DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Tuesday, May 7, 2002

8:30 a.m.

5630 Fishers Lane
Rockville, Maryland

# P A R T I C I P A N T S

Vincent H.L. Lee, Ph.D. , Acting Chair
Kathleen Reedy, R.D.H., M.S., Executive Secretary

MEMBERS:
Gloria L. Anderson, Ph.D., Consumer Representative
Mary J. Berg, Pharm.D.
John Doull, M.D., Ph.D.
Judy P. Boehlert, Ph.D.
William J. Jusko, Ph.D.
Joseph Bloom, Ph.D.
Nair Rodriguez-Hornedo, Ph.D.
Lemuel A. Moye, M.D., Ph.D.
Jurgen Venitz, M.D., Ph.D.
Marvin C. Meyer, Ph.D.
Arthur H. Kibbe, Ph.D.
Patrick P. DeLuca, Ph.D.

GUEST PARTICIPANT:
Ian Wilding, Ph.D.

INDUSTRY REPRESENTATIVES:
Leon Shargel, Ph.D. R.Ph.
Efriam Shek, Ph.D.

INDUSTRY GUEST PARTICIPANTS:
Aziz Karim, Ph.D.
Dr. Jack Cook

SGE PARTICIPANT:
Gordon Amidon, Ph.D.

FDA PARTICIPANTS:
Steven Galson, M.D., M.P.H.
Helen N. Winkle
Ajaz Hussain, M.D.
Larry Lesko, Ph.D.
Ameeta Parekh, Ph.D.
Dale Conner, Pharm.D.
Lawrence Yu, Ph.D.

C O N T E N T S

P R O C E E D I N G S

DR. LEE: Good morning. I am calling this meeting to order. I am Vincent Lee, the acting chair of this committee. It is the Advisory Committee for Pharmaceutical Science. I would like to begin by going around the table and letting the members introduce himself or herself, and we will start with my colleague on my left.

Introductions

DR. ANDERSON: I am Gloria Anderson, Fuller E. Callaway Professor of Chemistry at Morris Brown College in Atlanta.

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

DR. VENITZ: Jurgen Venitz, Virginia Commonwealth University.

DR. MOYE: Lem Moye, University of Texas.

DR. BOEHLERT: Judy Boehlert, consultant to the pharmaceutical industry.

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

DR. SHEK: Efriam Shek, Abbott Laboratories.

DR. SHARGEL: Leon Shargel, Eon Labs

Manufacturing.

DR. WILDING: Ian Wilding, Pharmaceutical Profiles.

DR. KARIM: Aziz Karim, Takeda Pharmaceuticals, in Chicago.

DR. CONNER: Dale Conner, FDA.

DR. GALSON: Steve Galson, FDA.

DR. WINKLE: Helen Winkle, FDA.

DR. HUSSAIN: Ajaz Hussain, FDA.

DR. LESKO: Larry Lesko, clinical pharmacology at FDA.

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

DR. DOULL: John Doull, KU Medical Center.

DR. JUSKO: William Jusko, State University of New York at Buffalo.

DR. DELUCA: Pat DeLuca, University of Kentucky.

DR. MEYER: Marvin Meyer, emeritus professor, University of Tennessee, College of Pharmacy.

DR. KIBBE: Art Kibbe, Wilkes University School of Pharmacy.

MS. REEDY: Kathleen Reedy, FDA.

DR. LEE: Once again, Vincent Lee,

University of Southern California. Let me ask the committee members to raise their hand so everybody knows who is on the committee. Thank you very much. I think the committee is wide awake and ready to go. Kathleen, would you please read the conflict of interest?

Conflict of Interest

MS. REEDY: This is the acknowledgement related to general matters waivers for the Advisory Committee for Pharmaceutical Science for May 7, 2002.

The Food and Drug Administration has prepared general matters waivers for the following special government employees, Drs. Marvin Meyer, Mary Berg, Judy Boehlert, Vincent Lee, Lemuel Moye, Gordon Amidon and Patrick DeLuca which permit their participation in today's meeting of the Advisory Committee for Pharmaceutical Science.

The committee will discuss, one, the current status of, and future plans for the draft FDA guidance entitled guidance for industry, food-effect bioavailability and fed bioequivalence studies: study design, data analysis, and labeling; two, discuss and provide comments on the biopharmaceutics classification system, BCS; and,

three, discuss and provide direction for future subcommittees.

Unlike issues before a committee in which a particular product is discussed, issues of broader applicability, such as the topic of today's meeting, involve many industrial sponsors and academic institutions.

The committee members have been screened for their financial interests as they apply to the general topic at hand. Because general topics impact on so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each member. FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee these potential conflicts are mitigated.

We would also like to note for the record that Drs. Leon Shargel of Eon Labs Manufacturing, Efriam Shek of Abbott Laboratories, Thomas Garcia of Pfizer, Tobias Massa of Eli Lilly & Company, Aziz Karim of Takeda Pharmaceuticals North America and Jack Cook of Pfizer Global Research and Development are participating in this meeting as industry representatives, acting on behalf of

regulated industry. As such, they have not been screened for any conflicts of interest.

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

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

DR. LEE: Thank you, Kathy. Now I would like to call Helen Winkle, Acting Director of OPS, to introduce the meeting.

Introduction to Meeting

DR. WINKLE: Good morning, everyone. It is really nice to see everybody here. I think this is one of the few times everyone has actually been in the room and present because normally we have a lot of people on the telephone. So, it is good to have all our members here.

I want to welcome everyone to the meeting today, and I think this is really going to be a

great opportunity for us to meet with the committee and to discuss what I consider to be a number of really important scientific topics. My job this morning is just basically to give everyone a rundown on the agenda for the next two days, and it is a pretty full agenda but I think there will be a lot of things we can discuss and I think it will be very worthwhile.

Today, Dr. Hussain will introduce the Center's proposal for future subcommittees to this advisory committee. As you all know, Dr. Hussain has oversight for the advisory committee, and has been looking at a variety of ways that we might help in making the committee as effective as possible. I think it is very difficult with running this type of committee that is focused on a variety of issues because you have to have a number of different disciplines in the room to discuss the issues, and sometimes it is not as easy to flesh those issues out for presentation to the main committee. So, I think we have been sort of bouncing around ideas internally in OPS for ways in which we can help the committee members in being able to be better prepared to make recommendations. So, Dr. Hussain will talk about our proposal for

that.

Next, following that discussion, we will discuss two biopharm topics, and Dr. Larry Lesko, who has already introduced himself, from the Office of Clinical Pharmacology and Biopharmaceutics, will lead those discussions. The Office of Clinical Pharmacology and Biopharmaceutics, along with the Office of Generic Drugs, has been sort of grappling with these issues in order to finalize several guidances or to actually, in one case, expand on a guidance. So, we will present those issues today and talk about ways that we can move forward in these two really important areas.

The first issue that we will talk about in the biopharm area is regulatory recommendations on bioequivalence studies under fed conditions. In order to facilitate getting the guidance out we have basically two questions which need to be addressed today. One is regarding the waivers of in vivo fed studies for ANDAs for BCS Class I drugs and drug products, and the second is the confidence intervals and criteria to claim between fasted and fed states of new drugs and between fed states for generic drugs. This is an issue that I think will have a lot of discussion with it, and I look

forward to hearing that. We want to listen basically to what can be added to this scientifically, to get your feel on this and then we will go back and regroup internally, and decide where we need to go with this guidance.

The second topic we want to discuss under the biopharm area is next steps for the biopharmaceutics classification system. The BCS has been discussed here I think on several occasions. Basically, we have a guidance out which is what I would call conservative in those particular products that we allow to come in with waivers under BCS.

So, what we want to do today is talk about expanding the BCS; get your thoughts on the expansion of it, and to get some ideas as far as the next steps for justifying the expansion or extension of BCS. We have already come up against some challenges, and I think we would like to talk about how we can handle these challenges as far as BCS in the future.

There is already some work going on in PQRI, the Product Quality Research Institute, on expanding BCS and we will share a little of that information and discuss whether that research is

actually all that we need to sort of capture where we need to go in our efforts with BCS.

As I said, obviously this is a pretty full day. I mean, I think there will be a lot of discussion around these topics. Then, tomorrow we will have several items on the agenda as well. The first thing we are going to talk about is to give you an update on the process analytical technologies, PAT. You all know that we have a subcommittee that was formed. The subcommittee met for the first time in February. I think it was an extremely good meeting and I think a lot came out of that meeting as far as helping us focus on the whole initiative of PAT. Dr. Tom Layloff, who is chairing the subcommittee, will report on that meeting that was held in February. Then, Dr. Hussain will provide a progress report and describe what the next steps are for PAT. Then, we will appreciate your input into those steps and what your thoughts are as far as where we need to go.

Of course, this is an extremely exciting subcommittee and the issues I think are really good in helping us focus on what we need to do, and the underlying science for the whole initiative.

Also along the same line, at an earlier

meeting last year we discussed some of the general issues related to rapid microbial testing. Tomorrow we will update you on those issues. Then we will discuss whether the PAT program can adequately address the issues relating to the introduction of rapid microbial testing.

After that we will introduce the topic of blend uniformity again. At the last meeting we talked about the PQRI proposal that was coming out on the PQRI research that is being done, and PQRI has now formally submitted that proposal to the agency, and we are finalizing our decision on whether to incorporate their recommendations into our regulatory scheme. So, we will talk a little bit about that final proposal. We still have some questions we need to address as far as that proposal or recommendations and we will discuss that tomorrow as well.

Just to mention one thing along this line, as everyone on the committee knows, we did have a draft guidance that was out on blend uniformity for ANDAs and, because of the fact that we felt that guidance really didn't fit into our current regulatory scheme and with the idea that at least the recommendation from PQRI would stimulate our

thoughts and expand what we believe to be our regulatory position, we have withdrawn the guidance, the draft guidance on blend uniformity. So, that makes it sort of necessary for us to move on getting the new guidance out. So, we would really like to get to our final conclusions with your recommendations today and move forward on that because we have a lot of people who, you know, are sort of waiting to hear what the results of our decision is in this area.

The last item on the agenda tomorrow will be a discussion of regulatory issues related to polymorphism. Basically, I consider this to be an awareness topic, just to seek your input on maybe the direction we need to go in, and then we will plan a more in-depth discussion at a subsequent meeting on polymorphism.

Again, a very full agenda and I look forward to hearing the discussion. I think these are all very, very stimulating scientific topics and it will be very helpful to us as we move ahead in these areas.

There are a number of other topics that will be coming up in future meetings, including a follow-up on DPK. I know you all have been dying

to hear where we are with DPK. I think what we will talk about the next time we discuss this is basically not only DPK, but to look at other possible methods for determining bioequivalence of topical products. I think at the last advisory committee meeting we talked a lot about DPK and felt that it wasn't completely fleshed out, and that probably we did need to expand our focus as we looked at possibilities for determining bioequivalence. So, I don't think DPK is completely off our agenda for the future, but I think that what we want to focus on is other methodology and discuss that with you. I sort of call it a toolbox of methods that you could use for bioequivalence in this area, and I think it will be important for us to discuss these various methods with the committee in the future. We have put out a Federal Register notice--it should come out any day--which will withdraw the draft guidance on DPK.

This is just to touch on future topics, but I would also like to encourage members of the advisory committee to bring possible topics to our attention. I think, obviously, you all are out in the working world every day, dealing with a lot of these scientific issues, and we would be glad to

hear your recommendations for possible things we can discuss before the committee. So, if you do have any suggestions, please feel free to share those with Dr. Hussain and myself or with Dr. Lee.

Last, before I hand over the meeting to Dr. Hussain, I would like to introduce Dr. Steven Galson. Dr. Galson, who is sitting here, on the end, joined the Center last year as the Deputy Director to Dr. Woodcock. We sort of asked him here this morning because we thought it would be helpful to him to meet the committee and get a feel for the types of issues that we do discuss at this meeting. You know, Dr. Galson is already playing a very important role, despite the short time he has been here, in a number of things that are going on in the Center. Mainly he has been what I consider one of the main forces behind risk management implementation. I have asked Steven to say a few words today to sort of introduce himself and some of the things he has focused on, but what I would like to do is bring him back in the future to talk more about risk management. So, before I give it back to Ajaz, I would like to hear from Dr. Galson for a minute.

Comments

DR. GALSON: Good morning, everybody. I am really happy to be here. As you have heard, I have just been with CDER about a year, and I want to start out by really just apologizing that it has taken me a whole year to come and say hello to you as a group. The work of our advisory committees is incredibly important and in the Office of Pharmaceutical Sciences, headed by Helen and Ajaz, we really are on the cutting edge science in how it is applied to drug regulation. Without your advice frequently in the year, telling us what you think about changes that we may be making or other policy issues, we really can't stay on top of cutting edge science nationally and internationally. So, the work that you do is really extremely important and we are very, very grateful for the commitment of your time. We know that you all have lots of other things you could be doing. Also, your commitment to public service. It is really important for the agency and really important for the country to have people like you who are willing to commit to us.

The state of the Center for Drugs is very good. We have an excellent working relationship with the new administration. We have a new Deputy Commissioner, as I think you know, Dr. Lester

Crawford, and we have already been working extremely closely with him and he is very involved in some of our issues, and we have a great relationship.

Also, the state of the Center is very good with regards to Congress and our overall funding. I think many of you heard about the Prescription Drug User Fee Act. We have been working hard to negotiate a proposal to extend our user fees with the drug industry over the last few months, the last year really, and this has concluded very successfully. We have sent a proposal to Capitol Hill which we are hoping they are going to act on expeditiously. What this is really going to do is re-authorize and re-fund the user fee program in a way that will help us use our resources in a way to continue to apply the best science in a rapid way to get drugs on the market and to the American people, having a positive impact on public health. So, we are very positive about that. It is a very important thing going on. It will happen in the next year.

As Helen said, I would really like to come back at a further meeting and talk to you about many of our initiatives in risk management. This

is going to be very important to us, as it is now. Congress and outside groups are very, very interested, some of them quite critical, of how we make decisions about approving drugs and how we make decisions about the degree of risk that we allow in our products and in the way our products are used out there in the real world. So, this is an important initiative and I would like to come back and talk to you about it in general when I can and when there is time on the schedule.

I have been generally assisting Dr. Woodcock in running the Center for about six months. After September 11 Dr. Woodcock stepped down and worked on a detail on emergency preparedness in the Commissioner's office so I was actually running the Center on an active basis for about six months, and I got an incredibly intense introduction to what everybody was doing and I think I have a good understanding of the Center now, and am going back now, focusing on initiatives and helping in the general management.

So, again, I would like to come back later and meet with you more. I will spend a little time here this morning listening to the beginning of your meeting. Again, thank you for all your time

and commitment to being here with us.

DR. LEE: Thank you very much. Dr. Hussain?

## Future Subcommittees

### Introduction and Overview

DR. HUSSAIN: Good morning. At a previous meeting of the Advisory Committee for Pharmaceutical Science we had sort of briefly discussed the need for creating discipline-specific subcommittees under this committee itself. We perceived the need because of the broad scientific disciplines that are under the oversight of OPS. I think we are all familiar with chemistry and biopharmaceutics as the key area but clinical pharmacology is one of the major areas, and I think its importance is increasing tremendously. Also, microbiology. We have a subcommittee on PAT but I think I want to talk to you about other committees that we want to bring under this advisory committee.

The thoughts are to keep the Advisory Committee for Pharmaceutical Science broadly focused and have expertise from various disciplines that we need to address issues in OPS. The subcommittees will then essentially focus on more

detailed discipline-specific topics for discussion.

If I use the example of the PAT subcommittee and what we have learned from that subcommittee, bringing experts with hands-on experience in the areas I think really helps us to identify issues and find solutions quickly and more effectively. In that regard, how do we use the PAT subcommittee? Do we keep the PAT subcommittee or do we do something different?

The proposal that I will just discuss briefly, before I call on Dr. Lesko to talk about the clinical pharmacology subcommittee as an example of the new subcommittee structure that we want to present, is to look at PAT as a new technology area but in a sense it addresses issues in manufacturing. Chemistry manufacturing controls is a major part of review activities within the Center for Drugs. But, at the same time, issues related to GMPs, which are equally important, also need to be addressed.

Currently, for example, the gaps that exist between review and inspection--there is no mechanism to address some of those gaps. Blend uniformity, that you will talk about tomorrow, is one such example. Was blend uniformity a review

issue or was it an inspection issue? I think we will discuss that tomorrow.

But the frustration that we sometimes feel because of the organization structures and different roles and responsibilities, it is not often feasible, or we don't have a mechanism to bring issues which are on the boundaries of these organization structures or disciplines to address them more effectively.

So, the PAT subcommittee right now is focusing on a very specific charter to address process analytical technologies. That committee essentially could sort of be sunset after its initial assignment is over, and be replaced by a manufacturing subcommittee because manufacturing is a general long-term issue and we need a mechanism for addressing issues with respect to GMPs and review in the area of CMC.

We currently don't have any mechanism to have discussion or even analysis of issues that are technical in nature, which are in the area of manufacturing, and how do we do that? So, we are thinking probably that as the PAT subcommittee completes its charter of the assigned task, to sunset that committee and put in the place of that

subcommittee on manufacturing. That will bring the Office of Compliance, Office of Pharmaceutical Science and Office of Regulatory Affairs together. So, essentially it would sort of be a team approach from the FDA to bring issues to the subcommittee related to GMPs, manufacturing and so forth. Most of the time, we hope there will be focus on general technical issues that need to be addressed. This committee could then possibly provide a means for addressing technical issues that are not being addressed today.

One way of looking at the current situation is that the Center for Drugs is responsible for developing policies, especially in the area of chemistry, manufacturing and controls, but the field has to enforce that. We have internal mechanisms to address that but, from the industry perspective, we don't have a way to address technical issues or disputes which are technical in nature. The only solution right now is to issue a 483 or a warning letter. We want to see whether we can have a subcommittee that can be a mechanism to address some of those issues. So, that is sort of an example of what we could do with respect to manufacturing.

Microbiology is a very important discipline. Helen has essentially brought the microbiology review staff to the Office of Pharmaceutical Science level to give them visibility; to give them more recognition in terms of importance; and we are starting to discuss microbiology issues. Would we need a subcommittee on microbiology? I think that is a question that I will leave for now but I think we will have to come back to discuss it.

Clinical pharmacology will be the next committee, which probably will be the first subcommittee we will form under this new umbrella. I will ask Larry Lesko to walk you through his proposal of what he thinks the clinical pharmacology subcommittee would do, and how he feels we can constitute that.

Following that presentation, I request you to sort of have a general discussion on the concept of this, the subcommittee structure which will be focused on disciplines and what subcommittees do you think would be necessary and what we should move forward with. Our current thought is that the next subcommittee we will form will be the clinical pharmacology, followed by manufacturing by

sunsetting PAT and moving that into the manufacturing subcommittee. Pharmacology/toxicology is another idea we have; non-clinical studies subsection. I think how we manage that transition to a more general subcommittee on pharmacology/toxicology will be a subject for discussion later on, and so forth.

So, with that introduction, I will ask Larry to present his talk on clinical pharmacology and then we can have a general discussion on this concept. Larry?

Clinical Pharmacology Subcommittee

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

[Slide]

You should have in front of you two things that are relevant to my remarks this morning. The first is a one-page proposal for a clinical pharmacology subcommittee and the second is a set of slides that I am going to show to walk you through the steps of the formation of this subcommittee.

I like what Dr. Galson said in his introductory remarks. He said that OPS is on the verge of cutting edge science. I think this is

really no more true than in clinical pharmacology where we are seeing many rapid developments that can impact drug development to the regulatory processes, and it is because of this that we feel that there is a need to develop this clinical pharmacology subcommittee.

