriate PK/PD bridge, can be in the approval of modified release dosage forms, different doses, dosing regimens, formulations, etc. There was also discussion of interpolation of data within the range of doses studied in the efficacy database to allow more individualization of doses for special populations and to allow approval of doses that were not formally studied within the Phase III efficacy studies.

Finally, an important application was in the area of special populations when we see a change in exposure with regard to demographic factors, intrinsic factors such as disease states, or extrinsic factors like drug-drug interactions, PK/PD can allow for appropriate label languages that relate to the dose adjustment in those circumstances.

Now, sort of raising the bar a little bit, we talked about market access and some of the precedents that have used the non-model dose-response data for market access. Then we moved into a discussion of new uses of model-based PK/PD to bring more certainty to confirmatory trials and play a pivotal role perhaps in that context of confirmatory evidence.

[Slide]

Well, that is the history that brought us to where we are today. And, when you think of that background document in the package, think of it in terms of the building blocks that preceded it. I am going to go briefly into the proposed guidance, as I call it, speaking about the backgrounder in Tab A.

[Slide]

Where we are currently at in that document is we have included an introduction and background. The purpose of the introduction and background is to really lay out the purpose and goals of the guidance. We want it to be useful to the industry. We want it to be useful to the regulatory authorities when they are making regulatory decisions using this information. So, the key goal here is value. We need to have value and credibility in this proposed guidance.

We also go back, as we do many times, to the regulatory authority to utilize this information for regulatory decision-making, and you will see in there some references to the CFR that provide a basis for applying PK/PD information. We have also tried to link to the preexisting guidances at the ICH and domestic levels and build upon some of those statements in those guidances, perhaps elaborating upon them some more, providing some details that may have been omitted for various reasons, and we are looking a little bit ahead to another ICH guidance,

called the common technical document. The common technical document is something that is being proposed as a submission vehicle for the three major regions of the world. In that common technical document there are certain sections of it that deal with PK/PD, and we envision some connection between this backgrounder and eventually what comes out of ICH perhaps in a year or two in terms of this common technical document.

[Slide]

The next part of that backgrounder gets into the input/output measures. We are speaking very broadly now. We get into a discussion of the dose and concentration time relationships and the need to carefully select those input measures versus the intended use of the information when the study is done. I think this is an important point.

We get into the response and response time relationships, again emphasizing the careful selection of the output measures and the various ways that those output measures can be obtained.

Finally, in this section we get into linking PK and PD and we amplify the use of PK/PD information and the value that a pharmacokinetic-dynamic model can provide.

[Slide]

A key part of that backgrounder is the design of PK/PD studies, and one of the points we raise here, which

hasn't really been discussed too much in previous guidances in this area, is the notion of population versus individual exposure-response relationships. The currently designed Phase III trials generally are population type studies, parallel design, single doses or limited number of doses which provides at the end of the day an expression of a population exposure-response curve. If we are thinking PK/PD in more mechanistic terms, and even to the extent of applying mechanistic models, one would find a lot of value in individual PK/PD relationships, and we provide some thoughts on that within the guidance for readers to think about.

When we talk about measuring exposure from a pharmacokinetic standpoint we put in a lot of the caveats that need to be thought about in terms of getting to the right active species. We also talk about time variant and time independent measures of exposure both in terms of single dose and steady state.

[Slide]

We elaborate a little bit on the sponsor in the backgrounder, talking about general terminology, what we means by these terms. I think this is going to be subject to change based on the NIH consensus document that will be published shortly. We would like to harmonize with the definitions that are coming out of the NIH paper. Then we

talk about some specific measures, and go through a series of response type measures -- continuous challenge, etc., and so on.

[Slide]

The next section is the whole concept of modeling. We provide a couple of general considerations -- the importance of a model in providing a mechanistic understand of exposure response; some of the characteristics of modeling that allows for interpolation and extrapolation; and some of the things to be thinking about if the model is going to be intended to be used for simulation. So, this is the sort of characteristics of a model for its future application.

A key part of this section is the modeling strategy and a prospective thought of stating the problem accurately -- what do we want to know; very careful statement of the assumptions that are built into the model; selection of the model based on the data and the analysis; and then, finally, something we call the validation of the model for the purposes of prediction and simulation.

[Slide]

Finally, section VI gets into what is really the heart of this guidance from a regulatory decision standpoint. It lays out for the reader the opportunities to apply this information for certain regulatory decisions, and

I think this is a very key part of the guidance. There is a short section on drug discovery and development and the role of PK/PD there. We don't elaborate on that. I think it is self-evident to industry where it has a role.

I think what we tried to do is pay a lot of attention to where PK/PD comes into play in regulatory decision-making, and one of the primary roles is in the determination of safety and efficacy. Exposure response's position is playing a supportive role in this sense, for example, when lesser certainty is appropriate based on prior knowledge; when confirmatory trials are equivocal or ambiguous; or perhaps when extrapolating to new patient populations or populations with closely related diseases. PK/PD in these situations can play a pivotal role.

[Slide]

Some of the areas where lesser certainty is appropriate or PK/PD can play a bigger role are when we have a good understanding of pathophysiology and the mechanism of action; we have a surrogate endpoint that is an established substitute for some clinical outcome. An example of that is the accelerated approval regulations.

[Slide]

Other examples -- when confirmatory trials are equivocal these are the possible situations that one would encounter where PK/PD comes into play as supporting the

weight of evidence to make a final regulatory decision; and, finally, when extrapolating to the new patient populations which I previously mentioned.

[Slide]

Beyond market access there are some other decisions that PK/PD can play a role in. It can support doses and dosing regimens. These are some of the examples of where exposure-response data is supportive and some of the decisions that could be made using that information in terms of the various areas listed here.

[Slide]

A key part of this guidance is the regulatory application we think of in terms of adjustment of dose and dosing regimen in subpopulations. I think this is an important area because one of the decisions we make is the label language for the dosing section of the label, and this information can be used to establish boundaries for therapeutic equivalence and provides a rational basis for label claims. The label claim may take the form of no adjustment is necessary in a drug-drug interaction or no adjustment is necessary for a patient with renal impairment. So, this application I think is an important application to deal with exposure changes related to intrinsic and extrinsic patient factors.

[Slide]

Finally, the backgrounder touches upon submission information. Again, this is important from the standpoint of reviewing information to have a consistent format. It is important in terms of analysis of data in terms of addressing certain questions, and we would like to be able to have a consistent electronic study report.

What we have chosen to use for this backgrounder is a model that has been developed under ICH. It is an E3 model for study reports. We are thinking ahead to the harmonization via the common technical document. So we will be looking to suggest electronic format files in this sequence of information, which really relates in a lot of ways to the model building process, to the study design data analysis issues, and finally the proposed application.

[Slide]

Now these next steps I put on the slide were part of the initial strategy for this initiative. I think it is overly ambitious. We currently are having this backgrounder reviewed by the Office, representing it here today for some general comments. The next step during the month of October is to present it to the members of the Medical Policy Coordinating Committee which is made up primarily of representation from our Office of Review Management. We are also going to present it widely in the Center to division directors at a meeting coming up in October as well.

This is part of the time that I think is very aggressive, and I think our concern here is that we want to make sure that we are patient with this initiative. It is an important capstone, if you will, to all of the clinical pharmacology work plan that Roger laid out in that early slide, and I don't want to be held necessarily to these time lines. I think it is important that we have the appropriate discussions. Last night, with some of the issues raised by the expert panel, I think we need to focus on addressing certain of those issues as well. Also today, when we hear from the advisory committee, we are going to have to take that into account. So, these are very tentative.

I think I am going to pause at this point. I have more slides in that handout but I think it is more important to move on with some discussion.

DR. BYRN: Any questions for clarification for Larry?

[No response]

Then we are going to go ahead and Don Stanski is going to summarize the expert panel perspectives.

Expert Panel Perspectives

DR. STANSKI: Thank you very much.

[Slide]

I first want to recognize the work that Larry Lesko and Peter Lee have put in to pull together the expert

panel. They have worked late and long to be able to both make this presentation and get us together. And, also my colleagues, some of who came on very short notice. The actual list of who was involved in these discussions is somewhat different. In addition to some of the names indicated in your handout, Les Benet, Lou Sheiner was also present last night, Bill Lebling, Marl Sale and Sandy Allerheilegen were also part of the deliberations.

We finished at ten o'clock last night, and by six in the morning we got some slides to show you and some overheads. So, I want to share some of the thinking of the group. I also want to recognize that many of the thoughts and ideas will take a period of time to both formalize with Larry and Peter in the Center, and to then go ahead an appropriately integrate into this document. Some of what I am going to show you may not get in this current version. There were a lot of ideas, a lot of comments, and the time frame of this document may not allow all of it to become integrated in this first pass.

[Slide]

One very early comment that the group made had to do with the nomenclature. The term exposure response is new. It is a term that Lou Sheiner has coined in some of his publications, but it is a term that I think the industry may be less familiar with, certainly people outside of this

scientific discipline. We think that it is a better terminology than necessarily PK/PD. It is more encompassing in terms of including both dose, and blood level, and other metrics of what the body sees, and response is more appropriate also relative to dynamics. But we are going to have to carefully educate this new terminology to the community.

The issue of validation, evaluation, qualification and calibration was a very sensitive one, and we will see a little later on, when we talk about the various surrogate markers versus biomarkers, that the issue of validation is very loaded. It has a lot of intense meaning, and it may be necessary to use some other softening terms even as Roger did, something that gives you a little more band width in terms of what actually is being demonstrated.

These discussions may have to be integrated with other components of the agency, and certainly the clinical and the biostatistics communities.

[Slide]

What became clear last night as we discussed issues is as PK/PD becomes more ingrained in drug development it has significant implications on study design issues. In other words, in the past there has been a tendency to try to take traditionally designed trials, measure blood levels and retrospectively extract some sort

of PK/PD relationship when things didn't go right, or when you had an extra person to do it. It is kind of the data dredging retrospective approach which has worked and has been helpful, but much of what we are talking about in the future, and what we talked about last night, involves prospectively designing these studies, certainly for the supporting efficacy, in essence creating a whole new paradigm of studies that are based upon PK/PD relationships and the definition of which you are going to do before you do it, not after.

I think Carl Peck may want to speak to this later on because this is something that is important and sensitive to him. So, it means that we may be looking at a different kind of Phase III trial in the future, one that is going to involve model-based parametric approaches to the data analysis that will be different from the traditional intent-to-treat and one that will basically explicitly state what the modeling and simulation is going to do before the data is actually gathered.

This, again, has a lot of implications for drug development, and some of this will be in the guideline but probably not all. It will take a longer period of time to evolve what we mean by this.

[Slide]

A lot of discussion on surrogate versus

biomarkers, a recognition that the industry, in fact, is probably one of the unique collection points of gathering this data as drug development proceeds; a recognition that Greg Downing and his NIH efforts are really very fundamentally important here; and that basically this document is going to borrow from the NIH efforts in surrogate and biomarkers and will be consistent with what they do; and that basically we are going to enhance the description of biomarkers versus surrogate markers, the linkage of these in several ways in the document.

The issue of what is the industry responsibility for gathering this body of knowledge probably won't necessarily be in the document but, clearly, is a discussion point. In other words, if this information is being gathered it needs to be used. Basically, society needs to understand the ability to use the linkage of the ultimate clinical endpoints to surrogates and biomarkers, and this needs to be part of drug development in the future.

[Slide]

The modeling, again, had a lot of discussion. We had a group of dedicated, hard-core modelers in the room, realizing basically that skill base of modeling and data analysis is highly variable both in companies and in the academic world.

One important point came up, and this had to do

with the development of good modeling and simulation practices. Already there is a draft document that Carl Peck and the CDDS has developed, which will become an important starting point of how to think of modeling and simulation, and the degrees in which this predescribed methodology will become, again, referenced and leveraged in this draft document was something that, again, will be considered.

Again, another very important principle, prospective data analysis plans in model development, and very clear descriptions of what kind of model do I have? Is it empirical? Is it mechanistic? Time factors and both the strengths and the weaknesses of models need to be indicated if these tools are being used as we are proposing.

So, we can see that there is going to be much more quantitative thinking and objectivity in the issue of models in the future than what we have had in the past, and maybe Louis can speak to that a little later on.

[Slide]

Some technical issues which we struggled with but, again, couldn't resolve last night are how do you evaluate a model? What became clear is that model evaluation can be very dependent upon the specific application one has. The ability to evaluate dose blood level and bioequivalence models isn't the same with dynamics because of the highly variable degree in which the drug effect, either biomarker,

surrogate or true clinical effect, relates to the available model. So, we are going to have to think carefully of how different kinds of models get evaluated, and issues such as prediction error versus the measure to be predicted will need to be evolved. Again, I don't expect this to be highly described in the current document but represent future thinking.

[Slide]

The confirmatory evidence and the role of PK/PD modeling is going to be emphasized much more in the document when it is released compared to what we have now. Carl Peck pointed out in our meeting that the reference to the Food and Drug Administration Modernization, as Roger alluded to, is very clear from Congress, the need for stronger discussions, more mention of the fact that this is fundamental in pediatric, and potential confirmatory for new formulations. So, the document will have a strengthened section on the confirmatory role of PK/PD information in basically market opportunity.

[Slide]

In terms of where do we see all of this going, basically we are going to clearly try to spend more time on the role and integration of kinetic and dynamic modeling in study design methodology. We mentioned that earlier, specifically in Phase II/Phase III methodologies. The whole

issue of evaluating models and the methodologies to do that need to be better defined and evolved.

In the document we are going to try to give as many real-life examples as possible of where the agency has used PK/PD information in its decision-making because the examples become a good reference point of what might be done in the future. Then, again, a clarification of the role of what is a confirmatory evidence when using PK and PD information.

[Slide]

So, finally, we felt at the end of the evening that there is a lot of value in using PK/PD information in regulatory applications. This value really starts in the whole drug development and, in fact, is an integral component of it. The value will be evident in terms of market access, the ability to use it to access markets in ways that we haven't before. Basically, we will be developing potentially in the future guidances on study design, model building, and regulatory applications.

So, I think that we ended the evening tired, kind of exhausted but, at the same time, looking forward to the ability of this quantitative clinical pharmacology quantitative science being much more a part of both drug development and regulatory approval. Thank you.

DR. BYRN: Questions for Dr. Stanski? I might ask

my colleagues on the expert panel if they have any specific thoughts that they would like to raise. This may be a good time because some of them have been seminal in this thinking. Carl? Lou?

Why don't we just make these presentations part of the open public hearing since no one submitted their name. If you will just come to the microphone and identify yourselves, and maybe we will go for five minutes. Is five minutes enough time? No more than five minutes per person.

Open Public Hearing

DR. PECK: Thank you. My name is Carl Peck. I am from Georgetown University at the Center for Drug Development Science.

First of all, I want to commend Roger, and Larry, and Peter and their colleagues at FDA for what I think is a very bold advance of the application of this maturing technology in the realm of regulatory and drug development science. I certainly want to encourage them to bring this particular document to full publication so that it can be utilized in these areas.

I also want to commend you, Don and Peter, for spending your night up after coming in from the West Coast yesterday. You captured actually every single one of my inputs from last night so I have nothing new, but I do want to emphasize the two pieces that you assigned me.

The document is weak at the moment in the area of design of experiments to gather PK/PD, and the exposure-response relationship. As you point out, the typical practice in the past has been to extract this information retrospectively from studies that were designed for a different purpose. I think therein lies one of the major sources of lack of perhaps serious respect for this information that statisticians and other scientists have in that it is a retrospective approach. So, in the spirit of good science, we know that to optimize the value of an experiment we design in advance prospectively what we want to get out of it, and create the design to match that. So, the use of titration designs, dose or concentration control designs that specifically seek to establish the concentration effect relationship is, I think, key to minimize the bias.

Inherent in that is a prospective plan. This was very eloquently argued by Lou Sheiner last night, that a prospective plan with announcement of the goals of the experiment and the analytic tools that will be used is really key to the valid extraction of the data and to the respect that this information will gather from it. Thank you.

DR. BYRN: Any other of my colleagues who would like to have a word? Louis? You have never been speechless!

He is being modest today! Okay, thank you very much. As I said, we haven't had any request to speak. Are there any people who would like to speak in the open public hearing?

[No response]

Then let's move ahead to the committee discussion. Larry, do you want to restate what you said that your goal is?

Committee Discussion

DR. LESKO: Yes, the goal here with the discussion is to get from the committee members any general observations they have of that backgrounder with respect to its utility in drug development and its application to regulatory decision-making. More specifically, after looking at it, are there elements that are missing, or are there some issues that ought to be discussed in more detail? Are there some things that are just unclear? So, I think we are looking for really a sort f qualitative view of that document and any comments along those lines.

DR. BYRN: So, does the committee want to go through the backgrounder, or do you want to just discuss issues that are on your mind? Okay, we are going to discuss issues on our minds. So, the floor is open. Robert?