[Slide]

What we have in mind is a membership that would consist of external recognized and respected experts in the general field of clinical pharmacology. However, we would like to emphasize three specific areas. The first is pharmacometrics, which has certainly been growing rapidly over the last five years; the field of pharmacogenetics and pharmacogenomics, which is an emerging field; and the field of pediatrics.

I want to point out that none of these areas are the sole domain of clinical pharmacology, so we anticipate that any issues that come before the clinical pharmacology subcommittee would be issues that we would work on collaboratively with our medical staff and with our biostatisticians within the Center.

[Slide]

What would be the responsibilities of the

subcommittee? Well, we see this as a committee that would advise and counsel us on a broad range of issues and questions from new and emerging areas of clinical pharmacology, specifically to talk about the science and how we might use it or apply it in specific areas relative to regulatory review of INDs or ANDAs and then, further downstream, how we might integrate this new information into research or into regulatory policies that might take the form of, for example, guidances.

[Slide]

Let's talk about those three areas and explain a little bit more specifically what I mean by those. The first is pharmacometrics. Pharmacometrics encompasses, in our mind, three broad areas. The first is the area of population PK/PD analyses, using samples from clinical trials.

The second is modeling of exposure-response relationships, whether they be broadly speaking dose response or more specifically PK/PD. The third is clinical trial simulation.

What we see as potential applications of this technology and where we would like to go in working with the subcommittee is to develop standardized approaches using each of these

technologies in regulatory decision-making. That is to say, what are the best practices given the current state of knowledge?

Secondly, in particular we are interested in developing a standardized approach to adjusting doses in special populations when we see an increase or decrease in exposure as defined by area under the curve or Cmax.

Third, we would like to apply this knowledge in a more integrated way in the selection of optimal doses for drug approval and, last, to use clinical trial simulation in the design of Phase III trials to try to focus a little bit more on optimized doses.

[Slide]

The second area is very exciting. It is the area of pharmacogenetics and pharmacogenomics. We are quite interested in this area because of the rapid increase in the number of NDAs and INDs that contain this type of information. In our Office we recently conducted an informal survey and found that over fifty applications have this type of information in them. Two-thirds of those applications utilize genetic information from the polymorphic aspects of drug metabolism. Many of

these applications have come about in the last two years, even though our informal survey covered five years.

But some of the things we would like to bring before the committee for discussion include the role of genotyping in the management of risk of previously approved products. We have some very good examples where prospective trials of TPNT polymorphism, for example, has been shown to influence the toxicity of the purine drugs such as 6-mercaptopurine. If you look at the label for those products, there is no indication in the dosage or administration section of the label that a physician should utilize these genotypes, which are now becoming widely available, before prescribing the drug.

Secondly, we are beginning to sense a development of drug-device combinations where approvals are based on the measurement of genetic markers, oftentimes linked to clinical outcome, utilizing pharmacodynamic measures of one sort or another. An example might be the haplotype-dependent receptor polymorphism that has been reported publicly in the literature and on the web page of certain companies.

The third thing we would like to think about in the subcommittee is the study design and analysis of early phase clinical trials. These could be Phase I trials or Phase II trials but basically with the ability to genotype patients as potential entry criteria. It would be worthwhile to talk about enrichment strategies for Phase I and Phase II trials.

[Slide]

This is a slide of a pediatric study decision tree that we developed in the Center with our other disciplines. I am putting it on here to illustrate a framework which we have used in approving drugs for pediatrics under the exclusivity arrangements that we have.

If you look down that tree very carefully you see that many elements of it have to do with clinical pharmacology, whether it is PK studies, whether it is concentration response relationships or PD measurements.

[Slide]

We have been using this as a general framework but it brings us to the next issue, which is the fact that over the past couple of years we have had a huge number of written requests from

sponsors to conduct pediatric trials. As of March 1 of this year, we have had 241 written requests which embodied 568 studies and over 33,000 pediatric patients. That is not to say that all of these studies have been or will be conducted but they represent the intention of sponsors to gain pediatric drug approval.

Where we have seen these types of written requests and, in fact, where we have seen studies conducted, the breakdown of those studies is illustrated on this slide. Notice that efficacy studies represent 34 percent of the studies; safety and PK, 30 percent; safety, 17 percent; and PK/PD, 10 percent. The point is that many of these studies rely upon clinical pharmacology to provide the evidence of efficacy or safety in the pediatric population. We see this across all medical divisions, the exception being imaging where we have had not much activity, and that slide gives you a range from 0-45 in cardiorenal.

Following that, we have had 56 approved active moieties that have been given exclusivity. We have changed about 30 or 40 drug labels with regard to pediatric dosing. But it brings us to the question that we would like to interact with

the subcommittee on, and that is to say what have we learned from all of this?

[Slide]

What we would like to do in the upcoming months is to do a retrospective characterization of this database on pediatrics, and look at the magnitude of age and body size dependence of PK and PD of the studied drugs, compare those to the adult population and check whether our assumptions going into these studies were accurate or whether they need to be refined. We have a tremendous database here that needs to be looked at very critically, and I think we would like to do that and bring the information to the clinical pharmacology subcommittee.

Why would we like to do that? We want to do that because with this experience in hand we could then discuss the general principles that underpin the types of studies that the agency requests for pediatrics, and begin to look at the role of clinical pharmacology studies and whether we should continue with that role or refine it based on the evidence that these studies have provided.

[Slide]

That is the initial charge of the subcommittee. What we would like to do going forward is to nominate a chair and at least one other member from the current advisory committee, the ACPS; constitute this clinical pharmacology subcommittee with no more than nine members. These would be renewable terms of three years. We hope to meet at least once a year for general briefing on these and other issues. However, we would like to also have the ability to consult on more occasions on specific issues that might relate to the areas I just mentioned. Thank you.

Committee Discussion

DR. LEE: Thank you, Larry. Ajaz, shall we take questions now or do you have other subcommittees?

DR. HUSSAIN: Well, I think the discussion, if you could focus specifically on clinical pharmacology but also broadly on the concept of specific subcommittees.

DR. LEE: So, you have no other subcommittees to introduce?

DR. HUSSAIN: No.

DR. LEE: Any questions for Larry? I think Larry has introduced a very important topic.

In fact, maybe I can begin and ask you a question. You identified three topics and those three are pretty diverse, and it would seem unreasonable to have one subcommittee to cover the entire waterfront.

DR. LESKO: We thought about that and, you know, at the core each of these topics we have basic principles of clinical pharmacology relating exposure to response. You know, response can be a genetic marker; it could be a pharmacodynamic measure in a pediatric population; and, of course, pharmacometrics is the tool that we would use to analyze that data. So it is a lot like three overlapping circles and I think they have some commonality to them that will allow us to nominate a strong subcommittee group.

The other aspect of this is that we would like to take, as I mentioned, nine members of the group and try to identify three or four experts in each one of these areas as lead individuals on the subcommittee so that they can take the discussion based on their specific expertise. So, we kind of think the specific expertise of three or more members in a given area, plus the general background of clinical pharmacology would provide

an excellent committee for input.

DR. LEE: Thank you. Dr. Doull, you have comments to make?

DR. DOULL: Yes, I am delighted to see that you are going to deal with the pediatrics problem. What you are really dealing with is the issue of sensitive populations. As I am sure you know, EPA in regard to pesticides, has well as Congress, has simply established a dose factor of ten in the Food Quality Protection Act for pesticides. It would be a disaster, I think, if we were to do that in the drug area. So, this makes much more sense. You are going to use science to decide in which cases you do need, in fact, a protective factor.

But my question is there are lots of other sensitive populations, and how would you deal with those? Add those on? Old folks, diabetics and what-have-you?

DR. LESKO: That is a good point. I think the pediatric population is particularly interesting now because we have so much data in-house that we have gained from the pediatric exclusivity situation. That is not to say our other special populations may not be of interest.

In fact, we are looking at gender, ethnic origin and other intrinsic factors that define special populations in other settings. But that is not to say this committee's purvey wouldn't include a discussion on, for example, exposure response and dose adjustments in those special populations.

I think that is kind of the beauty of the subcommittee. The principles that underlie all these are pretty much the same. How do you bridge data acquired in one setting, for example in an efficacy/safety trial, to a special population whether it be pediatrics, or a population defined by genetics, or a population defined by age or gender. So, I think that is something that we would certainly be open to in the subcommittee. It would depend on the priority and what is going on in other working groups and other committees.

DR. LEE: Dr. Berg?

DR. BERG: Yes, in regards to gender and the special populations, just so I understand, you would be looking at products already on the market as well as new applications? In other words, what we have on the market and then also new ones in the hopper?

DR. LESKO: I think we need to look at

both. We certainly have a database of products that are on the market for which information, for example in pediatrics, has been obtained. Ideally, I think we want to look at this information in a more prospective fashion to learn as we are moving forward and I think treat it as a continual refinement of the paradigm for assessing pediatric information and drug dosing.

DR. BERG: I know just recently FDA received some appropriations for a database for gender--for the globalization through the Office of Women's Health--

DR. LESKO: Right.

DR. BERG: I think that is very good for the new products.

DR. LESKO: Right.

DR. BERG: But looking at the products already out on the market, I know we have been looking at this back in Iowa for about three to four years actually with my students, and literally there still is question with regards to looking at gender analysis and then getting into the question of ethnicity analysis for a database. So, those populations are as sensitive as the pediatric group as well.

DR. LESKO: Yes, a lot of the analyses of databases are focused on the numbers, how many have been in clinical trials, as opposed to the results and what has the result signal in terms of need to look at something differently or reassess the way we interpret the data. So, I would see this initiative as really getting into the data in the population and really analyzing it in a systematic way. We have begun to do this in the Office with some projects that the Center has funded. It is not starting out from scratch but it is starting out with a preliminary assessment of the database that I think will be much more quantitative as we move forward, and then use it in a real-time fashion to provide us feedback on how we are approaching these special populations.

DR. BERG: Yes, this is really good because it gets back to the push for the GO reports in regards to gender analysis that came out last year. In other words, industry has been recruiting women into studies but there hasn't been a separate analysis. I know there was quite a big to-do last summer in regards to the report. So, this really helps to really push that issue for that subgroup analysis.

DR. LESKO: And I think we can go from the specific to the general. I mean, if we look at a class of drugs for which we have had some, say, pediatric approvals or other special populations, what can we say about the class in general so that one might take the next member of that class and perhaps treat it a little bit differently based on what has been learned so far.

DR. BERG: Yes, this is a really great start.

DR. LEE: Any questions from the other side of the table? Jurgen, any comments?

DR. VENITZ: I only want to support that wholeheartedly. I think it is an excellent idea. One of the things I guess I am still unsure about is what is the reporting mechanism in terms of reporting information back from the subcommittee to this committee.

DR. LESKO: I don't know if we have a precedent for this or not but, in my mind, what would happen would be that the chair of the clinical pharmacology subcommittee would report back to this committee at least once a year and if this committee met more often and there was a need, more than once a year. But I think the chair of

this committee will be very important and that would be the connection between the ACPS and the subcommittee.

DR. HUSSAIN: I think that the process would be similar to any other subcommittee. Two members of this committee would be members of the subcommittee and essentially the chair reports back, like, tomorrow Tom Layloff reports back to you for the PAT subcommittee. The subcommittee essentially is advisory to this and decisions essentially are made in this committee.

DR. LEE: It seems to me that this committee is rather proactive. Is that what you have in mind? A rather proactive committee identifying new issues?

DR. LESKO: You know, knowing the members of this community in clinical pharmacology, I expect it will be very proactive and we will be too. We have some issues in mind that we want to start with so I think that is important.

DR. LEE: What about the issue of life style?

DR. LESKO: Well, that is an interesting issue. I haven't thought of it in the context of this particular subcommittee but I am sure you are

leading up to another comment.

DR. LEE: If you have a global community and all this kind of stuff, I think it is very exciting and I will be very interested to see how this subcommittee will evolve because in my estimation it will probably work rather closely with your Office as well. Isn't that true?

DR. LESKO: That is what I expect will happen but, again, there will be other disciplines involved with this as well like, for example, if we start out with the drug safety group there will be multiple disciplines involved.

DR. LEE: Dr. Doull?

DR. DOULL: I think the only thing that still concerns me is that it seems to me that you are going to be right in the middle of the area of risk management in a sense when you deal with sensitive populations, and somehow the decisions that we make in clinical pharmacology are going to have some really broad implications in terms of risk management. I guess somehow one needs to coordinate so that you don't get crosswise in this subcommittee with, say, a policy that affects risk management for the agency as a whole, food and devices and all that.

DR. LESKO: That is a good point. I mean, risk management in the Center, as we think about it, is really not one-dimensional by any means. Any risk management strategy has had multiple dimensions and sometimes is pretty complex.

I think working with Dr. Galson and others at the Center level on various risk management approaches, this is going to be a piece of the puzzle but I think it is an important piece that we need to look at and integrate with other pieces of information. I can see the information being learned from this exercise going on to become part of other risk management plans that are being put in place. Maybe it will lead to a more systematic approach to risk management that I think the Center would like to get to.

DR. GALSON: Just one comment on that, I think that is an excellent point but it shouldn't be a cause of worry really because there isn't any other advisory committee that is working on this particular angle. We do need to put it all together. There aren't any other advisory committees with the expertise of this one that is being discussed that will be dealing with this specific issue. So, we will really count on what

is coming out of this group in figuring out what direction to go in for the whole Center. But coordination is very important.

DR. LEE: Any other comments? Efriam?

DR. SHEK: I have more general comments with regard to the characteristics of the subcommittees. If you take the PAT example, it looks like it was a specific task, an assignment to look at that. Now this committee, it looks like it is a more standing committee which will be a permanent, let's say, subcommittee. The same thing may be for toxicology and safety.

When we bring up the manufacturing the issue is should we consider broadly if that is going to be permanent for the whole area of CMC? I believe we, in industry, realize that CMC is an umbrella. We cannot just look at drug product manufacturing; we have to look at the drug substance; we have to look at the QC. Everything is tied together, and whether we should consider broadening it to CMC type of a subcommittee.

DR. HUSSAIN: That is a good point. What we will plan to do is bring a proposal, like Larry did, on the manufacturing committee and its makeup at the next meeting. The thought process is to not

only discuss CMC from the review side, but bring and invite Office of Compliance and our Office of Regulatory Affairs to be partners with us on that. So, it will be a whole umbrella of all CMC and manufacturing issues in sort of one direction. So, we will flesh out the proposal and bring that to you next time.

DR. LEE: Other comments? Larry, I think you have touched on a topic that is quite interesting so I have another question. What about geriatrics? People like me?

DR. LESKO: You have about ten more years before you worry about that! That was probably the first ever "special population" that the agency looked at back in 1983 or '84, '85, and we do have things in place that direct a sponsor to look at age on the high side, specifically within a clinical trial, along with race and gender.

Again, I am not excluding that from the domain of this subcommittee but I would say at the moment it is not a high priority, based on where we are with other policies in place with respect to the elderly. We usually have a pretty nice assessment of that within the clinical pharmacology database and look at it quite routinely for any

need of dose adjustment.

DR. LEE: Thank you.

DR. MEYER: Would you be more politically correct if you said pediatrics and other special populations?

DR. LESKO: I think that would be a good idea. It would really encompass a lot of the comments that the committee members made and signalled that other things can be brought before the committee. So, I would be in favor of that change, sure.

DR. LEE: Bill?

DR. JUSKO: I have a very strong endorsement of this plan and commend you for doing it. I imagine the committee membership will be somewhat like this one with independent consultants of sorts, as opposed to having representatives of scientific organizations?

DR. LESKO: That is correct. I envision the committee as being one of expertise based on the science and the clinical experience as opposed to organizational dependence, for the reasons that we have indicated the reasons for the subcommittee are.

DR. LEE: Ajaz?

DR. HUSSAIN: The plan is to move forward and actually hold the first meeting of the subcommittee to coincide with the next meeting of this committee. I think Larry has already looked at individuals he wants to be on this committee, and I think after this meeting we will be moving forward, contacting them and actually putting the subcommittee together.

DR. LEE: I am delighted to see this topic on the agenda. I think it is good to have a somewhat formalized system of subcommittees working with this full committee and also with the Office so that there will be tighter integration and continuity and a sense of progressiveness.

Are there other questions before we let Dr. Lesko off the podium? If not, we are doing very well. Thank you, Larry.

DR. LESKO: Thank you.

DR. LEE: Yes?

DR. HUSSAIN: One question would be since the thought process is clinical pharmacology, followed by manufacturing, pharm tox and microbiology are on the tabl, does the committee have any thoughts on what the priority should be with respect to the next few committees? Clinical

pharmacology, we thought, was the highest priority committee to move forward. What do you thing the other priority should be for the rest of the disciplines?

DR. LEE: Shall we turn to the industry representatives?

DR. SHARGEL: I would think manufacturing, from my perspective. I don't know if Efriam would agree.

DR. SHEK: Yes, I think as you raised the thing with regard to compliance and GMP issues, there are a lot of activities going on there.

DR. BOEHLERT: I would agree with the manufacturing, and I also would suggest that you broaden the area to include things like product development because they are all tied together. It is not just manufacturing of a finished product, an active ingredient or the control but product development is definitely tied in, as we found with PAT. That is a very important part of the process.

DR. LEE: Well, it looks like the committee is fairly quiet this morning. We are ahead of schedule. Shall we take a break?

DR. HUSSAIN: Yes, we could and then we can get started with the next part.

DR. LEE: All right. Let's come back at about, shall we say, 9:35? Thank you.

[Brief recess]

DR. LEE: I have been asked about why I didn't get a conversation going before the break because I do know that we have some substantive issues we need to talk about for the rest of the day. Kathy whispered in my ear that she new something about the difference between a subcommittee and a committee, and I thought it would be very useful for us to hear what the regulation has to say.

MS. REEDY: The structure is codified in FACA, the Federal Advisory Committee Act, for subcommittees and their relationship to parent committees and 21 CFR Part 14 delineates the report system, and it is as was described. So, it is codified.

DR. LEE: In other words, we cannot do whatever we want.

[Laughter]

Now we are going to the next agenda item, which is on draft guidance, food effect BE studies. You all have the agenda, and i would like to invite Dale Conner to introduce the topic.

Draft Guidances: Food Effect BE Studies

DR. CONNER: Good morning. First off, before I start I would like to thank Drs. Ian Wilding and Aziz Karim who have graciously come here to help us and the committee out. They are both experts who have worked in this area before, and the committee can call on them for opinions in this particular area and I am sure they will have some interesting things to say, perhaps not all agreeing with me but that is what makes it interesting.

[Slide]

It is my job today to introduce this topic, and then Dr. Ameeta Parekh will do the bulk of the work by actually showing the data and some of the thinking in that regard. I am going to try and give some background on this because one of the issues I found, even among the experts, is when you talk about--most of this topic is about bioequivalence and people often get confused and they sometimes mix up issues that are pertinent to bioavailability to those of bioequivalence. Sometimes the issues and the endpoints in what you are trying to accomplish are quite different. So in the next couple of slides you are going to see

quite a bit of information comparing BA and BE, bioavailability and bioequivalence, and that is mainly to try and introduce those topics to make sure that we keep each one straight and separate.

As my slide says, this is based on discussions of a portion of the new FDA proposed draft guidance. You will note from the slide that this replaces another draft guidance that was out for quite a few years, and has some substantial changes over that original. Larry keeps correcting me but I would say that we have been working on this draft guidance anywhere from about 7 years to 12 years, depending on how you count it. When you look at the guidance you are amazed that it took us so long. However, it has proven to be a very difficult enterprise and has gone to a lot of iterations, but I think that we, at least the authors, are content that this is something that was worthy to go out and be discussed in the public.