DR. BRANCH: I would like to compliment the development of this idea. I think this is one of the most exciting innovations that has come along in a long time

because I think that it is really providing a basis for industry to change certain amount of its strategy in terms of drug development. I think it really addresses the issue of the current major strategy of trying to develop drugs where one size fits all, and move to the realities of life of individualization, and provides a powerful incentive to do so because of the ability to use confirmatory evidence of a well-designed study.

I think that the particular potential benefit of note in this, what I think the expert panel pointed out last night, is the incentive now to develop trials that are designed to use this approach intelligently. So, it will actually change the structure and style of the confirmatory studies. I agree with Roger that confirmatory is a very poor adjective for what is a much more exciting potential, and some change in that language would really benefit the discipline.

I would also like to congratulate the expert panel on this move to move away from PK/PD, which is jargon, to exposure response, which is English. It also happens that ER is shorter than PK/PD in people's language, and it will be interesting to see how long that transition takes. But I think that we have really done ourselves a disservice by using PK/PD, and I propose to actively promote this idea of going to exposure response.

I think this is one of the more exciting presentations and initiatives that I have had the pleasure to listen to. I have one question, and I am sure it was discussed at the NIH conference, but I think it will become the major issue in terms of regulation, and that is, how do you define a biomarker as contrasted to a surrogate marker? It seems to me the key definition of the surrogate is that the surrogate actually has meaning with response to your final desired therapeutic effect. So, how you graduate a measure from one echelon to the next I suspect will become a major issue in drug development, and I would be interested to know what the expert panel thought about that particular issue.

DR. BYRN: Don, do you want to answer that, or select one of your committee?

DR. STANSKI: Greg Downing, from NIH, do you want to respond to that? Greg organized a major, almost international committee on this topic, and I think was representing this area last night.

DR. DOWNING: I am Greg Downing, from the Office of Science Policy in the Director's Office at NIH. We have quite a number of activities related to biomarkers and surrogate endpoints and definitions, held by a number of advisory groups to Dr. Harold Varmus on this issue to be helpful in clarifying the discussions that go on regarding

the approval of medications and therapeutic interventions, but also developing the scientific framework from which decisions are made, and recognizing that the discussions involving biomarkers and surrogate endpoints expand far beyond the regulatory approval processes and also have other areas of importance in decision-making on basically clinical perspectives.

I have an overhead that I guess would be all right to present. This group met almost 15 months ago and has gone through a number of drafts addressing definitions that have been used historically, and found that there is a wide range of terms that have been used by different disciplines, such as intermediate endpoints and biomarkers and surrogate markers, and so forth.

[Slide]

This is a rough schema of what we have come up with and, again, represents discussions from biostatisticians, drug developers, regulators and a variety of people, and we hope that this will be a publication relatively soon.

First of all, the emphasis on the term surrogate has been somewhat tarnished in the literature and we emphasize that the word surrogate is really intended to mean substitute for something. The group felt it is important to indicate what that substitution is representing. As was

pointed out, the confusion about surrogate markers is somewhat challenging, and the group actually discourages the use of this term, and prefers to use biomarkers as those things that represent a variety of things that can be measured to represent pathophysiologic, pharmacologic, physiologic events. I won't put the definitions up for these today, but there will be discrete definitions that will fit these terms.

The group also distinguishes that there are markers that can represent both efficacy of an intervention as well as toxicity or adverse events that are unintended from the intervention.

A subset of what we refer to as biomarkers, and these are anything that can be measured discretely in human response, meant to include a wide variety of measurable variables including behavioral and other kinds of assessments of how interventions affect the human.

A subset of biomarkers may have the potential to reach the status as a surrogate endpoint, and the evidence to accrue that has to be linked in some capacity to clinical endpoints in the long run. So, this is really a critical step as to what kinds of evidence needs to be accrued to reach this status. Based upon the evidence gained from establishing a surrogate endpoint, both from efficacy and toxicity aspects, can be the basis for a regulatory decision

or provisional evaluation of efficacy and toxicity.

Based on continued accrual of evidence, as we have seen in many other cases of surrogate endpoints used, that we continue to assess what is referred to as a benefit to risk ratio. This is by continued observations in the literature, meta-analyses, a variety of approaches in which ultimately clinical endpoints of toxicity and efficacy are integrated so that we ultimately have some discussion about what the true benefit of the surrogate endpoint is in assessing the clinical outcomes of disease.

The paper will describe some of these processes and provide some expamples of biomarkers that have reached the status of surrogate endpoint, but the committee overall felt that the term surrogate marker was really somewhat awkward and that the word surrogate means to substitute for and, in this case using the word surrogate marker indicates that you are substituting for a marker, which is actually opposite of what people actually intend.

So, in sum, there is a large group of things that are biomarkers for many, many diseases. Some of these have the potential to represent surrogate endpoints.

I will be happy to try and clarify any other issues at this point.

DR. BYRN: Greg, I have a question related to -- I was thinking of the term validation is what you are calling

continuing assessment of benefit to risk ratio. How does benefit to risk ratio and validation come into this are?

DR. DOWNING: The group feels that the term validation in itself reflects primarily a statistical connotation. Overall sentiments, if you will, are that the term evaluation represents not only statistical relationship of the marker to a clinical outcome when affected by an intervention, but also includes factors of biological plausibility and other kinds of supportive evidence, not just a statistical relationship between a correlation, if you will, of the marker's response to an intervention and the ultimate outcome.

So, the evaluation is a term that they would like to use as the overall process. Certainly, the statistical validation is an important component of that. Those are sort of the terms that the group has felt to be more meaningful.

DR. BYRN: And then, does the benefit to risk ratio -- what does that represent?

DR. DOWNING: We have struggled with this a lot, and alternate terms have been used here. It is basically a global assessment of how interventions affect a particular surrogate endpoint. Often what this refers to is how a particular marker behaves over a variety of classes that will affect the clinical outcome. I hesitate to utilize this one but, as an example, cholesterol has been recognized as a

surrogate endpoint for a number of different types of interventions. But that particular marker as a surrogate endpoint behaves differently under different classes of therapies. This is a process that goes on throughout the medical literature, consensus conferences, a variety of other approaches in which bodies of science come together to evaluation a mass of data, either through meta-analyses or other kinds of processes to ultimately try to understand how that surrogate endpoint plays through the whole realm of therapeutic interventions in that particular class of therapies.

DR. BRANCH: Is there any prospective planning to maintain the NIH-FDA cross-communication so that when it comes down to decisions being made on specific drugs the elements of this consensus are still reflected?

DR. DOWNING: Well, we are always open for suggestions. There have been lots of meetings and dialogues with industry. We have been spending a great deal of time gathering lots of opinions and concepts about how to better organize science.

The emphasis, I think, clearly has been, from an NIH perspective, in helping address this issue of characterizing, classifying, defining biomarkers in specific disease areas. As an example, we have been working in a number of disease areas to arrange conferences and meetings

with industry to help identify candidate markers and prospectively evaluate them into categories that will be useful in drug development, both in the preclinical phases, early phases and, as the science matures, evaluating them as surrogate endpoints.

I am not at liberty to discuss a lot of those examples right now but, for example, next Monday and Tuesday the National Institute on Aging is sponsoring a workshop meeting with a number of industries and scientists in this area to look at Alzheimer's disease biomarkers, and how to organize the science to evaluate them in a more efficient fashion; rather than having a variety of different studies going on, trying to do this as a collaborative unit that will ultimately form a framework for assessing markers as candidate surrogate endpoints.

These are all models that are evolving and we think that it offers a unique opportunity to facilitate drug development from a public health perspective, as well as helping organize the information in a more reasonable fashion for regulatory decision-making. We would welcome any comments or suggestions for how to organize this a little more efficiently.

DR. BYRN: Any other questions for Greg?

[No response]

Thanks very much, Greg. John?

DR. DOULL: Steve, I want to share Bob's excitement about this development. It is a very exciting, it is a very novel, it is a very new approach. It is going on in some other areas. I have been involved with some toxicology program things, in fact, which are similar to this. The SOT, for example, is planning symposia for the next meeting that are going to deal with some kind of similar areas.

In talking to some of those people, they are using the same concepts but the terms are a little different. They are talking about toxicokinetics and toxicodynamics, and so on. I think the argument that we need to have common nomenclature, and that we need to talk to each other so we don't get crosswise with terms is an important one.

Bob mentioned PK/PD for example. You know, when you first look at that you think PB/PK, which is kinetic. Those mnemonics I think are not helping us. We do need to talk in English, an exposure response is a great suggestion to do that.

The one thing that I find particularly exciting about all this is tox. and pharmacology, of course, years and years ago were common. They were all in pharmacology and they spread apart. I see this as a real powerful tool to bring those two disciplines together again. We are talking about effect, whether it is therapeutic effect or toxic

effect, and if the concepts bring us together I think that is desirable.