That is, indeed, what we did. The draft guidance was issued in October, 2001 and went through a comment period. We received comments back and basically some of the issues we have before you today are based on those comments. We

will talk about what those issues are.

[Slide]

Basically, I have started off by saying why do we do these studies? Why do we do bioavailability studies and why do we do bioequivalence studies, and what is the nature of the studies? Basically, the bioavailability studies are mostly done in NDA type of efforts, IND or NDA. They attempt to be descriptive and to understand how the drug substance and also the drug product, the formulation, behaves; how it is absorbed, over what time course; what factors affect that absorption; and also the interaction of the drug substance with whatever proposed formulation is made. So, the BA part is very much new drugs or an NDA type of question of how does this work. How does the drug behave? And, how do formulations effects affect that knowledge?

When we get to bioequivalence it is somewhat different in that, at least if you look at the way we do generic drugs or pharmaceutically equivalent products, the drug substance is the same. So, the BA part is merely a comparison of two formulations. If it is a generic drug type of situation, an NDA type of situation, the

formulations are pharmaceutically equivalent. So, if you have an immediate release tablet you are comparing it against an immediate release tablet. If it is a solution, it is against a solution. If it is a suppository, it is against a suppository and they contain the exact same amount of drug substance. So, the comparison is entirely on how that formulation performs. That is basically what I have said here.

What we are interested in is, is there a differential effect in this particular case, when we talk about food studies, of food on the formulation compared. That is not the same question you would ask early on in the BA, is there a food effect? It is a question of is the food effect different between the two formulations. So, we are looking either for a differential food effect of a lack of a differential food effect. In other words, are they equivalent in the fed state?

This can be a direct effect of food on the formulations or it can be based on physiologic effects because, as we all know, food has very significant physiologic effects on the GI tract and a number of other systems as well.

So just to keep it in perspective, when we

are talking about BE, and a lot of these issues and discussions that we are going to talk about are more about bioequivalence issues than bioavailability, keep in mind that it is strictly a formulation question or a comparison of two formulations containing the exact same drug substance.

[Slide]

I have expanded the first part into a series of questions, and these might be termed questions either the FDA asked, or a sponsor, or someone who is trying to develop a drug or drug product to answer the questions or points that I brought up originally.

First I am going to go over the BA or the bioavailability. The first one is does the food affect the drug substance? It is really a question of is there some property of that drug substance whose bioavailability or pharmacokinetics is affected by food? That almost says that that effect is going to occur within reason, no matter what formulation I put it in. It is just simply a property of the drug substance.

Furthermore, does food affect the formulation performance? When I use the term

formulation performance, I mean how that formulation--that tablet, that capsule, that suppository, whatever--releases the drug substance into an available state, usually into solution. So, does the food actually affect, in effect, the tablet or the formulation as a delivery system in a way that delivery system works or functions? Sponsors always ask, well, what food effect bioavailability studies should be done in an NDA? How should they be analyzed? Is it simply a descriptive effect with little statistics, or is it actually a rigorous statistical method that should be applied to make, for an NDA, eventual labeling statements? Are the effects statistically significant if I am doing statistics and, furthermore, beyond the statistical part of it, are those effects clinically relevant? So, I may get a statistically significant effect but, you know, does it really mean anything in a clinical sense?

[Slide]

For BE the considerations are somewhat different and in some cases significantly different if you read carefully. Does the food affect the formulation to different extents? Again, we get back to what I said originally. This is looking at

differential effects of two formulations. what we are interested in is perhaps two formulations that are pharmaceutically equivalent and in a fasting state perform exactly the same way but when I give them in the fed state I see a big difference in the way they perform. One is what is dramatically affected by food and the other one perhaps stays the same or goes in the opposite direction.

That is what I am interested in discovering with these studies, are these products equivalent and, therefore, interchangeable when I give them with food? Of course, the sponsors and even FDA reviewers often ask what fed BE studies need to be done to determine this. What strengths need to be studied? Do I need to do every single strength in the product line, or is one strength enough? And, we have ways in our regulations that instruct us on how to do that. How should these studies be analyzed, which is part of the questions we are getting into today, and what are the BE acceptance criteria is another part of the issue that you are going to be talking about today.

[Slide]

Just to briefly discuss, and Ameeta will go into a little bit more detail on what the actual

comments were from the industry, as I said, we put out the draft guidance for public comment. There was a comment period. We received comments from about 13 sources. Currently only 11 of them were submitted in the official accepted way, which is to the docket where all the public can look at them. Two more were sent in e-mails and we are trying to get those people to also submit to the docket as well, which is the proper method. Just as an aside, if any of you do submit comments to any draft guidance, whether this one or any other, please submit them to the docket because that is the proper way, and instructions are usually included with the draft guidance about how to properly submit those.

So, the total number of sources, including two that were not submitted to the docket, are 13. The approximate number of comments was about 130. I say approximately because some of them were text comments and it was very difficult to determine where one comment stopped and the next one began. So, I am saying approximately 130 by our count. It is not 130 different and unique comments. A lot of them were duplicates, either commenting on the same thing or actual identical duplicates of the other.

So, people obviously collaborated and sent in the same comments under different covers. So, there are really not even 130 unique comments.

When we distilled all those down--we actually took a couple of months and read them over very carefully and complied them and what we have come to you today with, based on those comments, is two issues that we felt were very significant to the commentors and very significant to the FDA as far as how the comments came in and the amount of controversy that those particular points raised.

[Slide]

The first of two issues in the draft guidance provide for a waiver of BE studies under fed conditions based on biopharmaceutics classification system. I think you have all probably heard talks in this committee before about what the BCS, the biopharmaceutics classification system, is but I will give a very brief review, and you will hear plenty about that this afternoon, probably as much as you can handle.

Specifically, the guidance tried to allow for the waiver of fed bioequivalence studies for Class I drugs. If you recall, under BCS the Class I status is achieved when a drug substance is

highly soluble, highly permeable and the drug product is rapidly dissolving. So, one has to have all of those three to be granted a waiver of fasting studies under the current final BCS guidance. As I say down below, when these characteristics are proven about a product or a drug substance through scientific studies, then that is suitable for waiver under Class I status.

I think the question comes down to should we also waive fed bioequivalence studies under this same rationale? I mean, if we put the science together that says that we can not only waive the fasting studies but we can also waive for many products the fed studies. My interpretation of this is that a deeper scientific question is when you have a Class I drug that is classified as such, does something that the food does change it into a different category? I think that is the heart of the question really. Do you believe or have any evidence that you would have a Class I drug clearly categorized that you would waive in the fasted state, yet, something about giving it with food changes its characteristics? And, I am talking about the characteristics that I have listed. For example, giving food with a drug substance might

change its permeability or might change its solubility. Or, giving it with that product may slow down the dissolution of the dosage form to such a degree that it could no longer be considered rapidly dissolving. Therefore, effectively it would essentially transfer that into another class which we wouldn't normally waive. I think that is the basic question.

[Slide]

This is a study that I have adapted from a talk that Ajaz gave. I think the question is, well, why is it BCS at all? Why is it so important? I think the justifications are that we have a need to decrease or reduce our reliance on in vivo studies as much as possible. A part of the regulations actually instruct us that no unnecessary human research should be done. So, when we get to the point where the science advances to such a state that we consider those studies unnecessary, then the regulations actually instruct us that we shouldn't be doing them anymore, or that we should find some method of decreasing those in vivo studies.

The additional factor is that, the more in vivo studies you do, the more the time of drug

development is extended and the more time on our part to review those studies as well. So, if good science dictates that those studies are unnecessary and that we can make the same decisions effectively with, say, only in vitro information, then the regulations, common sense and good practice force us to go and actually decrease the number of in vivo studies.

[Slide]

The second issue that came out of the comments, and probably the second significant part of this guidance is a proposed change in how we are going to be analyzing the fed bioequivalence studies. As you may recall, for studies currently that are done in the fed state for bioequivalence the criteria are that the geometric mean of the ratios has to be within 80 to 125. So, there is no real analysis of the variability of the comparison or variability of the products as we do with fasted studies.

So, the second issue of the proposal is to change the criteria for those fed bioequivalence studies to true equivalence criteria, identical to what we do with the fasted studies as well. This approach would also be used for NDAs to say that if

a BA study which is fed against fasted was shown to be not equivalent under this criterion, then it would be labeled as having a food effect.

For the fed BE studies it would say that two formulations are truly interchangeable. It is a scientifically and statistically rigorous approach that we already use in other types of studies, especially the fasting studies, to say that two products are interchangeable or switchable.

So, the questions that I pose under this issue or the questions that I think this distills down to are in two parts. These reflect what the concerns of the commentors were. A good deal of the comments were from industry. The first is, is an equivalence approach desirable? You know, I am guessing, purely guessing that if you went out to physicians or the public patients and said when you switched from, say, a brand name to a generic, do you want to be assured that when you take this with food that it is truly interchangeable? You know, perhaps the naive answer would be yes, of course, I want that. The second question is how much does this cost?

Number one, is it worth it and the second

one is in doing this are we going to be increasing dramatically the number of subjects that are studied and, therefore, not only the number of people exposed in these trials but also the dollar cost of drug development and eventual dollar cost of the product? Again, it is a benefit versus cost type of equation.

I think Ameeta will show you we did a survey of some of the studies, food studies done under ANDAs under current practices and what type of a change we would predict based on the data of studies that were done in the current way. Approximately how many studies would pass under the current power and how many wouldn't need to have an increased power and, therefore, increased subjects? Basically, that is the introduction to the two issues and now I will turn it over to Dr. Ameeta Parekh who will go into a lot more depth and show you some of the data that we have put together to support these issues.

Science Background and Issues

DR. PAREKH: Thanks, Dale. That was a nice comprehensive overview of the different components of the food effect bioavailability and bioequivalence studies guidance.

Since Dale started out with a comment on how long we have worked on this guidance, I would like to add a little bit to it because I have been with this guidance throughout. Just to clarify the history, I think we, as the agency, started looking into these since mid-'80's when theophylline issues surfaced and one of our visitors here, Dr. Aziz Karim, was directly involved in that. Since then, we started looking at the science of food effect studies. I would say that for the last ten, twelve years that Dale mentioned we were discussing the science of food effect bioavailability studies. Specific to the guidance though, we have been looking at the guidance for the last five years. That is a reasonable amount of time but, given the complexities, we are trying to make sure that everything is ironed out.

I would like to take this opportunity to acknowledge the food effect working group who contributed to the development of the guidance, and also several other people who helped in this effort.

[Slide]

I will just start with some background. As Dale mentioned, the draft food effect

bioavailability-bioequivalence studies guidance was published in November of last year and there were public comments that we received. We got comments from 11 sources to the docket but there were two others, as Dale mentioned, that we are trying to get to the docket as well. There was a total of about 130 comments and, as Dale mentioned, several were repetitious. A lot of them were editorial, format type of comments, but there were several that were very good scientific comments and we are looking through these. We have gone through all the comments and we have identified two primary issues that represent a change from our current position. We have taken these two comments for discussion with the advisory committee meeting today.

The advisory committee was presented with a background package that contains these two issues. These two issues were identified in the package, and related to these two issues, we also have a list of questions that we will try to focus on today.

[Slide]

Again, I am going to reiterate something that Dale mentioned already but I think it is

important to make a distinction between the food effect bioavailability and the fed bioequivalence studies here. The reason I think it is very critical is that the rest of the discussion really hinges on this discussion. Just to emphasize, we are not going to discuss the food effect bioavailability part of the guidance today. We are going to stay focused on the two issues that Dale mentioned that are related to the fed bioequivalence studies.

But just to reiterate what the distinctions are, the food effect bioavailability studies, the ones listed on the top, are typically sent with new drug applications, NDAs, and the question here is for companies developing a new product there is one product which is the test product and how does this test product perform under fed conditions as compared to the fasted conditions? When we say "perform" we are really looking for measures of exposure. How is the exposure, the rate and extent, different under fed conditions as compared to the fasted conditions? If there is a difference, how clinically relevant is this difference and how should it be labeled? Basically, as you can sense, the question is that

of prescribability. Typically, we ask this question of all new chemical entities, of all new products, new formulations.

The fed bioequivalence studies, on the other hand, are typically submitted to ANDAs. Here the question is I have two formulations; one is already on the market. Here is an ANDA product that is likely to be switched with this other product. How similar are they under these conditions of use? So, the question here is, is the test product, which is the ANDA product, close enough to the reference product under fed conditions that they could be switched in the patient population? The question here is that of switchability and approval. All modified release formulations for ANDAs typically are expected to do these studies. For immediate release dosage forms, however, whether or not a fed BE study is done, it really is label driven.

The current criteria, as Dale mentioned, for approval of these fed BE studies is hinged on acceptance of ratio within a certain range typically or commonly known as point estimates. So, it is basically the geometric mean ratio of the test and the reference product, called point

estimate, to fall within a certain boundary. In other words, is the test product given under fed conditions within a reasonable distance on average from the reference product given under fed conditions? Note that the acceptance is based on point estimates. The distribution around this is not taken into consideration based on the current criteria.

[Slide]

The two items that I have listed with an asterisk are the two issues that we are going to discuss today. Issue number relates to immediate release dosage forms, are there some types of products that could be classified as BCS Class I drugs and BCS Class I drug products, rapidly dissolving? Could we comfortably say that we could waive those fed BE studies in vivo provided there is in vitro data to support our comfort level on the equivalence of those products? So, basically using similar dissolution profiles as a surrogate for the measure of in vivo fed bioequivalence, and this is not the first time we are approaching this premise. We have done this in the recent past with the fasted BE studies as well. So, here we are trying to extrapolate this to the fed BE studies.

The second issue for discussion, again as Dale mentioned, is implementation of true a statistical equivalence approach and the criteria for the fed bioequivalence studies. As I mentioned earlier, right now we use point estimates and we are considering maybe moving to a more statistical approach of confidence intervals within a certain range, and that is what we currently use for the fasted BE studies.

[Slide]

I will discuss these two issues sequentially. Where possible, I will give a scientific rationale and, where available, I will provide some confirmatory and supportive data. Some justification for waiver of BCS Class I, and Dale has already touched upon that, but the primary supportive data that I am going to provide is from our University of Tennessee studies that were funded by the FDA.

[Slide]

Just to go into the scientific basis for this, and again we are revisiting this; this is nothing new, we use these for the fasted BE studies waiver and we are really extrapolating that to the fed BE situation now. Just to emphasize, the BCS

Class I drugs and drug products are defined as those that are rapidly dissolving across a range of pH's, therefore, the formulation effect is minimized. So, we have kind of negated any formulation effect if there is any. Once dissolved, the belief is that once you take this product it is practically in solution very rapidly. So, in solution the drug substance, with it comes from formulation A or B it is the dug substance, and the drug substance is highly soluble and highly permeable and, therefore, well absorbed.

So, given that there is minimal formulation effect, given that the drug substance, whether it comes from formulation A or B is well absorbed, there are several examples, and Dr. Aziz Karim has published on this, several BCS Class I drugs have no food effect. They are well absorbed. They are pH independent or, I should say, they are similar between the two formulations and generally there are no food effects unless they are high first-pass drugs or if there is some complexation but both of these are drug substance effects rather than the formulation effect. Therefore, the bottom line is if there are two formulations of the same drug that have minimal formulation effect, BCS

Class I drugs, rapidly dissolving drug products, they should be bioequivalent and if, in fact, there is some effect it is probably because of the drug substance and, therefore, we could probably waive fed BE studies for the two products.

[Slide]

To provide some supportive data that we collected from FDA-funded studies at the University of Tennessee, the objective of these studies--there were two studies and the objectives were to investigate the relative bioavailability of two FDA-approved generic products administered under fed conditions. So, the two model drugs that we picked were metoprolol and propranolol. They are BCS Class I and, in fact, metoprolol happens to have high solubility, high permeability boundary but they are, in fact, BCS Class I drugs. The two generic products that we chose for each of these drugs were based on the furthest possible in vitro dissolution. So, we chose the worst possible scenarios that we had for these two formulations for metoprolol and propranolol independently.

[Slide]

I will share some results with you for these bioequivalence studies that we performed

under fed conditions. Metoprolol, 18 subjects. As you can see in the last column, it met the confidence interval. The point estimates were reasonably close, three percent for AUC and seven percent for Cmax. Again, note that metoprolol is highly soluble, highly permeable boundary conditions, and note that both these drugs have an increase in bioavailability with food and that is theorized to be partly due to the high first-pass. So, in spite of this big food effect that we see for propranolol and metoprolol, we used those as the challenge drugs for testing this hypothesis of BCS Class I potential waivers and metoprolol shows that, yes, it could meet bioequivalence.

[Slide]

The same thing was shown for propranolol. Again, propranolol is a high solubility, high permeability drug; much more increase in bioavailability with food. When I say increase in bioavailability wit food, I am talking about fed-fasted comparison and also again for point estimated differences, two percent on average; five percent on average for EC and Cmax.

[Slide]

Just for completeness, I will show the

hydrochloric acid. I forgot to mention that. The propranolol that was used was from a combination product, propranolol hydrochlorothiazide. The consideration here is that there was no interaction; there is no pharmacokinetic interaction of propranolol with hydrochlorothiazide. We thought this would be a challenge to propranolol using a drug that doesn't have high solubility, high permeability in combination with propranolol. So, we used a combination product for the test of propranolol as the model for BCS Class I. So just for completion I am showing you the hydrochlorothiazide data as well. You can see that met bioequivalence as well.

[Slide]

Conclusion: Formulation factors are likely to play a minor role in the bioavailability determination of BCS Class I rapidly dissolving drug products. Studies with metoprolol and propranolol, which are BCS Class I rapidly dissolving drug products, demonstrated bioequivalence under fed conditions and, therefore, the data supports the BCS-based recommendation for the waiver of fed BE studies.

[Slide]

I will move on to the next issue, issue number two, again reiterating what Dale had mentioned, that this is basically saying we are going to try and see if a different approach, implementation of a true statistical equivalence approach for fed BE studies would be a better approach to go with the fed BE assessment. Right now, as I mentioned, we go with the point estimates for the ratio of the test and the reference, geometric mean ratios of the test and the reference. Here we are proposing the same criteria that we used for the fasted BE studies, namely, 90 percent confidence intervals for the test and the reference, log transformed ratio to fall within a range which is 80 to 125. This is both for AUC as well as Cmax. With this approach, the question I think we need to ask ourselves--

DR. MOYE: Excuse me. I am sorry to interrupt. I have to ask a question just to make sure I understand what this is about. Can you go back for a second, please? When you talk about the criteria for the 90 percent confidence interval, are you saying that the entire confidence interval has to fall within the 80-125? Overlapping is not sufficient? It must lie completely within?

DR. PAREKH: Right. So, it is a bioequivalence approach and we use the same for the fasted BE studies.

DR. MOYE: Thank you. Sorry to interrupt.

DR. PAREKH: Does that mean I can start talking?

[Laughter]

[Slide]

All right, the question is what is the purpose of these fed BE studies, and it depends on what your answer is. If your answer is to assure interchangeability of two formulations, and I snuck in another question, how certain do you need to be? then the answer is right there. This is nothing new. We have used these for fasted BE studies. If your answer is, yes, we want to be sure that they are interchangeable products under fed conditions, then we already have these criteria in place. So, the regulated criteria for the BE studies right now for interchangeability assessment is 90 percent confidence intervals for the ratio of population geometric means for the test and the reference treatments to fall within 80 to 125.

[Slide]

But every good thing I guess comes with a

price. So the next question relates to what is the price for this, and are these criteria likely to increase the regulatory burden? We are concerned about that too. So, what we did was, rather than just putting it in place, we thought let's go and see what it means if people will consider these criteria for fed BE studies.

So we went back and did a retrospective analysis for the ANDA database that we had. It is a partial analysis. We took a subset of 40 ANDAs. I just counted and I think there were about five that were repetition drugs; 35 were independent drugs. We looked at the fed-fed BE aspect of these ANDAs that were turned in and reviewed in the Office of Generic Drugs.

So, we looked at the fed BE studies. Remember, these studies right now are not powered for meeting the confidence interval criteria. That is an important thing to keep in mind. Right now the criteria, as I mentioned earlier, is point estimates to fall within a range. With that, we did consider are we looking at a biased piece of data and we thought not really because these studies are not powered for confidence intervals. These are really just assessment of point estimates

being close enough. So we thought let's go back and recalculate the 90 percent confidence intervals on these fed-fed BE studies. So, we did that with 40 ANDAs.

[Slide]

This slide summarizes the results of this small pilot retrospective analysis that we conducted. Of the 40 ANDAs, as shown in this pie chart, 35 passed the confidence interval. So you could say 87.5 percent of this small subset made it in spite of the fact that these were not powered for confidence intervals. There is a small subset that didn't make it and, again, keep in mind that these studies were not prospectively powered for confidence intervals.

For those five ANDAs that failed to meet the 90 percent confidence interval, it doesn't necessarily mean that they were not bioequivalent if they were powered right. If you look at the numbers on the top, that represents the confidence intervals for all of those five that didn't make it. But a small subset did not make the confidence interval criteria. However, it was a small subset and, keep in mind, these studies were not powered. Of the five, there were two that failed on AUC and

there were three that failed to meet the confidence intervals on Cmax.

[Slide]

In conclusion, if the current criteria for fed bioequivalence studies, which is point estimate, were to be changed to confidence intervals a retrospective analysis of the existing data suggests that for most studies no increase in number of subjects would be necessary, however, there will be a small subset that may need a larger sample size.

With that, I want to summarize and say that there are situations where in vitro dissolution comparisons could suffice or could serve as an acceptable surrogate for in vivo bioequivalence studies, the case being BCS Class I rapidly dissolving drug products. A waiver for in vivo bioequivalence studies, in this case fed conditions, could be considered. However, when the studies are conducted, depending on what the question is, if the question is what is the purpose of these studies, the fed BE studies--is the purpose to address a switchability question, then if so, we need to address the appropriate statistical criteria in that situation. Thanks.

DR. LEE: Thank you very much, Ameeta. There are two questions put before us, and I have asked Marvin Meyer to digest this information and provide us with some perspective. Before we start, since we have plenty of time, what is the definition of food? This is a half-serious question.

DR. PAREKH: That definition of food took us the first twelve years.

DR. LEE: I see.

[Laughter]

DR. PAREKH: We went through a lot of scientific discussion trying to debate what is food. There were papers that said there is no such thing as the right meal. You could be eating something; I could be eating something totally different. Rather than addressing it as a social question, we thought we could address it as what is the regulatory question here. The regulatory question is what happens when I take a drug with meals. Given all the physiology of food effects--gastric emptying time, cholecystokinin, all those things, bile acids, pH changes--we went through a lot of literature. We went through the examples that were tested for theophylline which

were bench-marking the meals that could be discriminating. We thought let's take a meal that would represent the worst case scenario for maximum perturbation of the gut, and let's use that as the meal. The meal that was chosen was similar to the meal that was shown to be discriminatory in those early theophylline studies.

DR. LEE: So, we are asked to think about food that way. Also, I suppose we should think about the subject not as pediatrics or geriatrics but the average population in age. Right?

DR. PAREKH: That is right.

DR. LEE: And also think about Class I drugs as the average of that range. Right? So, these are the boundary conditions. I am beginning to complicate matters.

DR. HUSSAIN: Yes, I am not sure. With respect to bioequivalence, we have always tried to have sort of a general population to study that. The issue essentially is making sure in vivo that the release of the drug from the product is essentially similar. So, that is the question we are asking. With respect to special populations, I think that is more a bioavailability question, not a bioequivalence question. So, if we can keep

those two separate.

DR. LEE: Thank you.

DR. CONNER: Just an aside, the meal was very high in fat, the meal that Ameeta was talking about. After a lot of discussion and a lot of research, they came up with a very high fat meal. Now, if you go to different places in the world or even in the United States, that is not necessarily a representative breakfast, hopefully, that most people eat. If they do, their arteries are going to be in very bad shape after a few years. So, in another country, that country may have chosen to do a much more representative meal. For instance, I have reviewed some ANDA food studies for Japan where they took a typical Japanese breakfast which was much, much different than what we are talking about here. It is interesting to look at those side by side. However, we chose something that would have the highest likelihood of being a challenge to the dosage form and the drug substance.

DR. LEE: Okay, I wanted to make sure we understand it because now we are looking at version two and pretty soon we will be working on version three.

DR. HUSSAIN: I think in terms of standardization, the question you raised also goes to the standardization of the meal because this is a quality assurance type of a test. We went to the commercial sources that provide this reproducibly.

DR. PAREKH: Yes, we went and picked up things from little fast food places. I remember a few years back Hank Malinowski took a group and we tried out the meal. It is a big meal. I could handle it!

[Laughter]

Just to get to specifics, Dr. Lee, the meal that is defined in the draft guidance is about 800-1000 calories, and we specify the meal as an example meal but 150, 250 and about 500 calories from protein, carbohydrate and fat. You don't have to stick to a certain meal in terms of the components as long as the fat, carbohydrate and protein are similar or close to this, because this is what has been tested in the literature to cause the maximum perturbation. So, we want to know what is the worst case scenario and so go with the meal that represents the worst case scenario.

DR. LEE: Very well. Thank you very much. I want to remind the committee that we have two

consultants, at the other end of the table, to collaborate with. Yes?

DR. ANDERSON: On page two of the handout you have something about similar dissolution profiles. Would you comment on how close the dissolution profiles have to be in order to qualify for this?

DR. HUSSAIN: In terms of the fasting study where the BCS guidance was first used, the rapid dissolution is defined in terms of a time limit in terms of the rate of dissolution. It has to essentially dissolve within 30 minutes, and it has to dissolve in a pH range of, say, 1 to 6.8 and three different pH conditions. The similarity is that it has to be within about 10 percent. The two profiles should be within plus/minus 10 percent; it is an approximate similarity.

DR. ANDERSON: Plus or minus, yes.

DR. LEE: Thank you. We do have two questions in front of us. We need to answer these questions and if there is time we can go into other questions. Marv?

DR. MEYER: I have a question of your presentation before I get to that, and then I want to make a comment before I get to that. You have

40 ANDAs that you sampled. Out of how many possible does the 40 represent, and were they a mix of IR and modified release? Thirdly, do you have a recollection of what the point estimates were for the five drugs that failed?

DR. PAREKH: I am glad I got up early this morning and checked that. Yes, it was a mix of IR and MR. We didn't select ANDAs based on a certain thing; we just took 40 and there were IR and there were MR. The ones that represent not making the confidence intervals are a mix of IR and MR. So, it is not just all MR or IR. For AUC, there was one that was as high as 151. The point estimate was about 20 off, so 1.2, 120. The other one was also close. It was 118 or somewhere in that range. You can see from the width that that is where it would be.

DR. MEYER: So, one could argue that of the five failures, the Cmax failures all could have been taken care of by a few more subjects, and maybe the AUC failures, the 120 and the 118 really shouldn't be approved anyway.

DR. CONNER: You know, in looking at that, and obviously I have the ability to know which applies to which product, but I actually just

looked at the overall and I had the same reaction. You know, when Ameeta and I were going over the results I looked at those five and I said, well, the Cmax, some more subjects, we didn't go through the exercise of calculating how many more subjects would have been required although it is perfectly reasonable to be able to do that. But when I looked at the AUCs I said, oh, these don't look so very good to me because the point estimates, although we don't have them on the slide, are obviously pretty far out. I mean, they are within the 80 to 125 but they are like about 120 or in that range. I don't have the exact numbers. So, I think that simply adding power to that, although theoretically if you added enough power it might squeak by, it is pretty unlikely that adding a reasonable number of subjects to that study would get those to pass the confidence intervals.

The open question still is do we really feel comfortable approving those? Now, it is important to say for the record that we are not in any way saying that what we have done in the past or what we are currently doing with the point estimates, that there is anything wrong with that. I don't want anyone to conclude that there is a

real hazard here. I think we have had some good experience with that. Doing it this way hasn't really created any clinical problems that we are aware of. Our attempt here is, I would say, just to tighten things up and to make a more rigorous equivalence evaluation rather than, you know, what is kind of a "feel good" type of approach but a more rigorous type of approach in what we are doing with point estimates. So, I don't think that what we have been doing in the past is wrong; I think this is just better.

DR. MEYER: One point of order, Vince. We have two invited guests and I think a couple of other speakers on this topic. I always wonder why we don't hear from those people before we deliberate.

DR. LEE: Because once they start talking--

[Laughter]

--but I am sure that they will interject at the appropriate time.

DR. MOYE: One advantage of moving away from just using the point estimate is that you really don't know what the operational characteristics of it are. You have historical

information. Sometimes historical information can be very leading and sometimes it can be misleading.

If I understand this process correctly, the way it currently is now, and please tell me if I am wrong and I apologize for interrupting you earlier but I was in imminent danger of being badly and irreversibly confused so I really needed to stop and ask you--the way it currently is now, a sponsor will carry out a research effort and come up with an effect size, a point estimate. Even though there is a standard error associated with that and even though the standard error is available, that standard error is set aside and the question is simply asked whether that point estimate is greater than 0.8 or less than 1.25. The suggestion is to replace that with the confidence interval of 90 percent and ask whether the 0.8 to 1.25 range completely encompasses and encloses the 90 percent confidence interval. That is correct?

I am not really sure why we need to go through this two-step process, the first step to compute the confidence interval and then, the second step, decide whether the confidence interval falls completely within 0.8 to 1.25. It seems to

me in order to determine how well that is going to work, again holding historical information aside, it is kind of a complex computation to ask about where the range of a confidence interval is going to fall. So why not, as an alternative, just ask the question how likely is it that the population ratio will fall between 0.8 and 1.25 given the point estimate and given the standard error? That is a fairly easy computation to do, and you can set a value for that probability. That probability must be above some value, and for that the computation is much more direct and, hopefully, much more interpretable.

DR. CONNER: It is important to point out that this is not a new method, which is what we are talking about, which is the two one-sided test procedure to determine equivalence. That is something that we have been doing for quite a few years for fasted studies. If you are saying that this, when applied to food studies, may not be totally understood I don't agree with you but I take that criticism. But as far as the properties of this calculation, the properties of the statistics, we understand those very well. We have been doing them for perhaps ten or twelve years

now, I think, on fasting studies.

DR. MOYE: There are two statistics here I think. Are you talking about the one that just uses the point estimate and asks whether that is between 0.8 and 1.25? Is that the one you are talking about?

DR. CONNER: No, no--

DR. MOYE: Or are you talking about the 90 percent CI?

DR. CONNER: The fasting studies are done in exactly the way we are proposing to now do fed studies. It was developed by Dr. Sherman and others, the two one-sided test procedure. In other words, what the test essentially does is run two one-sided tests, one in one direction and the other in the other, you know, one test one bound and the other test the other bound. They are run at the alpha equals 0.05 level. So, we have 0.05 on one side--

DR. MOYE: Right.

DR. CONNER: --and 0.05 on the other. So, the way of actually doing all this in one test, one calculation, is to calculate the 90 percent confidence interval so you get the 5 on one side and 5 on the other, and each one of those has to be

what we have determined to be a clinically significant difference. The actual operation of this, for the most part the point estimates of fasting studies, when we have done similar types of surveys, for the vast majority of the products we approve based on the fasting results the point estimates don't vary by more than about 4 percent either way from a ratio of 1. We have a few isolated cases where we have as much as 10 or 12 percent, but most of them cluster right around the ratio of 1, plus/minus 4 percent for both Cmax and AUC. So, the operational characteristics of controlling that point estimate, the experimental point estimate are actually quite good.

DR. MOYE: It sounds like the answer to my question is that this is a procedure that has been well established--

DR. CONNER: Yes.

DR. MOYE: --and has been used in other analyses looking at bioavailability for fed and fasting. Is that right?

DR. CONNER: It is used somewhat in the NDA world but primarily this is used to determine the equivalence or switchability of two pharmaceutically equivalent products. So, the drug

substance, the amount of drug substance, the type of dosage, all that is held constant and most of the studies we do are crossover so, you know, each individual gets both products. And, we want to make sure that in the end the judgment we make and the generic product we approve, if someone goes into their pharmacy and they are currently taking, say, the brand name, if the doctor switches them to this other pharmaceutically equivalent dosage form they will be getting essentially the same results without any distinguishable difference.

DR. LEE: So, you are answering question 2.3, what alternative approaches?

DR. MOYE: If you say so.

DR. CONNER: As an aside, I am not sure we should get much into it today, but if you have suggestions on how we might do this whole thing better--I mean, what we are doing now is simply expanding what we have done for many years to this. If you have some other, you know, just general comments that you might have a better method, perhaps another forum might be the time.

DR. MOYE: Well, I wouldn't say it is better at this point; I just say it is an alternative and it may be simpler.

DR. LEE: Do you have slides?

DR. MOYE: Not right now but I can prepare them.

DR. LEE: All right. Since the two consultants were mentioned, maybe I will just take the opportunity to see if they have anything to say.

DR. KARIM: You mentioned about food effect. I have been talking about food effect for the last thirty years, and one of the most usual and common questions asked is we never have this type of meal so why does FDA do a food effect study? The question here is it is not really the sort of food you would be taking every day. It is really performance of a dosage form under conditions which would produce maximal perturbation of the formulation. So, it is really a quality control test of your formulation, and that is the food which would produce the maximum effect. So, it is not the usual food you take but it is quality control type of food.

The second point I want to make is that, in fact, it is correct that I have found that drugs which belong to Class I do not show food effect response in terms of AUC, and in drug development

the very first study in humans that we do is a food effect study because if there is no food effect response, then we are able to categorize our drug as a Class I drug which, I think, is a new approach of food effect response. We use it a great deal in drug research.

One thing which I still feel hasn't been covered is that food will produce, even for Class I drugs, delay in absorption because 50 g of fat will result in stomach emptying time, and if you have a drug which is specifically used for very fast onset of action--an analgesic, antiarrhythmic--you will miss the point because the Tmax is not used in bioequivalency assessment. So, I think the agency needs to look at that before saying that the Class I drugs would not require food effect response because the question of Tmax has not been addressed, what is the effect of a given meal or of food on Tmax.

The third point I want to make is that if a drug or formulation is labeled to be taken with food, and if that is how patients take the drug, then it is obvious that the bioequivalency must be shown under fed conditions. I have said that again and again. We should use all the statistical

criteria used under fasting state to apply to the fed state.

I am surprised that the bioequivalency was shown in even 17 to 18 subjects with food because when you give the drug with food you are adding another variable, and that is gastric emptying time. I would be very interested to see whether in a crossover situation the gastric emptying time under fed condition is similar or not. I know under fasting state they are very similar, but I would have expected under fed conditions the gastric emptying time to vary more, and I would have expected that we would need quite a few more subjects to do bioequivalency testing. Thanks.

DR. LEE: Thank you.

DR. MEYER: Can I ask Aziz a question?

DR. WILDING: Can I pick up first because we do a lot of work actually visualizing what fat does to gastric emptying properties in formulation performance. It is certainly true that the current high fat meal as put into regulatory guidance has a maximum effect on the GI tract. That is, it effectively stops the stomach for a couple of hours in most individuals. The reality is that if you put that amount of fat into the stomach, it takes a

while to realize that it has that large amount of material to deal with and actually sits still for a period of time.

What you have to recognize also is that today's population eats less fat than the previous populations. Therefore, what was maximal for them is probably now super-maximal for today's individuals. That is an issue that is worth contemplating. So, I think what we see often is an effect on Tmax associated with significant delays in gastric emptying.

Now, the question is, is the CV percent greater in terms of intra-variability fed compared to fasted? Certainly, in our experience there will be no difference between those two that will be noticeable from statistical comparison purposes. Now, unlike Aziz, I don't think that Tmax is an issue because it is a bioequivalence issue or switchability, not prescribability. Therefore, I don't think in this context I could imagine where there will be a Tmax difference associated with a Class I drug that would lead to issues in that particular regard.

My final comment, food effects are a generic phrase and we do run risks with the phrase

food effects because it is, in many respects, an active pharmaceutical ingredient issue, a formulation issue, and there is the combination of the API, the formulation and the food. That is where I think, as Ameeta indicated, it is bioavailability in terms of API alone, formulation alone, but there is also a bioequivalence/bioavailability issue that kicks in when you are contemplating active forms of ingredients of the formulation and drug together, and that is the hardest one to tease out.

DR. LEE: Thank you.

DR. MEYER: Aziz, you were talking about Class I and saying you have not personally seen any differences in bioequivalence under fed conditions. You said AUC. How about Cmax?

DR. KARIM: Yes, what I do is we take AUC ratio fed/fasting and if they fall within 10 or 20 percent we categorize it as Class I drug. Now, Cmax I haven't looked at in that detail, but I would say probably it won't be as rigid as AUC.

DR. HUSSAIN: Let me sort of go to the issue of Tmax that Aziz raised, and so forth, and let me go through the thought process of the BCS in the fasting state. One of the reasons we designed

or devised rapid dissolution criteria for the fasting state was because of unpredictability of the gastric residence time and the rapid emptying that occurs under the fasting state, and there were concerns with volume and you will see that in the afternoon discussion also.

In fact, the 30 minutes that we have as rapid dissolution criteria was for fasting state. That is overly conservative for a fed state. Although we are not suggesting we change that, we don't believe there will be Tmax differences because of formulation effects. There will definitely be a shift in Tmax because of the gastric emptying time. But if you are going to retain the dosage form in the stomach, which is essentially a reservoir, for a long period of time, then you are giving far more time for dissolution to become peak before it gets emptied out. So, it is less of a concern under the fed condition. We were more sensitive and more conservative in the fasting state.

So, that is the reason dissolution-release in vivo under fed conditions, because of the large volume and because of the long gastric residence time, is less of a concern. So, I think our

proposal will be far more conservative for the fed state.

DR. MEYER: Ready?

DR. LEE: Yes.

DR. MEYER: The questions at hand then are posted there, as well as in the handout we received from Kathleen Reedy on April 22. The questions are really broken into two sections. To what extent can we waive fed bioequivalence studies for Class I drug? Then, secondly, should confidence intervals be applied to fed studies?

The first question then, can we waive fed bioequivalence studies for Class I drugs which, of course, are highly soluble, very rapidly dissolving and highly permeable?

One question I have, that will come up again this afternoon, is the definition of high permeability. Is propranolol really highly permeable? It is fine to do an intestinal intubation but then what other kinds of measurements can be made? My recollection is that propranolol is not 90 percent systemically available; large first-pass effect. How do we measure high permeability if all we have is bio data? I have no problem with the definition of

high permeability if it is 90 percent excreted unchanged in the urine or the AUC relative to IV doses is 90 percent. Beyond that, it becomes a little more arbitrary. I see Ajaz is shaking his head.

DR. HUSSAIN: No. The BCS guidance that was issued in September of 2000 actually went through and described several methodologies to assess permeability. It also includes a method based on in vitro and HeLa cell culture methods, PK studies, extent of absorption. So, you have a whole host or toolkit for assessing permeability.

You are absolutely right, metoprolol and propranolol are both high first-pass effect drugs. If I am not mistaken, the absolute bioavailability of propranolol is 35 percent but its extent of absorption is actually complete and that is the basis for the high permeability class membership. That is the reason we selected propranolol for the challenge studies that we did at the University of Tennessee. The reason is it is so sensitive to food effect. In fact, there is a study from an Australian hospital--I am not able to quote the reference of that, but you can actually induce fed effect studies of propranolol by just smelling

food; not even eating it. So, that is how sensitive propranolol is to food effects.