So, I guess my recommendation would be that we need to pay attention not only to what is going on here around the Beltway but also out there in the rest of the world in terms of how these concepts are developing. I think we need to facilitate, as best we can, those developments because they will help us substantially in all of our disciplines.

DR. BYRN: Mary?

DR. BERG: I too am excited about this because I think of it from several aspects. First of all, for the public health, essentially helping all the different populations in the United States and thinking about the NIH workshop that was in May, sponsored by the Office of Research on Women's Health, and co-sponsored with the FDA and eleven other institutes within NIH because when you look at subpopulations you start thinking -- I will still use the old terms right now -- PK/PD in regards to looking at gender differences; thinking sometimes with regards to men and women may have different kinetics and also may have different dynamics, but actually they may negate one another and so there may not be any dosing change, or you can think of other things occurring in regards to that combination of PK and PD in regards to what would occur with those dosing

changes. Then, obviously, you can expand it to age and, obviously, to the different ethnic groups.

So, from a public health point of view, it really individualizes the patients and medication. So, I think it is excellent with regards to the FDA here.

Also, getting to Bob Branch's comment when he asked the question about, gee, can NIH work more with FDA, and I truly think by having this type of science of combining PK/PD, to me, it would further the dialogue and really allow more inter-agency -- I hope it would -- contact with regards to the science because, again, you are getting back to the bottom line -- excellent public health because you are individualizing the dosing information. Thanks.

DR. BYRN: Lou Sheiner?

DR. SHEINER: I am Lou Sheiner. I am on the expert panel. I think there is an issue that was brought up but that was not sufficiently emphasized, and I don't have any solutions but I think you just began to focus on that again.

If I can turn to the three questions that Roger keeps on attributing to me, I think they are very relevant. Remember, when I first put out these three questions, it was these are the three questions that the subject matter, the domain expert people have to answer before you can turn the issue over to the technicians to tell you how to do it: What do you want to know? How certain do you need to be? And,

what are you willing to assume? What are you willing to assume means what are you willing to say that you know already so that you are not going to ask that of the new studies.

Those are domain-specific questions or, in this context, regulatory questions as well. Once you answer those three questions you can go to the statisticians, you can go to the modelers, you can to all the people -- the computer scientists, and say can we do this? How well can we do it? How good are the procedures we have for creating that piece of knowledge that we want, with the certainty that we want, under the constraints we have to operate, and how well will these things work? Can we do it? And, so on.

Today we are kind of overwhelmed with technical possibility in this area because of the advent basically of massive computing capacity on everybody's desk. That has just completely changed what we can do in terms of extracting information from experience.

When you get into this area and the idea that you are going to use scientific-based models to be both credible and to be more efficient in the process of understanding what drugs do, then the question that becomes much more essential than it ever was when you simply looked at an empirical study and said I want to analyze this study to see whether it supports or not a particular hypothesis, the

question that becomes absolutely key is that third question, what are you willing to assume?

When you do an empirical study that is addressed to a specific question, you do not have to assume anything almost once it is assumed that the randomization worked and that your measurements measured the things that you thought that you did. And, that is about it.

Now, when you start to do this, what we are talking about now, that becomes the key thing -- what is the known science? What can you rely on? What can we say we know already? With what degree of certainty? In fact, the Baysian framework is really the only intellectual framework that exists to handle that particular problem. You can't do it with any other sort of epistemological framework because you need to build in prior knowledge, and you need to be able to say about that prior knowledge that you are also uncertain of that. That is what the Baysian system does, it allows you to say I think I know this but I know this within certain bounds and I want to measure that with my data.

So, without getting into that part, the part that I want to focus on is that we have had, and maybe for good reason, a kind of dissociation between best scientists, the domain experts and the folks who know the technology, the modelers and the statisticians. And, this is not going to work in the future. So, I see that as the biggest challenge

of this, and I see that it comes in, you know, sort of as the rubber hits the road, at the FDA because they have to approve a drug perhaps, or they are opening the door to approve the drug. They are involved in interpretation of data that requires an assumption about science, done with techniques that are highly technical and require people who are experts in that to tell them whether those techniques work. And, we don't really have a good mechanism in the scientific community -- I think the regulatory community may be better than elsewhere -- to handle that dialogue, to get the domain people to understand what the technical people can do, to get the technical people to feel comfortable enough with complex domain models rather than saying, "well, I don't really understand that science so I am just going to, you know, do a linear model or do a polynomial model or that kind of thing." That is just not going to fly.

I don't exactly know what the solution to that is. But I am concerned because I haven't seen that -- you know, I have seen a few people who bridge both worlds but I haven't seen the development of systems that make these people, who are separate domain experts and are not going to learn each other's world too well, work together in a way that produces the kind of synthesis that we are going to need. So, I don't have a solution. I don't know what the FDA can do about it, but I do think that that is the crucial

issue.

DR. BYRN: Mary?

DR. BERG: Dr. Sheiner, I think that really gets back to what we were talking about with regards to the inter-disciplinary approach. It really is that paradigm shift that is forcing all of us, whether on an expert panel or an advisory committee or whether it is an agency one is talking about, it is a whole shift in thinking that we have always had our scholarly independence. Now we have to work together even to get our institutions back at our universities to recognize that interdependence that we have gone on for twenty, thirty, forty years never having to think about. So, it is truly a whole new thought.

DR. BYRN: Robert?

DR. BRANCH: In terms of following out your thought, Lou, you are talking about the mechanics of how you get into the modeling. That really goes back to the discussions that are going on between the NIH and the FDA as to what is the premise of the assumptions that go into the initial study design. How do you use cholesterol, for example? Does cholesterol for that particular agent -- is it a good marker in that particular instance or is it a poor marker for a select drug that is going through?

It seems to me that right now the door has been opened to industry to take an approach, but there is a high

risk that is going with that because of the underlying -- is there consensus of the underlying premise.

So, is there a way that some of these ideas can be thought about, discussed in advance? As this new paradigm is being developed, I think that this idea of the NIH taking its Alzheimer's disease or its asthma NIH-sponsored group and getting them together with industry is a great way to start, but out of that would the FDA accept a consensus opinion the way science is now because we are working with uncertainty. We are working with a continuously changing frame of reference and basic amount of information. If you are going to development a new drug and it is going to take two to three years, in two to three years time the science may well be advanced quite substantially and there would be a different baseline at the time of the evaluation.

So, it seems to me that for this approach to be successful, it really does require a larger group of people to come together to create a sense of consensus. If that doesn't happen, then the expectations and the hopes with this approach will be sort of damaged by some examples that will go through where there is a lot of good intent but it doesn't work out in practice.

So, I think the way that these guidances get translated into practice is going to be very important in terms of making this a successful way to development drugs.

DR. STANSKI: One way to link what Bob is saying and what Lou is saying has to do with the prospective trial -- in fact, Carl's comment. In other words, if a drug development program comes in and say prospectively, before they do the work, this is the current body of knowledge; these are the markers we propose to use; here is how we are going to analyze and validate them; and here is the distillation of knowledge, would you find this acceptable? And, the agency reaching out to wherever it needs to reach to get the domain expertise and get them in a room, just like we are all here, makes the decision of saying, yes, we will approve what you are going to do and if the results end up as you predict, you will have success in terms of the regulatory hurdle. That may be the way to provide the incentive for the work.

The problem has been that it has been retrospective. In other words, after the work has been done there is a lot of digging, shuffling and hand waving to try to explain, and there is a degree of suspicion that is never overcome. But prospectively it is a contract between the agency, NIH and the industry to go ahead and say if we do this, will you -- and if the answer is yes, you go ahead.

DR. BYRN: Roger?

DR. WILLIAMS: Several things are kind of rattling through my brain, and I want to say that the committee's

comments and those of the expert panel I think are really terrific, and we do want to look at the public record and see what this discussion is.

Just to share some thoughts about this, I think I almost feel sometimes, thanks perhaps to the NIH conference, that we sort of know what we need to do and the real question is how to get it done, which becomes more of a process question. But if I could look forward into the next two or three years, could I imagine and agency guidance that would say here is how you evaluate a surrogate marker -- can we imagine that? As I listen to people like Louis and Scott Zezer and some other people talk, I could imagine it. And, that would be a very powerful guidance.

Would it come out of this committee? I am not so sure about that. But it goes back to what I said in my beginning statements, you would have to bring in the domain experts, and our domain experts are in the fifteen review divisions. But it is a very powerful concept. I sort of have the feeling we know what to do.