DR. LESKO: I will address the same question and remind us that the propranolol and metoprolol were two of the drugs that we had in our initial database that defined the BCS. That means the permeability of these drugs was established in human volunteers through intubation of the small intestine. Thus, we have very accurate, gold standard type permeability on those two drugs as opposed to circumstantial data which might have come from CACO 2 or bioavailability studies.

As Ajaz said, the reason we picked those two recent studies in Tennessee on fed effects is because we had established previously their membership in the class. Propranolol is highly permeable in terms of passing through the gut wall. Metoprolol was picked because it was more of a borderline between Class I and some other classes based on its permeability characteristics. But they both succeeded in those two studies.

DR. LEE: Larry, are you saying that it has taken the metabolism into account, the permeability?

DR. LESKO: Well, we have to separate two

things, absorption from the lumen of the intestinal tract and the bioavailability. The permeability refers to the passage of the drug from the lumen of the intestinal tract into the blood stream. So, it is talking about transversing that border. After it transverses that border there may be some first-pass effects in the liver that will reduce the bioavailability. So, when we talk about permeability we are thinking about absorption as opposed to bioavailability. So, you could have a drug with good absorption characteristics but relatively low bioavailability if the reduction in bioavailability is related to a first-pass effect, say, in the liver.

DR. LEE: I think that maybe what Marv was alluding to is the metabolism during passage across the gut wall.

DR. LESKO: Well, if it is a 3A4 substrate that is being metabolized in that passage it still has permeated that segment of the wall, as indicated by its high permeability.

DR. HUSSAIN: One other way of looking at permeability is that it is essentially the ability of the drug to leave the aqueous compartment that is in contact with the epithelium and get into the

cell. Essentially, when we went to the BCS, as Larry said, we distinguished between transport and then subsequent metabolism.

DR. MEYER: Personally, I think I would feel if the regulation said a product that is 90 percent bioavailable relative to IV or maybe even an oral solution, that is something I can hang my hat on and I don't have to worry about gut wall metabolism or metabolism prior to reaching the gut wall. Short of intestinal intubation, let's say, the generic industry--I doubt very many of them are going to do intubation type studies to establish permeability, and CACO 2 and those other surrogates haven't been totally proven, I don't think.

DR. HUSSAIN: I think we have.

DR. MEYER: Have you?

DR. HUSSAIN: Yes. I think those are established.

DR. MEYER: Given that then, to what extent does the committee feel that in-house data, which I take it are partially propranolol and metoprolol--

DR. HUSSAIN: I think the challenge studies that we did in Tennessee were two products, one metoprolol alone; one containing propranolol

and hydrochlorothiazide. Hydrochlorothiazide is not a highly permeable drug. So, that was an additional challenge that we had. So, those were prospective studies designed to challenge the system, and we selected two generic products to have a head-to-head comparison. We didn't have such data before because we have looked at historical data that we have in-house and made that conclusion, and we wanted to truly challenge that.

DR. LEE: I think the question is very simple, you know, Class I and Class II and so forth, fed state, fasting. I think we all understood that. But I guess Marv was thinking about exceptions. He was thinking beyond the current definition and is not comfortable with the risk.

DR. VENITZ: To follow-up on something, Dale, that you mentioned, is there any evidence to suggest that for the Class I and non-Class I drugs there is a differential food effect between the formulations? Because you alluded to the fact that it is unlikely, and I guess based on my understanding of BCS I would agree with that, but do you have any experimental evidence to the contrary?

DR. CONNER: I am not sure I was trying to imply that it was unlikely. I think that is a question for you.

DR. VENITZ: Right.

DR. CONNER: You know, how likely you think it is. I posed the question because it seemed to me that the critical thing is do we have any examples, or do we realistically believe that one exists that when we gave a product that was rated as Class I that it would behave differently, that it would behave like it was another class which we wouldn't ordinarily waive? So, I will give you some theoretical examples, and I can't come up with any examples to say the food got in there and this would affect both the formulations equally, but if something in the food complexed with the drug substance and actually formed, say, a permanent or semi-permanent complexation which didn't have the solubility or, more likely, didn't have the permeability that the original drug substance had, I mean, then your resultant effect would be that it wouldn't be permeable anymore; it wouldn't have the bioavailability that it started out with if something in the food complexed with it.

DR. VENITZ: But it would be a bioavailability not a bioequivalence issue. Right?

DR. CONNER: Yes, but it would then mean though that this BCS system that we designed would technically no longer apply to it. It would not necessarily then result in bioinequivalence. It would take it out of the realm of the BCS system into another class and, therefore, even though we would think the likelihood that there would be bioequivalence would not necessarily increase, we would then, based on our BCS system, have to do an in vivo test to confirm that. But the likelihood of a differential effect on the drug substance is small, very small but it would still take it out of the realm of BCS.

DR. HUSSAIN: Let me sort of add to that. I think when we were going through this development we had extensive discussion on this. I said I want to have a formulation that would behave differently than the other one. For immediate release formulations it is very difficult to come up with an example, but since Dale raised the issue of complexation, how can I formulate two products, one which will have food effect and one which may not have food effect? If I use complexation as a

mechanism, then I could include in one of the formulations a chelating agent, sodium EDTA for example, and that could be a trigger for saying, if its a metal complex, you are essentially binding the available metal, and so forth.

But those are sort of theoretical assessments and we haven't seen any real examples that actually could be achieved. When we look at a waiver, we also look at the excipients and so forth. So, actually in a BCS waiver we go through an analysis of excipients, and so forth. So, that would sort of come up and be covered under that. So.

DR. VENITZ: So, it is correct for me to assume that you haven't seen any evidence either in-house or in the public literature that a Class I drug shows a differential food effect?

DR. HUSSAIN: We couldn't find any evidence of that.

DR. LESKO: I think I want to qualify that a bit though because in trying to find those kind of differences you described there are two obstacles. One is that frequently you can't identify the BCS class, say, in a new drug application based on the data submitted. So, the

best we can work on is a suspicion of what the class would be because the company had no reason necessarily to define the solubility at all pH's to measure permeability. So, when we looked at that question to look for the exceptions, we were flying a little bit blind by not knowing for sure whether these were Class I drugs. So, there is that aspect.

On the ANDA side, we are sort of a captive audience to what is being submitted to the Office so there are things that may be out there that we don't see or aren't aware of. That may address your question. But recognizing those two limitations, I guess the answer would be no, we don't have any direct knowledge of exceptions.

DR. LEE: There is another question about the issue about the mechanism of absorption as well. What if a drug falls in Class I because of an affinity for whatever transport might be in place in the gut?

DR. HUSSAIN: With respect to the fasting study, the mechanism of absorption I think came into consideration with respect to the methods of permeability. For example, there is no restriction that a carrier-mediated transport of an active

transport mechanism would preclude a drug from being a Class I or a highly permeable drug. But the methodology used to assess permeability then has to be looked at more carefully. For example, in the BCS guidance use of CACO 2 or in vitro, essentially we don't recommend using those for actively transported drugs, and so forth. So, that is how we managed that process.

DR. VENITZ: But don't you also have a restriction on dose proportionality--

DR. HUSSAIN: Yes. Dose linearity was one of the mechanisms to address some of that question.

DR. LEE: Other comments from the committee? Yes, Judy?

DR. BOEHLERT: I have a question coming back to the dissolution profile when you said it could be plus/minus ten percent. If bioequivalence were waived and then the manufacturers were relying on dissolution to show equivalence and if, indeed, they had test and reference products that were at the extremes of that range and one was plus ten and the other was minus ten, are there any data to say there would be clinical relevancy to that difference?

DR. HUSSAIN: I think we looked at that

quite extensively, and for Class I drugs we don't think there is a reason to believe that. If we were looking at only one pH condition, then I would not be confident with that. That is the reason we request multiple pH conditions. The reason for not relying on one pH condition is, for example, a wheat base. If you just do the dissolution in 0.1 normal HCL that may not truly be reflective or discriminating under, say, a less acidic condition, and so forth. That is the reason we went with multiple pH conditions.

DR. BOEHLERT: Would that imply that the product would be continually tested at those multiple pH conditions, or would you refer it just to the 0.1 normal HCL and would that be enough to show a difference in physical properties?

DR. HUSSAIN: The multiple pH conditions come into play when there is a request for a waiver or there is a substantial formulation change under, say, the SUPAC. For routine quality control or quality assurance you will have the traditional classification.

DR. LESKO: I just want to clarify that a bit. With the Class I drugs, when you talk about dissolution it is possible to have a single time

point. In other words, if the products dissolve within 15 minutes, 85 percent, then we will look at that and say they are the same because that is such a trivial difference. On the other hand, if the dissolution goes to 30 minutes, we then would look at a profile and what we are looking at is basically two profiles, a test product and a reference product. The statistics that are used to differentiate those are called the F-2 statistic. The reality is that to have an F-2 of 50 or greater, which is "passing," you need to have very similar profiles and they can differ by no more than ten percent between the test and the reference. So, you really can't have ten on this side or ten on that side. It is really comparing the two profiles. Generally the differences that cause something to not pass an F-2 statistic occur very early on, say, in the first five minutes or first ten minutes where, clinically speaking, I doubt that they are important but we do have that standard in place to look at that.

DR. LEE: Bill?

DR. JUSKO: I am in strong agreement with the theoretical and practical arguments pertaining to the Class I type of drugs in relation to

bioequivalence, but I don't have a very good feeling for the extent of literature that confirms these observations. There were early review articles and now I am hearing that it is rather difficult to determine permeability of these compounds so it is uncertain with a new chemical entity exactly what its permeability is so as to be able to preclassify it in this group.

Is there any better evidence for numbers of drugs that have been evaluated to find that there is no problem with bioavailability or bioequivalence for Class I compounds?

DR. HUSSAIN: I think the hesitation to say a drug is Class I and Class II has sort of regulatory implications, in a sense. Unless we follow the guidelines that we have provided to classify we hesitate to say this is Class I and Class II. But, clearly, we have a sense of what the likelihood is, and based on that, I think Ameeta did an internal survey and I think Aziz has published extensively on that too. So, maybe they can comment on that. So.

DR. KARIM: I think I agree with the theoretical background that if you have a Class I drug, in vitro dissolution specially F-2 tests

would be appropriate, and you don't even have to do the food effect study. But, believe me, I feel that determining permeability has not been established, and that is a big issue. I mean, you talk about absolute bioavailability of 90 percent. For how many drugs do we have absolute bioavailability or 90 percent? Very few. So, to me, the major unknown is permeability. I think to measure solubility is very easy. To measure dissolution is also reasonable. That is why I use the food effect response as a way of classifying whether the drug is Class I or not and it works very well.

So, to answer your question, if you have a Class I drug and truly establish that it is a Class I drug, then I think I am all in favor ofthe guidance that you don't need to do a bio study.

DR. HUSSAIN: Again, I would respectfully disagree with that in a sense because folks who are familiar with CACO 2 and other methodologies, and so forth, are very confident of their method. So, our position essentially is that in vitro methods are acceptable under certain conditions once you have established method suitability, and so forth. And, just relying on a food effect study to

classify a drug was not an acceptable method in our guidance. The reason is that permeability is based on extent of absorption and you do see food effect for highly soluble, highly permeable drugs that have a high first-pass effect, and those are the two drugs we selected for the study. So, that is sort of our position.

DR. LEE: I think we are caught in a circular argument. My sense is that question 1.1 is premature. Yes?

DR. SHEK: Just one comment, looking at the way the question is being phrased--

DR. LEE: Yes?

DR. SHEK: --it talks about bioequivalence about ANDAs. It doesn't say anything about the existing labeling for the reference, whether that indicates it might be a Class I and indicates specifically food effect. Will that be taken into consideration, or how is that going to be handled? I don't know how many of those 40 ANDAs have something in the labeling about food effect. And, if we don't do the study will the labeling be changed?

DR. CONNER: Well, I can tell you our current policy for what triggers us to ask an ANDA

sponsor for a fed bioequivalence study, and you have to differentiate between a food effect study which asks if there is a food effect on the product or the drug substance versus a fed bioequivalence study where the two products are compared under equivalent or the same fed conditions. The trigger that causes us to ask for a fed bioequivalence study is some mention of food in the innovator labeling, the reference listed drug labeling. People are often confused by saying, well, so it has to be some positive food effect; there is a change. Simply saying, you know, in the labeling we have studied it and there isn't any is enough to cause us to ask an ANDA sponsor for a fed bioequivalence study. So, almost any reasonable mention at the current time of food in the labeling will cause us to ask for a fed bioequivalence determination of an ANDA sponsor. I think that is actually in this guidance. This question simply says, okay, we have gone there; we have determined that we need some kind of decision or determination of fed bioequivalence studies but, further, if it is a Class I drug we could still waive the necessity for that in vivo study based on what we have just described here and discussed. So, that

is basically our current policy and how we hope or have proposed it to evolve in the this guidance.

DR. MEYER: I think we have to remember though that permeability is drug specific. It has nothing to do with the formulation. So, even if we are off a bit in our permeability assessment, the key measurements to me are the solubility that is fairly rigorous, that is fairly reasonably defined, the highest dose in a certain volume; dissolution over a range of pH's, which I think is excellent; and very rapid dissolution for Class I drugs.

So, given that scenario, I feel comfortable, I think, with the Class I waiver. Going beyond that I feel much less comfortable. So, I think there is a lot of rationale here. If you don't like what they are presenting, how are they going to fix it is really the 1.2 question. What additional data and what types of experiments, what does the committee need to see next time in order to say, well, they are right?

DR. LEE: Yes, Larry?

DR. LESKO: I want to get back to the discussion of the permeability issue because it is one that is already established in our guidance. In other words, we can now, today, allow a sponsor

to identify a drug as a Class I drug based on solubility and permeability in a way that we have indicated in the BCS guidance which came out in 2000. So, I think we have established some standards already on how to define permeability, and we can probably better not go back and debate that today but the question is, given that standard, can we then extrapolate it to the fed state?

Now, behind that standard, when we put the 2000 guidance out on the BCS for fasting studies there was a fairly extensive database of 30 drugs in which we actually measured permeability, extent of absorption, and then correlated the two. That then was built into the guidance in that a company would standardize their CACO 2's using internal controls that represent those drugs in that database. So, there was a continual linkage of human data to CACO 2 and to the other circumstantial evidence such as extent of absorption that gave reliability to characterizing something as permeability.

I am not sure how we can do much better with permeability, other than do human studies all the time. But we did get to the point, and we did

present to the committee here, the ACPS, the fasting BCS guidance and the standards we were going to use for permeability, and that has been in place now for a year and a half. So, I just want to remind people that we are not crossing new ground with this permeability definition.

DR. LEE: Art?

DR. KIBBE: Just a couple of things, and I love being a devil's advocate so I will probably raise some issues. But to start with, when drugs are marketed, in the labeling they usually have indications as to whether to take them with food or without food. If you have a drug on the market that is clearly indicated to take without food, then the question in my mind is why do we care about a food study if patients are told not to take it with food anyhow? If they follow the instructions, and if their physician and clinician get them to do it correctly, they are not going to even introduce that variable. So, if you have a Class I drug whose labeling from the innovator says take it without food, or take it on an empty stomach, it is almost a moot question to try to look for the other.

The second, what we are saying in effect

by waiving food studies for Class I drugs is that we cannot imagine a formulator formulating something where a formulation would interact with food differently than any other formulation, and I am not prepared to say that. So, I don't know how I respond to that situation because the classification is all about the active ingredient, and the interaction that we care about when we do a bioequivalence study is not about the active ingredient; it is about the formulation. So, at that point I am saying, well, as long as you use spray dry lactose for your direct compressible I don't care if you do a fed study because lactose dissolves so fast that it is out of the way and leaves the drug behind. But if you use a directly compressible product made out of the chick bean grown in Upper Uganda I don't like it. mean, that whole road is kind of difficult for me.

DR. HUSSAIN: Just to add to that, that is the reason why a waiver is limited to immediate release dosage forms, not even suggesting it is for modified release. In fact, Ameeta kept mentioning theophylline and the dose dumping situations that we have with theophylline were for modified release only. So, we are talking about immediate release

dosage forms that dissolve rapidly under different pH conditions. The focus is on formulation similarity from that respective. So, you are talking about pharmaceutical equivalence. You are looking at an excipient database of an acceptable set of excipients and then you are looking at similarity and dissolution as a function of the pH.

DR. KIBBE: So, what you are saying is that I could use starch 1500 as a directly compressible excipient, and the agency says it is exactly the same as lactose.

DR. HUSSAIN: No, we are not saying that the excipients are the same. The excipients could be different but as long as the product dissolves in a comparatively similar profile under different pH conditions that should be okay. In fact, I will turn that around. I say, all right, now you have a direct compression tablet, say, based on dicalcium phosphate. All right? Then you have a formulation based on starch lactose. So, if you look at it, the dose would still be pharmaceutically equal and they have very different sort of pH behavior. Dicalcium phosphate tends to be fairly highly soluble at pH 1 but the solubility goes down at pH 2, and so forth. So, a product containing that

will not have a similar dissolution profile as that of starch or lactose based formulation. So, actually dissolution is far more discriminating under those conditions for a formulation difference than in vivo. In fact, my concern is that I think the dissolution that we are recommending is far more conservative for the fed state.

DR. KIBBE: What you are saying is that the generic which has that is going to have to prove that there is no food effect because a dissolution study isn't going to be similar.

DR. HUSSAIN: Unfortunately, yes.

DR. WILDING: I would like to echo Ajaz' comments. I mean, that is the key here in the sense that if those two formulations are rapidly dissolving and meet the current requirements under the BCS guidance, then given the fact that they are going to be extended in their residence time in the stomach and they have longer to dissolve in vivo, it is a very conservative approach that we are taking in this particular regard. I think as was indicated by one of your colleagues, if we go outside Class I it is a whole new ball park. In the context of Class I, I think given we have an acceptance of in vitro bioequivalence for Class I

compounds taking it into the fed domain is actually not a big leap of faith.

DR. MEYER: Could I ask just one question? In all the comments that you received, did anyone cite an example that said, well--I like Ajaz' approach of if there are two formulations and I have all the wealth at my command I can make whatever formulations I want, can I make two that will dissolve in 15 minutes; will have similar dissolution profiles but will have a pronounced different food effect? Did anyone comment with an example?

DR. PAREKH: No.

DR. MEYER: So, we are dealing with a fear of the hypothetical or a fear of the unknown, and the only way to prove the unknown is to do everything which is going to be very expensive.

DR. LESKO: But related to that, there is prior information that we can go back to. When we did the original research with the BCS we did make formulations designed specifically to be far apart in their dissolution profile, huge differences in dissolution, probably more so than you would expect to see even with food and fasting. Those dissolution differences for the Class I drugs did

not translate into bioinequivalence in in vivo studies. They were very close to being superimposable in essence.

So, we know that. I mean, that is prior information. We have that document not only for the model drugs, in this case propranolol and metoprolol, but some other drugs as well. I think that is useful information as background to have with regard to differences in dissolution for Class I drugs and what it means in vivo for bioequivalence.

I also want to comment on Dr. Kibbe's comment, and maybe Dale can confirm it but I believe if the label says "take on an empty stomach" there is no food effect for an ANDA because, you are right, patients aren't going to take it that way. Is that correct, Dale?

DR. CONNER: Yes. I think that is supported by the language in this guidance. However, if you read a lot of labeling, you know, you expect these definitive statements which really aren't there. I mean, a lot of times that type of statement which you mentioned will say, we recommend--you know, I am not literally translating, we recommend that you kind of take

this with food, leaving the option open to the physician or the patient to say, well, you know, I don't really want to take it with food, or sometimes I want to take it with food and sometimes not. As long as you leave discretion open to the clinician or to the patient you don't have a definite "must take with food." So, I would say that if the labeling is very strong, the instruction saying "do not take this with food," or "take only on an empty stomach," then I agree with you, that should kick into place. But if it is very wishy-washy, giving discretion to the clinician or the patient I would say we have no guarantee that they are not going to instruct the patient, you know, if it will upset your stomach take it with food, or don't.

DR. LEE: I think we do need to move on.

DR. HUSSAIN: One point that has not been made and I just want to make is that in terms of bioequivalence studies, the fasting studies are far more discriminating than the fed studies. That has been our position. So, if we waive a fasting study it is logical that we would waive a fed study. So, we are actually caught in a logical bind here because when we put the BCS guidance together we

went for the most difficult part and left the easier part, in my opinion, behind. So, there is an inconsistency in our approach with BCS.

DR. LEE: Yes, I think this is the conclusion I want to draw. I am glad that you said it, and I think on that basis we should move on. Sometimes you don't have data in the literature because it can never be published.

The question then is what other additional evidence will you need to make yourself feel better? I think that has to be on a case by case basis. It depends on the mechanism, complexation and all that kind of stuff. Isn't that true?

DR. DOULL: Wasn't that Marv's suggestion? The question of what additional information would you need, the question is what do you really need to know versus what would be nice to know. The need to know would be additional Class I drugs. You know, we really only have the two just to prove this hypothesis. So, the question is how much more information do you really need in order to be comfortable with accepting that all Class I drugs should not meet that food criteria?

DR. LEE: More sponsor studies.

DR. DOULL: More drugs, information on

more drugs.

DR. HUSSAIN: I am not sure. Let me sort of summarize. The question is are we willing to agree or make a recommendation that with the guidance, as it is in the draft form right now, we can move ahead and make the recommendation that the waiver for food effect bioequivalence studies for Class I rapidly dissolving drugs is okay. That is the question.

DR. KARIM: Just to comment, who puts the rubber stamp that this is a Class I drug?

DR. HUSSAIN: It is a review decision. So, FDA.

DR. MEYER: Do we need to come to a consensus?

DR. LEE: Well, I don't think we need to come to a consensus. I think what is important is for the agency to hear what our individual collective thoughts are. Some issues may not ever come to consensus. It has taken them about seven years to--

DR. LESKO: That was the debate about food. But to answer Dr. Karim's question, the specific review division that is looking at the application makes that decision, but a lot of those

decisions are discussed within the BCS technical committee as well. So, it is really a collective, joint decision between the Office of Generic Drugs and the Office of Clinical Pharmacology.

DR. MEYER: In case my individual opinion then wasn't heard, I am in favor of the proposal.

DR. LEE: So, what about question number two, the confidence intervals?

DR. SHARGEL: I have a question on that, if I may, Vince. My understanding from the agency, as you mentioned, Dr. Conner, is the question of clinical risk. In the past we have only done point estimates. From what I understand, the desire for confidence intervals is to have a more rigorous test. If we use a more rigorous test, the data showed that five studies out of 40 failed. Those would not have been approved on the basis of the new guidance if it were formalized.

DR. CONNER: Basically, presumably if you knew the new criteria you would have done those studies all properly powered. You know, I am looking at them again not with a lot of in-depth analysis of those particular studies and probably three of them with somewhat more power would have likely passed. Two of them would have had a great

deal of difficulty and would probably have failed no matter what the power. But we can't definitely say that. It just looks like to me that the ones that had such extreme AUC values, I am not really sure power would have helped those if the criteria were changed.

As you know, when you change the criteria people then adapt to the change and design their studies accordingly with, hopefully, appropriate power calculations. I actually found this even a little surprising, that so many from a randomly selected group like this would have passed using the power that people use to power for point estimates. I was pleasantly surprised. I expected it to be a small difference but the results of the group we picked surprised me. I would have expected a few more to be on the edge but I was pleasantly surprised when we actually looked at the values.

DR. SHARGEL: May I just continue on this a little bit because I am just curious in terms of if there is no risk, clinical risk, what the basis is for a more rigorous test. What we are doing is we are using a meal that gives maximal perturbation, as has been mentioned, and this would

give the largest variability to be observed on Cmax and AUC. Generally in the labeling it would say food effects of the drug but it never really specifically says what kind of food, so that any sort of diet--I prefer a bagel and cream cheese in the morning; that is my preference--we would know if there is a clinical effect of the food. If there is a clinical effect, then you would say take it without food, in the development of the product if there is a big effect in the bioavailability study. Or, if there is reason to take it with food, we already require the 90 percent confidence interval. So, my question here really is, is the requirement here really necessary to have a more rigorous test? And, what does it mean if we fail in terms of safety risk?

DR. CONNER: Well, there are a great many products that are labeled out there with simply a descriptive statement of a food effect and, in some cases, how much, the estimate of how much. It doesn't mean that those are unusable products. It doesn't mean that they are automatically restricted from taking with food. A lot of it is in that area of concern where I think the firm and the division that is reviewing it at FDA feel that it is

important to let clinicians know about that. But, based on the labeling, the physician can still use that drug under those conditions as long as that effect is known.

Granted, although there is some variance in the type of meals that people do for NDAs, I think in most modern NDAs we have a very similar meal used. In fact, part of what this guidance does is to bring the ANDA meal and the NDA meal to be the same thing. So, basically what we are saying is, no matter what other food studies are done, the NDA will have a determination of the effect on bioavailability with a virtually identical meal. So, I mean, that will be part of the NDA and part of the labeling.

I think from a statistical standpoint, this is really just saying that, you know, we are doing a test here. The meal that we have chosen, as has been said before--you know, we can't really test every conceivable meal. I don't think the generic industry would want to go in for that kind of thing, doing 30 different meals and 30 different studies. So, if we only have one study to do, the meal that we have chosen I think has the most likelihood of being extreme and causing an effect.

So, if we don't see an effect under those conditions, we are reasonably confident that lesser meals or meals that are less stressful to the dosage form are going to have any effect. I mean, if you only have one chance you use the maximum possibility to obtain an effect.

From a statistical standpoint, we would like at the end of the day to say that these are equivalent, that a generic is equivalent to the reference listed drug under reasonable conditions of us. You know, what we have been doing for many years is good but it hasn't really been a true equivalence statement, based on a true statement of equivalence. And, what we are trying to do here is perhaps improve that somewhat so that we can with total confidence say that these two are equivalent under reasonable conditions of use.

DR. LEE: Jurgen?

DR. VENITZ: I would like to follow-up on that because I am still trying to understand what it is that you are exactly proposing. You are saying for any non-Class I drug, regardless of the label of the reference drug, a generic has to show fasting and fed bioequivalence?

DR. CONNER: No, that is not what we are

saying at all. We are saying that based on the label of the reference listed drug, should that label contain any statement about a food effect and most, if not all, of the modern drugs that were recently approved, within the last few years, will have some type of statement about food effect. If you look at, you know, twenty years ago, NDAs or products that are still out, a lot of them didn't do food studies or they didn't think it was worth putting in the labeling, and so forth, a statement about food in those old products may be totally absent. Those would not trigger us to ask for a food study. But any statement of a food effect in the reference listed drug labeling will trigger a question about whether it is bioequivalent in the fed state as well. And, based on the type of product or the type of drug substance we are proposing dealing with it in different ways. You know, if it is a Class I drug we will deal with, you know, what the first part of the discussion was. If it is not a Class I, then we will do a food study, which we would do today. The only question is how should we power that study, and how should we analyze it, and what kind of conclusion can we come up with based on that approach.

DR. VENITZ: So, as long as there is any statement but it says there is no food effect, then the official bioequivalence for the fed state--

DR. CONNER: Yes.

DR. VENITZ: --or if there is a food effect.

DR. CONNER: I can tell you during the five, seven, twelve years, whatever, we went through a lot of discussion, a lot of proposals to perhaps not make it such a label-based trigger for having food considerations. We looked at a lot of information on whether the original effect was drug substance related, formulation related and so forth, the assumption being, well, if we can absolutely prove it is drug substance food effect it is going to be the same for a generic versus not. We went through a lot of this and had some proposals to do that, but we finally figured out that 99 percent of the time we don't know or are unable to determine. So, we seldom, if ever, have the data to answer it and we would end up doing food studies virtually for everything anyway.

DR. VENITZ: But the consequence then of having done a generic fed study and having failed that study would be the generic would not be

approved or you would relabel?

DR. CONNER: No, the generic would not be approved without a passing study. But that is true today. I mean, with the criteria that we are looking at today, and really the major change here is not doing more studies but simply how we are doing the studies that the generic sponsor would do anyway.

DR. VENITZ: And how would that compare to the NDA route?

DR. CONNER: I mean, what we are talking about here is a bioequivalence study, which is one of the few studies that is done to get a generic product on the market. The NDA has literally sometimes hundreds of studies of different types, many of them bioavailability, a lot of them clinical studies, studies on a lot of aspects of the drug substance and drug product and how it performs clinically. With a generic you essentially have anywhere from one to perhaps three or four, at the maximum, small in vivo studies to be able to make the decision to approve that and put it on the market.

DR. VENITZ: But in terms of assessing a food effect you would use the same approach

basically?

DR. CONNER: We are not assessing a food effect.

DR. VENITZ: No, I understand, but I am saying if you are in an NDA situation so you are not talking about generic bioequivalence and you want to assess the food effect you would use the same approach?

DR. CONNER: A very similar one.

DR. PAREKH: But the final decision is not that of non-approval for NDAs. The final decision is if you fall within this window you can say in the label that there is no food effect.

DR. LEE: Let's come back to question number two. Art?

DR. KIBBE: Just to go down another wonderful side path, you decided to limit the waiving of a food study to an immediate release because you can get good dissolution data that would overlap on immediate release, as well as the fact that the Class I drug is highly soluble, and what-have-you. But if I make a sustained release product out of a Class I drug and someone else does and we have clearly overlapping dissolution data, and the criteria that we are looking at clearly is

the effect of food on dosage form, is there evidence that there will be a problem with food when you have delayed release products?

DR. HUSSAIN: I think to answer that question, if I look at the example of theophylline controlled release, modified release, the mechanism for dose dumping there was different. Jerry Skelly and others have actually done in vitro work that actually showed that could be predicted. But our confidence in in vitro is not at that level at this point to go in that direction. So.

DR. KIBBE: If it is not an effect on the drug moiety itself, the active ingredient, then it is a matter of how confident you are in the formulations being truly similar even if they give the same dissolution profiles.

DR. HUSSAIN: The question is can you rely on in vitro dissolution to understand the complex mechanisms. Our answer is no, not at this time.

DR. LEE: Marv?

DR. MEYER: I tried to jot down the reasons why not to use confidence limits. One, no one takes drugs with a meal of any type. Well, that is obviously not true and since we don't know what type let's use the worst condition, confidence

limits are not a valid measurement of bioequivalence. I think if they are good enough for fasted, they are good enough for fed. Highly variable drugs will pose a problem, and if they somehow scrape by fasted they may not scrape by fed. Well, that is an economic issue and that is a statistical issue and it may be that we need to change the stats for both fed and fasted to somehow capture a point estimate and the variability of the reference relative to the test, or vice versa but that is a side issue. Too many failures. Well, we have shown here that about five out of 40 would fail marginally. With a proper designed study they wouldn't. There would be like two or three out of 40. It would cost too much money; too many subjects. We would have to again change our statistics. I think FDA can't worry about public health in the context of a $50,000 or $10,000 bioequivalence studies that some sponsor may have to conduct. Numbers of subjects, we are still only talking 30, 40 subjects. So, I think the reasons why not to have confidence limits aren't substantiated, and I have always felt that if fasted need confidence limits, then fed need confidence limits.

DR. LEE: Other points of opinion?

DR. MOYE: I guess I should say on the record that at the conclusion of this session I will turn over a synopsis of an alternative analysis that would avoid the indirect approach of confidence intervals, and would allow one to now include this measure of variability that has been excluded from the analyses.

DR. LEE: So you will have this synopsis as food for thought.

DR. MOYE: As an admissible alternative.

DR. PAREKH: This is just for the record, Dr. Meyer, you asked a question earlier about the point estimates. For the two products that failed on AUC the point estimates were 1.22 and 1.20. For the three that didn't make it on Cmax, it was 0.86, 0.87 and 0.88.

DR. LEE: Are you satisfied?

DR. MEYER: Yes.

DR. LEE: Are there any other ideas or suggestions, opinions? If not, thank you very much. That concludes the agenda item on food effect of BE studies. Now we are into the public hearing. We have three submissions. The first two cannot make it here, and we do have the last person

here, Russ Rackley. For the record, I have asked Kathy to read the first two, and you all have that in your notes.

Open Public Hearing

MS. REEDY: Yes, the right side of your red folder has your agenda, your questions and the open public hearing submissions in writing. On the left side are the slides that were submitted in advance. For the slides that were not submitted in advance, they may show up at the time of their presentation.

But for the open public hearing, the first submission is from Brian Kearney, senior scientist, clinical pharmacology, Gilead Sciences.

Guidance for industry food effect bioavailability and fed bioequivalence studies, commentary on the following issues is not currently included in the draft guidance and FDA Pharmaceutical Advisory Committee perspectives would be much appreciate. One, please comment on the acceptability/utility of parallel study designs and/or secondary statistical analyses of PK data, collected across studies, to evaluate food effects. For example, could pharmacokinetic data derived from fed studies in later stage PK studies b

compared to fasted, reference data from a previous, formal crossover food effect study?

Two, while single dose studies are preferred as they are the most sensitive to food bioavailability effects, please comment on the role and acceptability of steady state comparisons for compounds with a short elimination half-life and/or with predictable, reproducible PK profiles. Those are Brian's comments.

The next is David Fox, writing to present the views of Abbott Laboratories on a matter scheduled for discussion at the upcoming meeting of the Food and Drug Administration's Advisory Committee for Pharmacologic Science on May 7th and 8th, 2002.

Specifically, we wish to comment on the draft guidance document titled, "Food Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis and Labeling." We ask that the committee carefully consider our written submission in the course of its deliberations.

The food effect guidance recognizes that foods and beverages often have a clinically significant effect on the bioavailability of an active drug ingredient or on the bioequivalence of

two different formulations of the same active ingredient. Food effect guidance at 2. A growing number of drug products now bear labeling that describes a significant food effect, a trend which Abbott believes is good for patients. Food effect labeling contributes to consistent and more accurate dosing and can help patients adopt a routine set of conditions under which they take their medicines.

Second, the food effect guidance recognizes the need for bioequivalence studies under fed conditions, particularly where the reference of the pioneer product bears food effect labeling. Food effect guidance at 4.

Food effects may be formulation specific, and two different versions of the same drug may react differently in the presence of food. In fact, two products may react differently depending on the quantity or type of food used. And, he uses a reference discussing an example of two products, each with the same active ingredient and dosage form that had clinically significant bioavailability differences depending on whether the drugs were taken with chocolate milk, apple juice or orange juice. For these reasons, the

guidance endorses the need for well-controlled and well-designed fed bioequivalence studies where the reference product has a noted food effect. Food effect guidance at 3, noting that the mechanism by which food may affect bioavailability is often unknown and cannot be determined by physical inspection of in vitro study.

Abbott agrees and compliments the agency for recognizing these points. Abbott's concern,however, is that the agency has not gone far enough to address the variable bioavailability seen by many drugs under different meal conditions, nor has the agency taken steps to ensure that bioequivalence studies performed by applicants under abbreviated new drug applications follow the same meal conditions used in the study of the reference drug product. Instead, the agency recommends only the use of a high-fat, high-calorie test meal to provide the greatest effects on gastrointestinal physiology so that systemic drug availability is maximally affected, food effect guidance at 6.

For a product with a known sensitivity to food, the agency's approach in many instances is likely to mask or obliterate important formulation

differences. The better approach, we suggest, is to require fed bioequivalence studies under the meal conditions suggested in the labeling or, if the labeling is not specific, under the meal conditions likely to be followed by patients who use the drug. Alternatively, the sponsor of a bioequivalence study should follow the meal conditions that were used to support the efficacy of the reference drug product. Patients on a low-fat diet who are instructed to take their medications with meals should be assured that a generic substitute will behave the same under low-fat conditions as the pioneer.

Finally, while the food effect guidance allows for the use of other test meals, food effect guidance at 7, the guidance puts the decision within the discretion of the sponsor. It is the generic drug sponsor's choice, for example, to conduct a bioequivalence study with a test meal other than the maximum 50 percent fat meal described introduction he guidance. Abbott disagrees with this approach. The guidance must recommend the use of a test meal that closely reflects the labeled conditions of use or the conditions under which the reference drug was

studied. In fact, by allowing the sponsor to select the test meal, FDA invites the real risk that the sponsor may use food selection to drive or optimize the showing of bioequivalence.

In short, the agency's thinking on the need for bioequivalence studies is pointed in the right direction but, at this stage, is too general. For products that are food-sensitive, it may be impossible to know in advance whether the product will behave in a linear or predictable way under different meal conditions. Simply comparing two products under fasting and high-fat conditions may be insufficient, especially when the drug is labeled for us under low-fat or other dietary conditions. Food effects are not yes/no propositions. Far too little is known about food effects for FDA to assume the use of one type of meal for all drug products.

For these reasons, we respectfully request that the committee consider three related points. The first, the need for fed bioequivalence studies under conditions other than the maximum 50 percent fat meal described in the food effect guidance. Secondly, the need for fed bioequivalence studies under the conditions of use recommended or

described in the labeling; and, thirdly, the need for fed bioequivalence studies that follow the same study design used in the clinical testing of the pioneer product. We greatly appreciate your attention to this issue.

DR. LEE: Thank you very much, Kathy, for reading it, and I don't think we can ask any questions because the presenter is not here. So, next I would like to invite Dr. Rackley, from Mylan Laboratories to give a ten-minute presentation. He is going to be speaking on behalf of the Generic Pharmaceutical Association.

DR. RACKLEY: Thank you. It is an honor to be here to speak before you today on behalf of the Generic Pharmaceutical Association.

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ANDAs have been approved and marketed since around 1985 with no documented safety issues. The demonstrated safety and wide acceptance of these products by the general public are indicative of the robustness and adequacy of the current approval process. We propose that the current system for the evaluation of bioequivalent drug products be maintained.

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For current fasting bioequivalency studies this represents a standard bioavailability comparison of test and reference drug products. Ninety percent confidence intervals are well accepted as demonstration of bioequivalence.

[Slide]

For current fed bioequivalency studies, the OGD breakfast represents an extreme food condition. The standard breakfast allows for effect of food on GI motility, the effect of food on the bioavailability of the drug in vivo, the effect of food on the formulation of the drug.

[Slide]

Point estimate criteria is well-accepted for the fed studies as further confirmation of bioequivalence. The requirement for 90 percent confidence intervals for a food effect study does not improve the safety of the generic drug product.

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Regarding post meal administration, logistically it is difficult for everyone to consume a standardized breakfast in exactly 30 minutes and then immediately take the dosage form. Study subjects should be allowed to consume the standard meal within 30 minutes and the dosage form

will be administered 30 minutes after the start of the meal.

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Pharmacokinetic parameters to assess bioequivalence, AUC and Cmax should remain the primary parameters upon which to assess similarity of rate and extent of absorption. Expectation of Tmax to be comparable is vague and tends to be subjective. Tmax should be provided for information purposes only, and not held to a statistical criteria.

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Regarding sprinkle studies and special foods, if a dosage form is shown to be bioequivalent after a stringent fasting study and similarity is confirmed by a fed study, there is no reason to believe that it will not be bioequivalent when taken with a small amount of food.

We acknowledge there are no examples where vehicle has had a significant effect on bioequivalency, and these should be well documented in labeling under dosage and administration.