Now, when I think about knowing what to do it leads into another challenge, which is that my understanding is as you evaluate a surrogate you are going to need a lot of data about the surrogate vis-a-vis the clinical outcome that you care about to see if it can be a substitute. And, the question is where does that data come from? Well, some

of it can come from the government, and I understand that NCI is thinking about this in a very sensible way. But, obviously, it also would come from the people who do this, who are the pioneer industry.

There you sort of get into one of the challenges of our society, which is public access to this information. You know, the agency is very sympathetic and sensitive to what we call confidential commercial information, and I can imagine that a sponsor, after they went to a lot of trouble to evaluate a surrogate, might not be so willing to share it publicly. Steve can imagine that too.

DR. BYRN: I am sure they wouldn't because this would be very valuable researching for the next generation of drugs, and so on and so forth.

DR. WILLIAMS: But if I had to move us collectively as a society beyond that, I would argue even for industry the value of perhaps creating a way to share this publicly would be tremendously to the specific pioneer who did the work as well as everybody else. But you are getting into a very general societal debate that is certainly beyond anything that I am responsible for.

DR. BYRN: We might be able to argue that just the lead time in knowing that first was worth it. Do you see what I am saying? I mean, they would have to evaluate economically, but it would seem to me that the lead time --

they would know first that it was truly a surrogate marker. Do you see what I am saying? So, they could do a number of studies prior to it becoming generally known.

One other thing I wanted to suggest, it just occurs to me even the computer programs that we are using to analyze these data are under development, I assume, and there is a question about validation in this technical area even of those programs. How do we know that everybody is using a program that does what it is supposed to be doing? And, we are going to need experts to come together and help us with that. Go ahead, Gloria.

DR. ANDERSON: I would like to commend the committee for the approach that it is taking in this whole area. I am particularly pleased that you are going to take PK and PD, I guess, to English. I am a physical organic chemist and I have been struggling to remember what PK and PD stand for. So, English would be helpful.

As a physical organic chemist, one, I assume that you are going to use the modeling, or that the modeling will be particularly helpful in terms of a predictive kind of model for what you are doing. In one of the slides, and I don't remember what the statements are but there is a bullet that deals with empirical versus mechanistic models. In terms of the PD and the PK, I think about chemical reactions in those respects. I wonder how you are going to -- maybe

you haven't gotten to this point, but I wonder how you are going to deal with all the parameters, all the variable that come into play when you change from one drug to another. I mean, will that be done statistically, if it can be done, or how are you going to eliminate parameters so that you get an equation that is manageable? And maybe you haven't gotten that far but it is something I would think of based on the way that I have to do things, and I have much more control over the systems that I used, the solvents and all the interactions. There is a question in there somewhere I think.

DR. LESKO: I will start answering the question and then maybe turn to Peter for some more technical response. But I think we are both talking about the same thing in terms of the value of having a model that has some mechanistic meaning to it. Certainly, an empirical model is one where we have an input and output, and perhaps that output is predictable from that empirical model. But I think as we get into PK/PD the value of having some mechanistic models that give us insight into the drug's mechanism of action or the therapeutic target is well worthwhile. Certainly, the parameters from such a model would have some therapeutic meaning, I would think.

But I think the next set of questions is the use of the empirical model versus mechanistic model for

subsequent predictions. Maybe I will let Peter answer that one. Was that kind of the thought you were getting at?

DR. ANDERSON: Well, yes, to some extent. I was thinking more in terms of, I guess, generalizations because if you move a functional group around on a drug it does something else and it becomes very difficult. Given the medium that the drug reactions take place in, it becomes very difficult to predict what is going to happen. I mean, maybe that is what the study is about, to figure all of that out.

DR. LESKO: Yes, I think to some degree the study is designed in such a way that one takes that transformation into account in the kinetic part of that model. In other words, what is the material that is input, and what is the conversion that is important there? What is the species that is responsible for the mechanistic action? I mean, I think that is thought about and taken into account to the degree we can.

DR. ANDERSON: And then we throw in the discussions about the individual versus the population and a whole number of other variables and we have a real problem.

DR. LESKO: It is possible to sort it out with the framework of thinking which is important in terms of what is the question, and so on. And the question to something like that, I believe, would be, you know, what is the variable

that you are interested in, in terms of that input/output relationship, and taking that question in designing that study prospectively to address it.

DR. BYRN: I think Lou Sheiner has a comment.

DR. SHEINER: That is right on. That is one of the big questions in modeling, in a sense, what scale are you trying to model at? Clearly, if you are trying to talk about the marginal distribution of something, the average across the population of some gross feature like living or dying, writing a model in terms of molecules makes no sense. It is just like when you are building a bridge you don't write models about molecular structure of the materials.

It is fortunate in a way that the world is kind of hierarchical and operates on multiple scales, and there is almost a discontinuity between those scales. So we can take advantage of that.

The other, more technical point again gets back to the idea of a Baysian sort of an approach. You can have lots and lots of parameters in your model if you have reasonable prior distributions on them because that essentially cuts down the effective degrees of freedom that you have to extract from the data. So that gets right back down to how much science do you know.

You can't do what we are talking about unless you know science. Without science we just wouldn't be having

this discussion. The whole point of this thing is that there is a body of information out there called scientific knowledge which we can add to our empirical observations to get more out of that than if we just use the empirical observations. Drug development is a process that has not, many of us believe, adequately exploited that body of knowledge. It is there, and sitting there, and there are techniques now that we can do it.

The fascinating interaction between that is a scientific issue, and the regulatory public health, protecting the public, you know, that interaction I think is a very productive place to do this. Don sort of suggested that one way to deal with this problem is to set ourselves little tests, like somebody comes forward and says I would like to do this. Then we have to answer. Can you do that? Will we approve it? It may be a way that we want to mix that with the kind of more thoughtful, academic debates on academic issues -- using that word, academic, in a common sense of nobody cares really which way it comes out because it doesn't make any difficult in the world. This makes a difference, and that may be the thing that will be forcing us to deal with this in a very practical way and we will get some experience doing it.

DR. BYRN: Roger?

DR. WILLIAMS: A nomenclature question for Louis,

which is sometimes people sort of jump when you talk the way you just did, Louis, because they --

[Laughter]

-- this is a minor question; it is not a big question. When we use the empirical method based on adequate and well-controlled studies people say we are using a scientific method. I think when you talk about science you talk about it in a different context. Could you distinguish?

DR. SHEINER: We are getting to the philosophy here. Science is theory. That is what science is about. Science is about creating the smallest set of rules from which everything that you observe can be deduced. That is what science is. Science creates theories. Now, in the process of creating theories which have good predictive power that are accepted, what you do, you expose them to empirical tests. You ask, does the world work the way this theory predicts it does? If it doesn't, then you throw that theory out and make another one.

So, empiricism, the testing of predictions against observations, is a scientific method but empiricism is a whole other way of knowledge. You don't need any theory to work from empiricism. You just need a method to know whether or not what you have observed is credible. A lot of statistics deals only with the question of making empiricism corn fed. How well did you learn that that thing really did

happen, will happen under those circumstances? How certain can you be about that? That is what a lot of statistics is about.

But science is not statistics. Science is the business of creating theories of how the universe works. When I say science I am talking exactly about that because if we have a theory about how something works, then we don't have to actually do it and that saves us time and money. We can predict what will happen without actually having to do it.

So, if you take the simplest case that you have already accepted so everybody doesn't feel like I am going off into the stars, if you study a bunch of difficult doses it doesn't take much to say that there is some kind of smooth interpolation of the response, such that I can talk with some confidence about the response to a dose that I never tested that is somewhere in between the ones I did test. It is going to be somewhere in between the responses.

Now, if you are a total empiricist, you say I have no theory; there is no smoothness in the universe; there is nothing going on, you could say, well, any dose I didn't give you could get any response at all. The dose response might just hit zero at exactly 5 mg and then pop up to a good response at 6 mg and then zonk off to infinity at 7 mg and drop back down to a reasonable response at 8 mg. There

is no theory that says that has to be smooth. Science says it has to be smooth because there is a basis for that.

Now, there are a lot of rules of thumb of theories that we use, like smoothness, that don't involve any specific domain knowledge. Things don't tend to vary greatly on a local scale and the further you move away they vary. That seems to me a sort of rule of the universe with respect to everything. But it would be much more powerful if we can use one that is domain specific, and that is what the different sciences use.

But I have great respect for empiricism but it is not science. Science is the theory about how things work, and there is a wonderful quote -- I don't remember who said it, "there is nothing so practical as a good theory."

DR. BYRN: Roger?