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However, requirements to demonstrate bioequivalence, when taken with special foods or

vehicles, will lead to anecdotal stories and open a flood gate for an infinite number of study requirements for generic approval. There is no doubt that this will be taken advantage of to delay generic approvals.

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Standard breakfast, the FDA standard breakfast is adequate for demonstration of food effect on bioavailability. The use of alternate or unusual food studies may be used as a tactic to further delay generic approvals.

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In conclusion, the current approach for performing food effect bioavailability studies using a standardized meal is adequate. Unless the current methods and criteria represent a danger to public safety, we, as responsible scientists and citizens, should challenge unreasonable regulations and requirements. The existing fasting BE and fed BA studies are time-tested methods. Changes to these methods increase the burden to the industry, delays approvals and does not seem to be justified.

DR. LEE: Thank you. Are there questions for Dr. Rackley?

DR. SHARGEL: Dr. Meyer mentioned about

variability drugs, where you have a highly variable drug it would seem to me that food effect and trying to match 90 percent confidence intervals would be very tough. How do you feel about that, or widening the intervals past the 90 percent confidence intervals, from 0.8 to 1.25?

DR. RACKLEY: Clearly, a highly variable drug product would have had to be powered adequately, probably with large numbers of subjects, in a fasting study. If the same inter-subject CV were to be held or shown for the same drug products in a fed study you would likely be doing, again, huge size studies. So, where there is 10 percent of studies that might not pass confidence intervals, you might also factor in that some of these studies might have to be done with perhaps even over 100 subjects to do a fed study, whereas today they demonstrate or reaffirm what a rigorous, stringent fasting bio study has demonstrated.

DR. LEE: Larry?

DR. LESKO: Are you aware of any evidence that food can reduce the variability in a highly variable drug case where a drug is highly variable under fasting conditions, but when you give it with

fed the variability actually is reduced? I mean, as a general assumption the variability is going to go up with food, and I would say we haven't seen that in the analysis of our own data. When Ameeta showed the ANDA data where 35 out of 40 applications met confidence intervals, it suggested that the variability did not change compared to the fasting studies, or else not that high number would have passed. So, I am not sure of the assumption that food increases variability, unless we have some evidence to suggest that is one that is necessarily valid. Perhaps in the FDA survey that was done with 40 drug products, or if they want to add more to it, they would provide those point estimates and what the estimates for inter-subject variability were under fasted and fed conditions. That is just a thought. I mean, the data is out there. There is plenty of it that comes in every year.

DR. RACKLEY: I guess one question I was going to ask about our own database is what was the size of the fasting studies for the corresponding applications for which you showed fed data. In other words, was the fasting study larger or the same size?

DR. CONNER: I don't know the exact numbers that correspond to these 40 but generally what we usually see is around a 24-subject study for most products. You know, we might see up to 36. The highly variable drugs are, you know, special. Fortunately, in the scheme of things they are a relatively small problem but they are a very special problem which we have to deal with for fasting studies as well. I mean, for most drugs that are very highly variable we are talking about 60 or 80 subjects, but there is a very small subset where it is over 100, if not more. So, we are currently thinking or working on ways to do different types of analysis, say, with perhaps the ideas on scaling that came out of the individual bioequivalence efforts, but those things are not ready yet. We still have a lot of work to do on working that out, but we hope to eventually have a way of dealing specifically with highly variable drugs whether we are doing a fasting or a fed study that will, you know, come in with a valid approach at a reasonable sample size.

DR. LEE: Very well, thank you. Let me summarize this morning. I think this morning we have witnessed the progressive approach to

reexamine the guidance as science evolves, as drugs change, and so forth. I think we can come to some cautious conclusions, and I think we are kind of cautious because we, as scientists, always think about exceptions. Also, as a member of the committee I would like to suggest thinking about meals, new composition, as a possibility to see how far that thinking would go. As you can hear from our discussion, what is the intent of the guidance to look at the food effect.

On that note, I think we are ahead of schedule but in fear of a long discussion this afternoon--yes, Art?

DR. KIBBE: One quick question. Am I right as I read the guidance that you have eliminated now therapeutic index drugs a priori from consideration, or did you just eliminate the ones that don't meet the criteria for high solubility? The therapeutic index is an indication of their interaction with the receptors and not necessarily an indication of the nature of the chemical itself or the dosage form.

DR. LESKO: When you say eliminate, eliminate from what?

DR. KIBBE: I thought there was a

statement in there.

DR. LESKO: The waiver of NTIs in the food guidance is similar to what we did in the BCS fasting guidance, and I believe they are excluded from bio waivers in both guidances.

DR. KIBBE: But my point is that that isn't necessarily necessary. If the therapeutic index is a function of the way the drug behaves in the body and our guidances are a way of helping us determine equivalence between products, then I am having a hard time getting my hand around eliminating a narrow therapeutic index drug from a waiver just because when you give it, no matter who makes it, no matter how it is administered, it is the way that it works in the body that is at issue and not the dosage form.

DR. LESKO: I think that is a good question and it is probably an open question. We have discussed it here in this committee and it was related to the level of certainty about the science that you wanted to be careful about expanding this to each and every drug, even those that have narrow therapeutic index. On a scientific basis, mechanistically speaking, you are right in arguing that they should not necessarily be excluded

because the therapeutic index is related to the pharmacology and not the pharmaceutics of the dosage form. You know, it is something if the committee feels we should revisit, I think we can do that.

DR. VENITZ: But I would argue all we are doing is risk management. The stakes are higher. That is what it really comes down to.

DR. MEYER: It is okay to continue a little bit with the proposed guidance, or do you want to break?

DR. LEE: What would you like to bring up?

DR. MEYER: Well, I have a couple of questions. Dr. Rackley raised the issue of sprinkles and special vehicles.

DR. LEE: Sure.

DR. MEYER: That wasn't one of the questions we should deal with. Can we comment now?

DR. LEE: Go ahead.

DR. MEYER: I guess my one question about the sprinkles is it seems to make sense if it passes a high-fat meal, why also make people put it on apple sauce and swallow the sprinkles? Is there evidence to suggest that that is a problem?

DR. CONNER: I don't view that they are

studying two totally different things. With the sprinkle it is I think most of the time it pertains to beaded, modified release dosage forms, which depend on their mechanism of release with a coating or some other mechanism that, on direct and perhaps slightly prolonged contact with the food of given properties--pH, fat content and so forth--we are talking about not mixed up in the milieu of the stomach but in actual direct contact, dumped in and mixed into this food, that there is at least a possibility that that coating could be broken down where you wouldn't necessarily see an effect when it is mixed up with stomach contents, and so forth.

And, for these type of products often it is stated in the labeling that they are labeled to be given this way. If you have ever worked at hospitals or had small children that had to take this type of dosage form, you know that frequently they are dumped into food and left around perhaps for half an hour, an hour on normal use. So, the worry is that at some point that mechanism that we depend on is disrupted. Now, in a bioequivalence sense what we worry about is not that both products are going to be disrupted in the same way; we are worried that we could have a differential effect.

If I put the innovator product in apple sauce, it is perfectly stable; no breakdown; you take it after five or ten minutes, and then I put the generic in and it immediately dissolves, you know, I have a real problem with that because those two products are not going to be bioequivalent under those conditions. A lot of people say, well, it is the same thing as the food study we have always done. I think it is a very direct challenge of the coating or mechanism of modified release by direct and very concentrated contact with the food. That is the rationale for doing it.

DR. MEYER: It almost seems like that could be studied in vitro with apple sauce mix in a basket, or something.

DR. CONNER: I can imagine pouring the apple sauce after the dissolution. You know, theoretically I am not saying that you couldn't develop some kind of in vitro method to get at this. I don't really think that we know enough about it to know what the properties are or how we should approach that. If people have some research or some ideas in mind, we would love to see the data on that. But right now the most direct way of studying this is with an in vivo study. Perhaps

later on we can develop a system to do it in vitro in a valid way. We are just uncertain of how to approach that with our current knowledge.

DR. SHEK: There is at least on case for a liquid where it makes a difference with what type of juice you are using.

DR. HUSSAIN: In that case I think it is far more complex. I would rather not discuss that particular case here.

DR. LESKO: It is worth mentioning one thing, the problem you were going to bring up is with a fairly old product, I believe. But nowadays any NDA that comes in that wants to make a claim about administering the drug with food, either sprinkles or orange juice, or whatever it is, is going to have to have some evidence to make that claim in the label. Whereas, in the past I don't think we appreciated all the various mechanisms of interactions and we sometimes let some of that go with the vehicles. But I think that has changed today and the label is pretty much going to reflect the evidence that company submits.

DR. LEE: Marv, a second point?

DR. MEYER: Yes, the one about special vehicles, if the label of the reference listed drug

says apple juice, orange juice, grapefruit jelly, what-have-you does not affect the absorption, as I read this guidance the generic has to do all of the above to show that they do not affect the generic formulation. Is that a reasonable thing for us to be allowing to happen?

DR. LESKO: My sense would be it would have to be case by case. You would have to look at the reference listed product and see what data is available that supported that claim in the label and with there is any mechanistic reason that a study needs to be done. I wouldn't generalize on that issue.

DR. MEYER: But the guidance does generalize.

DR. LESKO: I think the guidance makes some recommendations rather than exclude it, and you would have to interpret that I think on a case by case basis.

DR. KIBBE: Just following up on that, would the generic company then who sees that type of labeling on a product they wish to duplicate do well to talk to you about whether they need to do that study or not before they even go down that road?

DR. LESKO: I would. I think Dale is going to comment, but I think it might be something we can clarify and deal with because I think we know what the intent is. It is a matter of getting the right words around it.

DR. CONNER: It comes up with our recent experience with certain products, which we don't want to talk about today. Fortunately for us, these products that are covered by that are very few and far between. I think we are not dealing with a huge number here. So, we wanted to really leave ourselves the option of dealing with these problems, not only option but the ability to deal with these problems as we saw them. You know, should we see a very complex dosage form or a liquid dosage form or one that needs to be mixed with a beverage, we will have the ability and the sponsors will know that that is a potential problem and they can put that into their thinking as far as how they develop their dosage form, whether it be the original innovator dosage form or a generic, about how to approach that and what to ask us about and what they would like to propose themselves. It really just puts both the FDA and the industry on notice that this is a potential issue and that they

need to work it out prior to being approved.

DR. HUSSAIN: Vince, just to sort of clarify, I think if we discuss that example it brings up the issue of a particular product, and so forth. I think it would be a good question and I think we will go back and consider it maybe at the next meeting. We could actually make that a case study for discussion because for that to happen, I think the key sponsors would need to be present in the room.

DR. LEE: Certainly, I think so. As science evolves and we know more about something, you know, what should we do about it? Yes, Leon?

DR. SHARGEL: Yes, I agree. You know, for specialized diets the guidance sort of leaves open possibilities of last minute labeling changes, which certainly slows entry of generic products. I think it needs to be clarified a little bit more clearly when a food is required for specialized issues, and I think the innovator who is making the claim when there is an issue should actually show data.

DR. LEE: Thank you very much for the discussion. I think that we are going to move on to the afternoon about the BCS and I don't know

what this discussion is going to lead to. It hopefully won't lead us to come back to revisit the food effect today but maybe in a future session. Kathy does have some announcements to make.

MS. REEDY: For those who have contracted for the convenience of having your sandwiches here, in the building, they will be directly across the hall. For those consultants, members and guests who have not yet done so, you may do so by finding Beverly O'Neal and handing her $10.00. For all others, it is a lovely day and there are a number of sandwich shops in the neighborhood.

DR. LEE: Thank you. We will come back at 1:15.

[Whereupon, at 12:05 p.m., the proceedings were recessed for lunch, to reconvene at 1:20 p.m.]

A F T E R N O O N  P R O C E E D I N G S

DR. LEE: Welcome back. We heard about BCS all morning. So, this afternoon we will find out what exactly BCS is, for those of you who don't know about it. More importantly, we want to talk about the next steps. These are not baby steps; these might be giant steps. We have Lawrence Yu, Acting Deputy Director of Science, OGD/OPS, to introduce the topic.

Biopharmaceutics Classification System - Next Steps

Introduction and Overview

DR. YU: Good afternoon. Dr. Vincent Lee, Chairman of the FDA Advisory Committee for Pharmaceutical Science, members of the FDA Advisory Committee for Pharmaceutical Science, my FDA colleagues and distinguished guests, this afternoon we will cover the biopharmaceutics classification system - next steps.

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We will have three presentations. Dr. Gordon Amidon, chairman and professor of pharmaceutics at the University of Michigan, will give a talk entitled history and applications of the biopharmaceutics classification system. Dr. Jack Cook, from Pfizer, will give a second talk

entitled the industrial experience with the BCS. I will give the third talk entitled regulatory implementation and potential extension of the biopharmaceutics classification system.

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Following the three presentations there will be two questions which have been slightly modified. The first question is should the agency consider revising the pH range of the solubility class boundary to be consistent with the dissolution pH range?

The second question is should the agency consider expanding the application of the BCS based biowaivers to rapidly dissolving and immediate release products of the BCS Class III drugs, namely, highly soluble and permeable drugs? With that introduction, I will turn the podium to Prof. Gordon Amidon.

Presentations

DR. AMIDON: Thank you, Lawrence. It is a pleasure to be here, talking about and seeing the evolution of the biopharmaceutics classification system, something that I have worked on I think for almost 15 years. At least if you count the very, very beginnings for an FDA workshop on dissolution

and absorption, since 1988, I believe, so it has been a long time and I will show some of that history. Then, to see the application of BCS this morning being used as a basis for providing waivers for Class I drugs, waiver of food studies for Class I drugs, I think of that as a superb extension of and use of the BCS concept because how else could you come to that conclusion without having a mechanism for biowaivers? So, I think that is a superb application and I was pleased to see that go so well.

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The process of BCS is based on looking at the systemic availability versus the absorption processes controlling appearance of drug into the plasma, and transitioning from the systemic availability view to the absorption view, and then using that, in turn, to set standards for drugs. Because if we can ensure absorption, we will also ensure systemic availability. The advantage of ensuring absorption is that now we can talk about processes in the gastrointestinal tract and develop scientific hypotheses to formulate and proceed.

That process led then to the guidance, the so-called BCS guidance which says waiver of in vivo

bioavailability and bioequivalence trials. I think that choice of terms I am fairly happy with because it says waiver of in vivo bioavailability and bioequivalence trials. We are not waiving bioequivalence. No one has ever proposed that, and I think bioequivalence, Cmax and AUC is the gold standard and BCS doesn't change that. It provides alternatives to ensuring in vivo bioequivalence. Our goal is to ensure bioequivalence and to meet that standard. In fact, I will argue that I think it is clear that for BCS Class I drugs that dissolve rapidly the in vitro standard is actually a better standard. It is not as good; it is not a substitute; it is actually better because the in vivo test is not very accurate.

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BCS is a scientific framework for classifying drugs based on their aqueous solubility and intestinal permeability. This is fairly straightforward. I will say a little bit about the science today and the extensions. I do want to provide some overview of the process that was involved in moving this guidance along.

When I became involved in bioequivalence in the mid to late '80's, it was Cmax and AUC,

empirical; you do the test and reference and get the result; do the statistics and you pass or fail; and that was kind of the end of the story. When we developed the concept of BCS we also needed a database and scientific support to develop the standard.

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So we began some research with the support of the FDA, at that time the Office of Generic Drugs in 1990 at Michigan and Uppsala and at Maryland. Over the period of the next five years that led to substantial research. The first application of BCS was incorporation actually into one of the SUPAC guidances in 1995. We actually formed a working group at the FDA. I think we made our first presentation to the ACP panel around 1996. I can't read that well. In 1996 we made our first presentation and proposal to this committee regarding biowaivers and the BCS approach. It was supported at that time and led to more research. Also, at that time I took leave of absence and spent four months at the FDA, working with Ajaz and Larry.

I should say at the very beginning that Larry Lesko was the initiator with me. He referred

to himself as the grandfather when he passed me this morning after the BCS discussion. If he is the grandfather, what does that make me, Larry? I was trying to think that maybe we could be grandparents but that doesn't work somehow. But we worked on this over about a five- or six-year period, building up the science and the draft guidance.

The actual draft guidance was drafter in 1995 with Ajaz. So, Ajaz was instrumental. He came in, in 1995 to replace Larry because Larry moved up and took on other responsibilities and Ajaz did a superb job writing the draft guidance. I say that so that if there are any problems with it, it is Ajaz' problem.

Many of the extensions, I would say we are talking about today, were discussed at that time. I can't say all of them because I can't remember everything. But in the process of developing the guidance we came up with what we thought were the most conservative and sure-thing in terms of biowaivers because if we were going to change the paradigm of biopharmaceutics we wanted to do it carefully so that it is accepted. We don't want to make a mistake going out there with that first

application for biowaivers. So, we ended up with a very conservative guidance.

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The actual draft guidance was published in February of 1999 and then the final guidance was published in August of 2000. You can see the number of workshops and scientific discussions we have had--the U.S., Europe and Japan, as well as Latin America, including a workshop at PAHO, the Pan American Health Organization, because this guidance is important in developing countries as they develop or phase in bioequivalence standards throughout the Americas. So, there is a great deal of interest in this approach.

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There was a lot of discussion and I think I can say it is generally accepted. At least we have been out talking about it enough so no one stands up and argues with me anymore. This is kind of the principle of bioequivalence as I think of it, kind of like the central dogma in biology which we now know is wrong because one gene produces more than one protein. At any rate, this is the dogma, similar plasma levels, similar pharmacodynamics; similar in vivo dissolution, similar plasma levels.

That is similar in vivo dissolution. Then, in vitro dissolution can match in vivo dissolution. Oftentimes when we talk about dissolution, we use that term too generically, like cancer. You know, there are so many different versions of it. Dissolution in what? So, what we want to do is establish a BE or bioequivalence type dissolution methodology which would be more complex and more elaborate perhaps than the usual QC or quality control dissolution methodology that would be used when you make major changes in your formulation that engender a bioequivalence question.

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So, we have changed from systemic view to the fraction absorbed view. Marvin, I think your point was well taken this morning that bioavailability is much easier than fraction absorbed. It can be very hard and sometimes even impossible if your drug is unstable in the gastrointestinal tract and the metabolite or active compound, like an ACE inhibitor, is not well absorbed. So, it can be impossible almost to determine what actually is the fraction absorbed. But in the majority of cases you can determine it by mass balance studies or IV and oral excretion

studies or bioavailability.

Now, the initial rationale for the BCS waiver was the following: If a drug dissolves rapidly like a solution and becomes essentially a solution in the gastrointestinal tract, particularly the stomach, a rapidly dissolving drug, then the rate-determining step for absorption is gastric emptying. It is not a formulation difference; it is gastric emptying. So, on the basis of that rationale, if gastric emptying is a slow step for a high solubility, high permeability, rapidly dissolving drug, plasma levels tell you no information about formulation differences. Consequently, an in vivo test is not the best test for ensuring in vivo bioavailability. In this case then a dissolution test would be more than an adequate surrogate for an in vivo test. And, that is where the waivers are currently allowed for a high solubility, high permeability, rapidly dissolving drug.

[Slide]

As you think about extensions of BCS, we are going to propose several extensions. We had one workshop on January 31, February 1 on extensions. We have had one meeting at the FDA

with the internal working group on extensions, and I would say there is a list of about six or eight areas we are considering for extensions, of which the two that we are proposing today represent what we think are the next steps that we should take.

[Slide]

I will say a few things about other areas of extensions and illustrate them. First is the extension to Class III drugs, which are high solubility but low permeability. Those are drugs like atenolol which are less than about 50 percent absorbed, or maybe 60 or 70 percent absorbed. So, the remainder of the drug is in the intestine the whole time. Fifty percent of the atenolol dose is in the colon all the time, or just about that, because the majority of the residence time is in the colon. That means the colon permeability has to be pretty small.