DR. WILLIAMS: I have another comment for John, which is I think you had a very important concept, that a lot of what we are talking about here goes on in all sorts of environments -- clinical safety and efficacy, nonclinical pharmacology, toxicity, even product quality. I sort of tend to put it under the heading of alternative tests, and it goes back to the willing to assume statement. Are we willing to rely or willing to assume based on our prior knowledge that we can rely on some kind of surrogate as opposed to something else?

Now, we have always relied on these two large animal studies for carcinogenicity testing, John, as I am sure you know. More recently we have said, via the ICH process, that perhaps you could rely on something that is a little bit more mechanistic, more sensible, I guess I would call it, based on a scientific approach to allow reduction in those large animal studies.

I would even argue that sometimes when we say in MBCS where we want to look at the solution we are relying on an alternate surrogate perhaps as a predictor of what we care about.

DR. DOULL: Let me just comment, Roger, one of the things, if you are involved in different committees and so on, like the Science Advisory Board at EPA, they really have the same kind of problems over there, of course, as Food and Drug does. But they tend to go off in somewhat different directions. What I am saying is that we need to be aware of the fact that different disciplines and different agencies and different sciences, and so on, are really talking, like Lou is saying, about fundamental questions and we need to do what we can to bring that together.

There is a federal agency group, for example, that gets together -- I forget what it is called -- to talk about looking at dose response and how you interpret that. The implication comes out of that you do that difficultly in

toxicity than in pharmaceutics. You don't really. Fundamentally there are the same principles, the same theories that we use. We put different names on it, and that is what Bob is saying. We need to be careful about how we name it because putting a different name on it somehow gives it a different role. But, basically, we need to recognize what each other is accomplishing and build that into our protocol in order to affect public health. And, I think we are doing that.

DR. BYRN: We have gone over about fifteen minutes. I know Larry was hoping to conclude this in the next couple of minutes. Are there areas of focus or issues that anybody else would like to raise about Tab A, because we are going to go forward now with the time table, or at least approximating the time table that Larry outlined?

DR. LESKO: Again, I want to compliment the advisory committee for their questions and issues that they raised in the expert panel, and for the contribution of the sponsors. I think when I started this session I asked for some general comments and impressions. I think we got some excellent comments and impressions, and in particular the notion that there is a need to create venues for collaboration between the dimensions of disciplines that relate to this whole issue of exposure response, and also that whole area of linking biomarkers to clinical outcomes,

which leads to the decision on something becoming a surrogate.

I just want to comment on that. I think it is an important point that we don't go a whole lot into that backgrounder, but one of the things we do say in the document is that the acceptance of a biomarker as a surrogate depends, again, on weight of evidence and the prospective thinking of preclinical-clinical links throughout drug development I think tells the story in a way that facilitates a biomarker eventually linking effectively with that clinical outcome and becoming a surrogate. So, I think that is a key point as far as implementation.

DR. BYRN: Thank you very much, and thanks to the expert panel for their input. I am sure we will be discussing this further. Let's take a break until 10:40. We will start at 10:40.

[Brief recess]

DR. BYRN: The session for this morning is on drug-drug interactions, and Roger Williams will provide an introduction.

Drug-Drug Interactions

DR. WILLIAMS: Thank you very much, Steve. I will try to be very brief because we certainly have a lot of interesting things to say.

[Slide]

I will show on this particular overhead that the agency, working sometimes in the International Conference on Harmonization, has produced guidances that attempt to deal with dose individualization in specific patient populations. I won't go into any of these. I think they are very interesting and they all, in some way or another, relate to that E5 document that I talked about in terms of intrinsic and extrinsic factors.

Now, in the next part of the advisory committee discussion you are going to hear some very interesting presentations from Dr. Shiew-Mei Huang and then hear some other discussions about guidances that we have developed to focus on drug-drug interaction studies.

[Slide]

I would now like to intrude a thought, at the risk of driving everybody crazy, that when we talk about intrinsic and extrinsic factors there are issues related to prescribability and switchability. If you look at the list of extrinsic factors you will see all the things that are kind of characteristics of the patient or the person. If you look at extrinsic factors you will see, first and foremost, the drug-drug interactions topic and then diet and tobacco and alcohol, and some other things that happen to people externally.

Let me go on because I am going to raise, of

course, the prescribability and switchability question, and I have tried to make a preliminary cut as to whether I think some of these questions are prescribability or switchability questions.

Let me give an example. I think for gender, for example, it is pretty much a prescribability question because the clinician, healthcare practitioner, is confronted with a patient who is either male or female and asks the question, do I need to do a different dose based on gender? And, I would say if you accept that paradigm you can kind of extend it to some of these other things.

Now, there is an interesting switching aspect to some of these things that relates to age. The reason I put a question mark there, as you all know, we have defined four age categories. I think it is 0 to 1 month, 1 month to 2 years, 2 years to adolescence and adolescent to 16. That raises an interesting an interesting switching concept that in the early years of life a single patient may be switching over a relatively short period of time, from being a neonate to being an infant. Of course, you could ask the question what happens when people gain or lose weight, or their body composition changes. So, I tend to put question marks over here; some "no" but, for the most part I would argue that intrinsic factors are prescribability questions. This is useful because, remember, I will argue that the

prescribability goal posts are much wider compared to individual goal posts.

Now, I am going to make the claim, and I don't want to belabor the point -- you can certainly ponder this later on, that for the most part drug-drug interactions are switchability questions. I argue that on the thesis that you usually have somebody who is stabilized on a substrate drug, for example, and you add an interacting drug which, to me, is a switching concept.

[Slide]

Let's go on and I will just show three more overheads quickly. I think I will recall for you all that this is the window for the population which tends to be wider than the individual window. You heard me say that yesterday. Let's go on.

[Slide]

This is a hypothetical study design for a switching drug-drug interaction study. Now, if you talk about this as being the individual therapeutic window our default would be 1.25, perhaps going up to 1.37 if we add epsilon. Then you think about the substrate being stabilized here and, at this point in time, with the interacting drug being added.

Now, you could imagine that there would be several outcomes based on interaction. First of all, there could be

no interaction. The mean could go up, the mean could go down. The mean could dramatically go up so that you would have no question about there being an interaction. Then, connected with each of these mean changes there could be variance differences.

If you apply the individual bioequivalence criteria, you could imagine something that would look like this. And, I think one of the most interesting questions is what would be the equivalent of a sigma D for a drug-drug interaction in a switching setting. I don't even know what the name of this would be. We call it different things -- drug by interacting, drug interaction or something like that. But let's focus for a minute on a sigma D, and I will go on to the next overhead.

[Slide]

This is a very truncated data set where we had drug X coupled with an antifungal. Up to day 4 it was just drug X. Here is the antifungal and you begin to see here a difference between males and females. Now, I would argue that this is possibly what we might call a gender-based, subject to formulation equivalent for a drug-drug interaction study.

Now, I say all this to just challenge you to think about what we are dealing with here. I am not suggesting that these are the kinds of study designs we have to do but

it is a very interesting data set and, you know, somebody three years from now, my successor or whoever it is, will come to you and say, what about this? Let's talk about it more at an advisory committee.

Having said all that, I will remind the committee that we actually talked about this a couple of years ago, and I raised the possibility of the criterion you would use to assess a drug-drug interaction study. And, we can go back and get those records.

Back to a more general approach, I will turn it back to Steve to carry on with the presentation.

DR. BYRN: Thank you very much, Roger. Any questions for clarification for Roger from the committee?

[No response]

Then, Shiew-Mei Huang will present a curt presentation on drug-drug interaction guidance.

Drug-Drug Interaction Guidance

DR. HUANG: Thank you.

[Slide]

In the next fifteen minutes or so I would like to update the committee on the status of our development of the in vivo drug-drug interaction guidance; talk about where we are going from here; and provide some topics for the committee to discuss.

[Slide]

I will give a brief status of this guidance development and talk about issues that were not discussed in the guidance, which evolved as the guidance was being prepared. I will also describe some recommendations from the working group which was formed in the last few months under Dr. Lesko, a quality assurance, quality control initiative, to look at the review processes, especially in the clinical pharmacology, particular drug interaction areas. And, I will have questions for the committee members.

[Slide]

The guidance in vivo drug metabolism, drug interaction studies, discussed study design, data analysis and recommendations for dosing and labeling. The draft guidance was released in November of last year. The committee members have a copy in your packages. We have presented this several times since '97 to this committee.

[Slide]

The key philosophy of this guidance is that we in the review process we would like the sponsors to evaluate the drug-drug interactions with an integrated approach. Early on, at the preclinical stage, we would like to use in vitro methods to look at the metabolic potential for drug-drug interactions, and the issues have been discussed in the guidance that was released in '97.

Depending on the in vitro data, if we think there

is a need for in vivo evaluation, then the details of a study design analysis are described in the guidance I just mentioned.

Finally, we also recommend using the population pharmacokinetic approach to evaluate drug-drug interactions in the patient population and, therefore, maybe we can detect unsuspected drug interactions or interactions based on other mechanisms.

[Slide]

So, there are various mechanisms of drug-drug interaction. Our current guidance focused on metabolic-based drug interactions. In the guidance we detail the study planning. For example, we talk about the size; the type of subjects to use, females, males; the study design, whether to use single dose or evaluate steady state conditions; to use a randomized crossover design, parallel design, and so on. We also talk about data analysis and, most importantly, how to translate the results to proper dosing recommendations and labeling language.

[Slide]

The key message of our guidance is that metabolism and drug interaction information is key to the benefit-risk assessment. If you don't know the metabolism of a drug or the drug interaction potentials have been evaluated, then we don't think the drug's safety and efficacy has been

adequately evaluated. We also advocate using an integrated approach, as mentioned earlier, which may reduce the number of the necessary studies, and can optimize our knowledge based on focused studies. We also mention in our guidance that study design and data analysis is really critical in providing information for labeling. Further, in our guidance we also talk about the concept of establishing a therapeutic equivalency boundaries, or therapeutic windows, or goal posts as we mentioned several times.

I think we really want to translate what we observe in drug interaction studies. What does a 30% change in AUC means? What does that mean clinically? We heard earlier this morning about the importance of PK/PD or exposure-response relationship.

[Slide]

So, in essence, our guidance is talking about this approach. We think initially we would like to have information on <u>in vitro</u> metabolism of the compounds in development and ask the question for each important cytochrome p450 enzymes, if this drug is a substrate of this particular enzyme. If it is not -- there should be an arrow here -- then we can stop and have general labeling. If the answer is yes, then we want to ask another question, is the pathway important? If it is not important for overall elimination, then we can also stop and do general labeling.

However, if the answer is yes, then we are proposing in our guidance to use the most potent inhibitor or inducer to study. If the results are negative, then again we can stop right here. If the results are positive, then we can continue to look at the extent of the interaction for substrates and then look at the possibility of coadministration.

Similarly, we also ask the question if the compound is a modulator of cytochrome p450s. Based on in vitro evaluation, if the compound is not an inhibitor for certain compounds then we can stop, right here, and do labeling. If the answer is yes, then again our guidance recommends that we evaluate based on the most sensitive substrate. If the results are negative, then we can stop right there. If the results are positive, then we use other substrates based on possibility of coadministration.

We further discussed that in cases where we have stopped labeling, try to use population pharmacokinetics to catch some unexpected interaction.

[Slide]

The guidance, as I said, was published in November, '98 and we have received public comments up to March. There are several comments. In general, comments are very positive. We have comments on suitable substrates to use, especially on 384. There are discussions on the use of

population PK/PD in evaluation of drug interactions, and there is also discussion on the proper drug data analysis approach. We have incorporated these comments and the final guidance should be out any time now.

However, there are also comments about other issues which were not addressed in this guidance and I would like to discuss that.

[Slide]

There is some discussion about predictability of in vitro systems. For example, sometimes the in vitro metabolism is negative when it is positive in vivo. We have cases were a metabolite is an inhibitor, which we have not caught in the in vitro system. So, we have a false-negative situation.

We also have cases where the compound effect has various pathways and it may be inhibiting certain pathways which we have observed in vitro, and it may be inducing a different pathway, and you may not see an interaction as you would have expected from the in vitro data, resulting in a false-positive.

There are also several other situations that we have not discussed in our guidance, like other metabolic pathways, phase-II metabolism, how do we evaluate that, or other transporters -- the involvement of p-glycoproteins, ketone transporters which also contribute to the

non-predictability of some in vitro studies.

So, how do we address these issues? We are actively involved in another working group, trying to prepare a manual of processes and procedures, which is an equivalent guidance for industry but is a guidance for internal reviewers to address these issues. In addition, there are also comments about lack of PK/PD or exposure response in order for us to set a therapeutic equivalence boundary. We heard this morning from Dr. Lesko's talk that the PK/PD data were not really provided when the NDA was submitted.

[Slide]

I will continue to discuss these remaining issues when we come to the questions for the advisors. I would like to talk about the recommendations from the working group I mentioned earlier in which we looked at our review process, especially in the drug-drug interaction areas.

[Slide]

A working group was formed to look at a few compounds which were recently withdrawn from the market, in part because of their drug interactions. We looked at terfenadine, which was for symptom relief for allergic rhinitis. This was approved in '85 and it was withdrawn from the market after 13 years.

Similarly, we have astemizole, which was approved

in 1988 for a similar indication and was just withdrawn about two or three months ago.

Mibefradil, which was approved for hypertension and chronic stable angina, was just withdrawn from the market after one year.

What is common in these areas is they are all 3A4 substrates. In addition, mibefradil is a very strong, potent 3A4 inhibitor.

So, the working group looked at the data that were available at the time of the submissions, and also based on the postmarketing availability of data. We have essentially evaluated the literature data that we have so far to see if we can develop some strategic paradigm for us when we review new drugs, and how to treat a drug interaction. In addition, we also looked at another drug which is a 3A4 substrate and was not approvable earlier this year, again, due to drug interaction liability.

[Slide]

The working group had gone through all the files and information from the literature and came to the conclusion that in our future review in our evaluation of drug interactions we must answer these questions. We must have data to answer these questions: Is the drug interaction initial? Is the compound a substrate that is going to be affected by other drugs? Is the compound affecting other

drugs' metabolism? If the answer is yes, we want to make sure if the benefit outweighs the risk. Is this compound for medical needs? Is it for a life-threatening disease? If the answer is still yes, then can we manage through labeling to convey the liability of interaction?

[Slide]

With all the data that is available right now, and looking at the guidance that we have in place now on in vitro metabolism and in vivo drug interactions, we think if we have all this information available and evaluate them again, then probably for these compounds the answer for the earlier question will be, no, the risk does not outweigh the benefit.

Actually, this was demonstrated very well with this drug which as S-3A4 substrates. It has undesirable serious adverse events when the concentration becomes too high. And, this compound is not for medical needs; it does not treat life-threatening disease. So, the drug is not approvable.

However, if we find a compound which has a serious drug interaction liability and, yet, it does meet the criteria that it is for medical needs, how do we manage the labeling? So, the working group looked at it and made some recommendations. They said we would like to consider -- actually, this is one of the comments submitted to the

agency that perhaps we can assign risk levels to drugs, for example, like mibefradil. If we can classify it as a potent inhibitor early on in development when it is first released, perhaps that can help us identify its potential for drug interaction better. That is our second recommendation, more prominent labeling when it is first introduced to the market.

Based on the experience with terfenadine, astemizole and mibefradil, there are several "dear doctor" letters. Some of the information was not available at the time of review or approval. A lot of information came out and so there are "dear doctor" letters issued; a lot of information is displayed on the FDA web page. But the drugs which should not be prescribed together are still being prescribed. So, we need to find a more effective way of disseminating the labeling information for healthcare providers and patients.

[Slide]

So, this leads to some of the topics for the committee members to discuss if the time is available now. The first question -- how do we address some of the issues that evolved after our guidance was prepared? Are we ready to provide guidance on the assessment of other mechanisms of interactions, for example, p-glycoprotein? Do we have the substrate inhibitors, the standard ones that we can

recommend, just like we did with cytochrome p450? What about other transporters? How many studies are we going to recommend to the sponsors before we get proper information for labeling? What about phase-II metabolism? We have a working group addressing that internally right now.

In the meantime, is the population pharmacokinetic analysis the answer to this question? Should we use it more in evaluating other interactions that were not revealed using the in vitro metabolism screening? We know the population PK approach has been used but really not to the extent of a similar percentage, like 10%, 20% in the submissions, especially for drug interactions. So what are the issues? When can we make use of that analysis to help evaluate interactions based on other mechanisms of interactions?

Again, hopefully, we will be able to get more information on PK/PD or exposure-response information to help us translate what we observe in the drug interaction study to useful labeling.

[Slide]

My second question -- it is really very important, what we have done. I mean, the sponsor and the agency may have worked together and done a lot of studies, and we know the risk of drug interactions, but how do we effectively translate this into labeling? Will the assignment of risk

levels be communicated if we put it in a black box, even though we are not contraindicating any particular list of compounds with the new drug but indicate that it is a potent inhibitor, would that help so that the information is not lost in a volume of information? You have seen some product labels where you may have three or four pages of drug interactions, but would that communicate a different message, or is really the message lost because of the set of information there?

In other cases, even when we have done our job in the labeling, how do we better communicate the labeling to the healthcare providers and patients? The FDA has the web site and I think it has been appreciated. Every time we have a "dear doctor" letter sent out with market withdrawal or another compound which has limited dosing, it is posted on the web page. Is that sufficient? Is there another form that we should pursue in order to really communicate this information to the important parties of the drug users?

So, I will stop and let the committee take up these issues.

DR. BYRN: Thank you very much.

Committee Discussion

I think we can begin. Maybe we should put those questions back up, Kimberly. You can just leave them and you can go back to your seat. Maybe we should put those

questions back up and discuss those issues.

So, this question is asking us to address the remaining issues in order to allow, I guess, completion of this guidance. Go ahead, Shiew-Mei.

DR. HUANG: This what we are doing. The guidance is based on public comments. It has been finalized and is waiting for the last approval. So it could be released any time. This is for what we are going to do, the next step.

DR. BYRN: Okay. So, how about the committee? Are there recommendations on now to address any or all of these issues? Yes, Bob?

DR. BRANCH: It seemed to me that the issue that is addressed in the first item there really relates to the ability to predict on the basis of preclinical information or knowledge whether the drug is handled by a transporter or p-glycoprotein.

The direction of this would be probably most useful to go the same way as you have gotten in vitro guidance for the p450 enzymes, going in that direction. The fact that in your in vivo studies you are likely to collect the information, when you are looking for interactions in terms of systemic availability you, by and large, don't know whether it is due to 3A4 or p-glycoprotein, and our ability to predict what the outcome is going to be on those interactions right now is so poor -- Les Benet, who was here

yesterday but I don't think is here today, is sort of trying to get into the area of predictability but I don't think we are there yet.

So, it seems to me that this is a direction for the future but it probably is going to be directed more to in vitro than in vivo studies. You have already covered the in vivo situation in the current guidance.

DR. BYRN: Other thoughts on this matter?

DR. DOULL: It seems to me that when you talk about drug-drug in essence what you are doing is moving from considerations which you use for single agents into the mixture problem. The drug-drug is really a mixture problem. You know, you can have antagonism or synergism or no effect -- all those different combinations. What you are saying is that the best way to deal with a mixture problem is to understand the mechanism of action, and I agree with that. That is probably the only way to get out of the smoke and that, hopefully, will get you there.

But early on you talked about key messages, and you said metabolism and drug interaction information are, in fact, the key to evaluate benefit-risk. I am not sure that is broad enough. If you just say metabolism, that is only a part of kinetics. There is absorption, distribution, metabolism excretion. All of those things could influence drug-drug interaction.

I guess you really need better information on the mechanism of action of the components of the mixture, of drug A and drug B, in addition to the interaction kind of thing.

I guess the one thing that kind of bothers me about that is that you imply that somehow if we understand metabolism that resolves the benefit-risk we are able then to do benefit-risk. I think, you know, what we need to say is understanding the mechanism will help us to do a much better benefit-risk evaluation but it isn't absolutely essential because Food and Drug, you know, for fifty years did benefit-risk evaluation without really much information about how the drug worked or mechanism of action. So, you can't really insist that mechanism of action is the only way to do benefit-risk judgmentally. What Louis was talking about, the Baysian approach, and what have you, is another approach for doing risk-benefit evaluation. We will do a better job once we really understand what is going on, and that is mechanism of action.

So, I think the focus should be that in order to improve our ability to do good drug regulation, and so on, mechanism certainly will help us do that.

The other thing, in your next question you are really talking about reducing risk. But the example that you gave, as I recall, you said below a certain dose you have no

problem. It is only when you exceeded the dose that you had the drug interaction problem. Okay, in that case, it says to me that if you get down below that threshold you don't, in fact, have a drug interaction. What concerns me about using risk is that risk has no bottom. There is always some risk. You can always reduce the risk and it never gets to zero. But when you talk about mechanism and are able to say there is a clear mechanism where you have a threshold then, in fact, you don't need to get into the reducing risk argument because, hopefully, if you get below that threshold, and that is for the whole population, then, in fact, you have a mechanism that really is protective. It is more concrete than evaluating risk, which I think is a little more fuzzy.

DR. HUANG: May I respond to your first comment about the need to study metabolism for understanding interaction of the drug. Again, we are focusing on metabolic drug-drug interaction because that is what we have most knowledge of. If you look at the recent drug withdrawal for the most prominent drug interaction in the last few years, terfenadine, astemizole, mibefradil, they are very serious, and they are very serious adverse events and there were a lot of fatalities with terfenadine and astemizole, and mibefradil is affecting a lot of other compounds and causing toxicity of the other compounds For example, with Warfarin it is increased with time. With the immunosuppressants it

has renal failure. With the statins it has reptomyalysis and death. I mean, these are all very prominent. So we are trying to learn from these examples, and if we had known the drug interaction potential and if we had put more prominent labeling early on -- if we know all this risk it will change our decision. And, the drug that we decided not to approve early this year actually is a very good example based on what we know now. It is because the company has done a very good study and they actually came out with a risk assessment and help us evaluation the risk assessment and we decided not to approve this drug because it doesn't add any value to current therapies.

So, I think our position is very important. Now, the tools are there and we ought to use them. They are not very expensive, and they can be accomplished in a reasonable amount of time, and it is the other mechanism where we have missed. I mean, we have examples like terfenadine. We decided that the risk doesn't outweigh the benefit when we have its active metabolite, fexofenadine, available. The fexofenadines aren't metabolized so we wouldn't think that ketoconazole would affect its metabolism but actually when the sponsor did a study, it did. Some of the recent literature suggests that fexofenadine is a p-glycoprotein substrate and it also is transporter substrate and ketoconazole affects both pathways. So, that is where the

mechanism is. So, I think we have to continue to search for other mechanisms of action and try to predict, as best we can, in this area.

DR. DOULL: I would agree with that, and what you are saying is that mechanism is important and that is going to help you do that risk-benefit analysis.

My only point was, for example, our previous conversation about pharmacokinetics and pharmacodynamics. Let's say we have a drug that has an immense half-life in terms of its kinetic effects and has a very short dynamic action. Then the driving factor or the critical steps in how that drug is handled really comes from kinetics. Dynamics is less important, and so on. So, there are situations where kinetics could be a driving force as opposed to dynamics being the driving force in determining how the interaction is going on.

All I was saying is that, you know, it is more than just metabolism. It involves dynamics and all the other parts of kinetics, and so on, that are involved in drug-drug interaction, and you really need to look at all of them. The ones you have looked at, clearly these are the deciding factors but, you know, down the road who knows what you are going to have and the guidance has to be such that it will take care of all those cases down the road that might be a problem.

DR. BYRN: Are there any other comments from the committee on number two?

[No response]

How about number three? What are incentives in establishing therapeutic equivalence boundaries? Any comments on that? Yes, Robert?

DR. BRANCH: It is more of a question than a comment. It seems to me that the issue of drug interactions, from a regulatory perspective, is almost entirely based on PK studies and therapeutic equivalence boundaries don't really figure into it until you start talking about potentially removing a drug from the market. So at the time of approval, it seems to me that there is a major dissociation right now. So, my question is to what extent are therapeutic equivalent boundaries incorporated into decision-making right now?

DR. HUANG: As I indicated earlier, we do not have a lot of information, PK/PD information, to aid us in the decision-making. So, a lot of times it was based on whatever information we had available. I would just say early on a lot of interactions -- because there is maybe not a systemic approach so we have received submissions with a lot of interaction studies. A lot of them, mechanistically, may not need to be conducted. So, we can see a big majority of studies showing there is no interaction.

But for those that show significant interactions, many of them are increased in plasma levels. So, in that case we would need information on PK/PD or exposure response, not in the efficacy type but in safety. So, we have to turn to pivotal trials, a clinical study, to see if a patient has been exposed to higher plasma levels showing an increase in adverse events. This would be very difficult for compounds with rare events like statins. We really don't have a high percentage of reptomyalysis, or something; you have some idea of a higher percentage but that is what the information may have to go by, to look at the information available to us. Sometimes when the range was not covered, then this will result in more discussion between the sponsor and the agency -- what should we do with this? Do we contraindicate this compound? For example, this compound is a 3A4 substrate and it shows the increase in AUC eight times, but the patients had never been exposed to more than four times the AUC.

DR. BRANCH: If you step back from the question with the therapeutic bounds but you start saying what is the difference between statistically showing that there is an interaction to what is the magnitude of that interaction, and where do you start to place regulatory statements in product label or even approval for the drug staying on the market in terms of the magnitude of change?