So, there is position-dependent permeability along the gastrointestinal tract. While we think if a drug like cimetidine or ranitidine dissolves very rapidly in the stomach, a waiver should be allowed for those drugs, but they must dissolve in the stomach. So, we think probably a tighter dissolution specification is

important for low permeability drugs because of the position-dependent permeability, in most cases, along the gastrointestinal tract--position-dependent in the very least. We know some drugs are absorbed in the duodenum jejunum because we have plasma levels, and we know that it is in the colon all the time and it is not completely absorbed. So, there is clearly position-dependent permeability, although evidence for colon permeability is much harder to obtain. It can be obtained but it is much harder.

A third area of discussion is low solubility drugs or so-called Class II drugs that dissolve rapidly in the gastrointestinal tract. This is more problematical. Let's say there are more scientific issues here and we are not ready to make a proposal in the area of low solubility drugs, but I will give you one example of my own thinking, and that is if you take salicylic acids like NSAIDs, ibuprofen, ketoprofen, the high permeability drugs, we have measured most of them in humans, all of them in animals and they dissolve very rapidly at pH 6.8 because they ionize. The ionize around pH 4-5. So, the solubility goes up by two orders of magnitude in the intestine. In

this case dissolution occurs after emptying but it is still a very fast process. So, if we think of it kinetically, yes, there is a small effect of dissolution on absorption but the principal rate-determining step is in gastric emptying. So, I think for Class II drugs, there are some Class II drugs where we can extend biowaivers but that requires more evidence and more debate and discussion and we are not going to propose that today.

[Slide]

Here is the equation that started my career down this track, for those of you who are interested in it. I am very partial to this triple interval because no one has ever asked me a question on this thing, but that is good. When I had to give my first presentation in 1988, I was a late addition to a program on dissolution and absorption and had to talk about dissolution at an AAPS workshop. I came to the conclusion I was a late addition because it was a workshop on dissolution and no one wanted to stand up and talk about dissolution and absorption and bioavailability and bioequivalence, and I was still young at the time so I didn't know enough to say

no.

So, I wondered how do I handle it and I concluded in the morning before the presentation that if I showed this I would be safe. And, it worked and I have been safe ever since. Basically, it says that the determining factors are permeability and concentration. Absorption is occurring along the gastrointestinal tract. So, you have to add up absorption processes across the whole surface of the intestine. So, this is just a surface integral and then you have to add it up over time as well. But the key factors are permeability and concentration, and in the limiting case the highest concentration is solubility. So, that is very simply Fick's first law. The two critical variables are permeability and solubility.

Now, when I was on sabbatical at the FDA in 1990-91, thinking about looking at dissolution, working with Vinod Shah and Jerry Skelly at the time, looking at how dissolution was used to set regulatory standards, we had a regulatory issue regarding carbamazepine at the time. So, I began to think about is there a way--I could see that in the struggle to come up with a guidance for dissolution you would write a guidance that would

be so general that it was useless and it was a product by product regulatory basis, so I thought is there some way to kind of capture drug products into categories that would be simpler to manage and handle? Over the next couple of years, it took me about two years to realize that the place to start was Fick's first law. My major professor would be appalled at that, Bill Laguchi who taught me Fick's first law, but it took me two years to realize that the starting point for predicting absorption is Fick's first law, and that is P X C, Fick's first law applied to a membrane.

[Slide]

At any rate, the waiver is applied to high solubility drugs. We take the definition of high solubility of a drug that the highest strength must dissolve in a glass of water. What are you going to use for high solubility? What is your reference point? You have to come up with something practical. This seems very practical to me, the highest dose. Then I learned that sometimes you can dose two of the highest strengths and bioequivalence requirements currently use strength. So, we then used highest dose strength but then that was confusing too. The highest strength must

dissolve, the highest marketed strength must dissolve in a glass of water. That is a high solubility drug. I think it is a very practical definition.

High permeability, we decided to define high permeability and well absorbed as a drug that is absorbed to 90 percent or more. Maybe we drew that bar a little high, and one of the areas of possible extensions is to change that to 85 percent or 80 percent. We are looking at with that is important or not from the point of view of the database within the FDA. Further, if we extend waivers to Class III drugs, which are low permeability drugs, it makes this borderline a little less critical perhaps in terms of drug product regulation.

Then, the drug product must dissolve rapidly. Based on theoretical simulation work done at the time, we decided that 30 minutes would be the upper limit for rapid dissolution even though our simulation supported a 60-minute upper limit for Class I drugs, high solubility, high permeability drugs. But we chose 30 minutes, 15 minutes as a single point determination; 30 minutes, you would have to do a statistical

comparison using the F-2 metric.

[Slide]

This shows a partial database. Hussain referred to a data base of about 25 drugs which is being published over the past few years and over the next couple of years, studied under virtually identical conditions in normal subjects. So, we have a permeability database that shows I think around 15 or so of them. The high permeability definition is appropriate metoprolol, approximately where those red arrows are. Unfortunately, metoprolol was mis-plotted on that plot but near the intersection of the fraction absorbed curve and the 90 percent line. So, we have used metoprolol as our main reference compound. It is about at the borderline between high and low permeability and it is about 95 percent absorbed.

So, when we do permeability, and this is permeability in humans, we almost always do it with metoprolol being an internal standard. We calculate permeability relative to metoprolol. Yes, there are some potential interactions and they are more theoretical than practical because we rarely see them in vivo in humans or in animals. So, we use metoprolol as a reference compound. If

the permeability in rat of CACO 2, if the permeability is higher than metoprolol you have a high permeability drug.

This allows you to determine the fraction absorbed, the upper limit of the fraction absorbed. The beauty of this is that in 1990 if you said you could predict absorption people would have laughed at you because no one even tried. Now we can predict the upper limit. We just measure permeability. That is the upper limit to systemic availability. Systemic availability is always less than or equal to fraction absorbed. So, from preclinical data now we can predict how well we can do the upper limit. Knowing the upper limit I think is very important. We don't know the lower limit. That is harder and it also includes metabolism. So, the advantage of permeability is that it can be scaled to preclinical animal and even tissue culture methods for predicting absorption.

Solubility, I didn't know what to say about low solubility drugs so I put in my best example here. When I think of low solubility and I need a reference point of something that is low solubility everyone would agree that marble is low

solubility. Right? I calculated the solubility of Venus and she is ten mcg/ml, if I can remember my old physical chemistry. As a reference point, a drug like resiafulvin is about 15 mcg/ml. Some other drugs, like glyburide are around 3 mcg/ml, peroxicam about 7 mcg/ml.

So, I take about 10 mcg/ml as our definition of a low solubility drug. But the factors that we need to consider there in the future are drugs like peroxicam which is actually a high solubility drug at pH 6.8, not a pH 3 but pH 6. So, we will be looking at potential extensions for drugs that ionize and dissolve in the gastrointestinal tract in the future.

[Slide]

Just to illustrate kind of the effect of dissolution, I think we have lost sight of the importance of dissolution. So, I calculated the dissolution times here based on the solubilities and assumed particle size. Cimetidine dissolves in one minute at 25 micron particle, typical particle size. Glyburide, which has a thousand times lower solubility, takes 30 hours to dissolve. That is the reason dissolution is critical for glyburide but for cimetidine it is not. This emphasizes

compartmentalizing the drugs because some are simple and some are hard. Let's not try to regulate everything by the hard rules. Let's try to separate them out and say these are hard and these are simple, and there are some drugs where we may be doing in vivo studies forever because it is too complicated. I also tried to calculate the dissolution time for Venus. I had to use a particle size for Venus so that meant I had to go to the Louvre and see Venus because, you know, you can't tell from pictures. Venus is a big lady, if you have ever gone to the Louvre to see Venus. So, I used a one meter particle size for Venus and I calculated this number. I think it is like million, billion, trillion, and I don't know what the next number is. Does anyone know what the next number is after trillion? One thousand trillion? That is a long time although compared to the age of the earth it is not so long. At any rate, this is the reason solubility is so critical and why for high solubility drugs the dissolution is very rapid and there is not a problem with regard to bioequivalence.

[Slide]

The waivers of in vivo, so-called

biowaivers, and I will emphasize this again, biowaivers are not waiving bioequivalence. They are waiving the in vivo test. They are substituting another test which is as good or better. We require bioequivalence. The question is what test. Either a single point of 15 minutes or a minimum of three points if there is 85 percent dissolution at 30 minutes. Then, three pH's, simulated gastric fluid, simulated intestinal fluid and then an intermediate pH of 4.5 because that is a pH which a drug sees as a transition from the stomach to the duodenum and jejunum. In the duodenum you have the mixing of gastric acid from the stomach and the pancreatic bicarbonate secreted from the pancreas through the common bile duct, and also duodenum mucosal secretions. So, there is a tremendous pH fluctuation in the upper duodenum and so we included pH 4.5. So, the drug must dissolve rapidly at those three pH's. We felt that was a very safe criteria for allowing waivers from in vivo bioequivalence.

[Slide]

Just by way of reference, I included here one slide on the gastric emptying work that we actually did via intubation, where we intubated

humans and measured gastric emptying of a liquid. Here we used volumes of 50 ml and 200 ml of liquid and then measured the gastric emptying rate. We monitored motility, phase 1, 2 and 3, and then the overall mean. The overall mean for the 50 ml volume was around 22 minutes and the overall mean for gastric emptying for the 200 ml volume was about 12 minutes. So, the gastric half emptying time was typical volume we would administer. Actually a glass of water, the FDA requirement, is 8 oz. So, we used 200 ml here because this was a long time ago. The gastric emptying time is about 12 minutes.

That was the basis for choosing a 15-minute, 85 percent dissolution time. Other data from the literature--Ian Wilding has done a lot of that from pharm profiles; and Bob Davis in Nottingham. So, the gastric emptying time is very well established so we felt very confident in the gastric emptying time. We used 200 ml. I have come to realize that that is actually closer to the official Japanese glass of water which is 6 oz. When I realized that I immediately thought of harmonization. Do you think we could ever harmonize a glass of water? This is an example of

cultural differences. No matter what we, as scientists think might be possible, I doubt that we are going to get cultures to change their official glass of water.

[Slide]

I think I can summarize by saying there has been strong support or at least very limited resistance. I would like to think of it as strong support but I will take limited resistance for BCS and biowaivers. There have been some concerns expressed at the workshop and commentaries on the BCS guidance. For example, there is some inconsistency between the solubility and dissolution specifications. In particular, for solubility we specify up to pH 7.5 while for dissolution we only require a pH of 6.8. We think we should harmonize those, and one of our proposals is to look at the implications of changing the pH 7.5 solubility to pH 6.8.

Also, there are many completely absorbed drugs whose systemic availability is less than 90 percent. That is kind of a paraphrase. That is like what Marvin was saying this morning. Bioavailability is easy. Fraction absorbed can be hard. So, there is this concern out there that

fraction absorbed is actually hard to measure. Probably you have to do radiolabeled studies. You can use animal data for radiolabeled studies. You need to do IV and oral because some drugs may be excreted in the feces as well as the urine. You need to measure generally your unchanged drug in the urine, and the ratio IV to oral can be used to estimate fraction absorbed if it is not too highly metabolized. But estimating fraction absorbed is a little tricky. Nevertheless, from the point of view of the scientific approach, focusing on fraction absorbed from the point of view of setting dissolution standards is the correct view, I believe, and fraction absorbed is what we want to regulate.

Systemic availability contains absorption plus metabolism. Generally metabolism is not a formulation factors. Yes, you can add some things and that is another factor. So, the systemic availability complicates regulations because of the metabolism variability. So, this allows us to separate out. While we can't solve and simplify all drug products this way, we can simplify I think quite a number of them.

The third point is that we are overly

conservative. I think everyone agrees with that and we should apply waivers to Class III drugs as well.

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More broadly, this kind of summarizes the extension issues that we have been debating for the past--well, I would say it started in 1995 when Ajaz was drafting the guidance. Changing the pH for solubility determination to 6.8 from 7.5; reduce the permeability class boundary from 90 to 85 percent. We are not proposing that today because, quite frankly, we are not sure about that. We need a rationale to come to the committee and there are a couple of different ways of doing that using actual compounds and data, but we are not prepared to do that today.

Class II, we feel these require extensive research and they, again, are not subjects for extension at this point in time for this intermediate solubility class of drugs that dissolve in the intestine. If there is one solubility you want to know, it has to be the solubility in the intestine for oral delivery because that is where the drug is absorbed. So, pH 6.5 or 6.8 to be consistent. So, the solubility of

pH 6.8 is the single most important solubility for oral delivery. If a drug dissolves rapidly at pH 6.8 it may be a candidate for waiver as well but, again, that is going to require more studies.

Then you could ask the question about surfactant. What about if it dissolves rapidly in the presence of surfactants? Again, the Class II drugs represent more complicated formulations, perhaps more complicated dissolution methodologies--not perhaps, more complicated dissolution methodologies.

Then, for the Class III drugs the high solubility, the low permeability drugs we want to allow waivers if there is 85 percent dissolved in 15 minutes. So, again, it is a matter of getting data and evidence to support that.

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To conclude, I think we have established a new paradigm. It has been a long process, starting more than ten years ago with public discussion and debate, including the support of this committee and the FDA and the support of research, external research as well as the many internal meetings in developing the consensus in moving this new paradigm in bioequivalence ahead.

I think one of the big advantages, of course, is it reduces unnecessary in vivo studies. I didn't realize, this was in the code of the Federal Register, somebody gave me a new reference today that the CFR says we don't want to do unnecessary human studies. I didn't know that that was in there so I have to add that to my slides. But it reduces unnecessary human studies, and it is based on scientific principles that allow us to formulate a hypothesis, do some tests and move ahead.

To conclude, I guess it is a great pleasure for me to be here, talking to this committee again and seeing the progress that we have made over the past few years and seeing the interest in extending and in building on it where we can to improve, with our overall goal, of course, of improving public health policy standards. Thank you.

DR. COOK: For those that don't know me and probably for those that do, I am Jack Cook, with Pfizer Global R&D. My purpose today is to show you that at least some in industry would welcome additional guidance.

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The agenda is that first I want to talk about what I see are the benefits for industry with the current guidance. Second, I want to talk about the barriers because if you talk to Ajaz or Lawrence you will find out that there have only been six, plus or minus one, applications for waivers so far. Finally, I want to talk about what I see are the future benefits for the guidance.

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First the benefits, the BCS guidance allows bioequivalence to be shown by dissolution in lieu of in vivo studies, but the question is will it really save money, and at what cost?

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I looked at the data availability at the FDA web site, and I found over the period from January 1998 to May of 2001 that there were 229 different NDA approvals, at the rate of about 67 a year. Over the same time there were 466 ANDA approvals, at a rate of 136 per year. NDAs, I could find data from a recent study by DiMasi, that about 90 percent of those are approved. Also, from the DPQR site, we find that three to six studies per NDA submitted their bioequivalence studies and generics always get it right on the first time so I

assume that there is one bioequivalence study for an ANDA. When you massage all of that data, you get that industry as a whole performs 350 to 600 bioequivalence studies per year. That is probably a little low estimate because it doesn't talk about the drugs that didn't make it to market, and it doesn't talk about studies that aren't submitted. But at least that was a starting idea of how many studies are performed a year.

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The next thing I wanted to look at is what does it cost. At least at Pfizer, Ann Arbor, when you consider the cost for packaging and maintaining samples, the clinical cost to run a study, the bioanalytical cost, the data analysis and report generation or my yearly salary, and then the internalization, it costs us about a quarter million dollars a study to run.

[Slide]

Again, if you take that number, about 25 percent of all drugs are waiver candidates. I don't have a slide on that but that comes from a survey I did over the same period of time, looking at potentially how many drugs are waiver candidates--I should mention that very quickly.

What I did, I looked at labeling and additional data that were out in the literature, decided that a drug could be classified as highly soluble if I could find that the highest strength was soluble at some pH between 1 and 7.5, but there was no other pH that would preclude it from being a highly soluble drug. So, I didn't have extremely high evidence of it being Class I but I couldn't preclude it from it. So, it could be as many as 25 percent.

To me, for the permeability classification there was enough data in the literature where it would have to meet one of the BCS requirements. Anyway, if you accept that number of 25 percent you can find that the industry as a whole could save between 22 and 38 million dollars a year.

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If I were to apply that same thing to Pfizer in Ann Arbor, we would find that it is somewhere between half and one million dollars a year at our site, considering that we do about 17 bioequivalence studies a year.

[Slide]

I call that direct savings. There are some direct savings. It is not that unusual for us

to have bioequivalence studies that are rate-limiting to submission. A typical scenario is that we are changing the site of manufacture and we want to include that bioequivalence study in our submission. So, we, those that would do the in vivo testing, end up being behind the eight ball as rate limiting. Typically, it takes us about six weeks to actually run the study and get the results back. I won't talk about how long it takes us to generate the report, but let's say six weeks to say that we have a product going forward. Assuming that we have peak sales of a drug of one billion dollars, not one trillion dollars, a year, that ends up being that there are 110 million dollars that one can save by doing the in vitro testing rather than the in vivo testing.

[Slide]

That is all well and good, I want to assure you that there is a cost savings. If you go out and do the formal testing of something to classify something as an in vitro methodology you do, indeed, save money. The characterization cost, depending on how you choose to characterize your compound as highly soluble, highly permeable, ends up being between $10,000 and $60,000 per drug.

Then, to evaluate a formulation, because that is the second step because not only to you have to have a Class I drug but you have to do the in vitro dissolution for the formulation, is about $15,000 per formulation. I have stolen this slide from another talk, but it ends up that that total cost of that $75,000 is far less than the quarter million dollars it costs us to run a study.

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A few years ago I had the opportunity to try this at Pfizer, and I likened it to a favorite poem of mine by Robert Frost, the Road Not Taken, that talks about decision in life and I thought the BCS was the more attractive road and chose to take that less traveled path. I have good news with drug X, which is that we were able to obtain a waiver of in vivo studies and show that it met in vitro bioequivalence requirements. We saved four bioequivalence studies and, like the last line of the Robert Frost poem, that has made all the difference in that it saved Pfizer, Ann Arbor, one million dollars.

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So, why isn't everybody else jumping on the bandwagon? We have seven applications but,

yet, a quarter of all drugs could potentially meet BCS classification. There are a couple of barriers that actually are not within the agency but within industry itself. One is what I call wrong attitudes, mainly because they don't agree with me--

[Laughter]

--secondly, about wrong wiring. When I first proposed going this different path within the company, saying I don't want to run a traditional in vivo bioequivalence study; I want to run an in vitro bioequivalence study, it wasn't my decision alone. I needed to take it to the head of my department, the head of regulatory, the head of formulations department.

[Slide]

To a person, this is the kind of response I get, "you want to do what? Does the agency allow such a thing?" I said, "well, sure they do. Here is the guidance on it." "Has this been done before?" I said, "no." They said, "what, are they crazy?" There is a good scientific rationale behind that.

[Slide]

So, some of the questions I get are "you

can't release a new product on the market without testing." That is questioning the science. I do point out that we have been doing this all along with solutions, and the BCS Class I is something that is very similar to solution; it is something that is dissolving very rapidly, behaving very much like a solution.

As I mentioned, "the FDA won't allow it." They question the procedure. Actually, what I have been doing to my colleagues in industry is advocating that they get an advocate within the agency to talk to their regulatory people within the company and say that, yes, indeed, it can be done. "Has this been done before?" Fear of the unknown. I go all the time and talk about our success with trying to encourage it.

[Slide]

There is another thing that kind of stops industry from doing it and that is wrong wiring. This is kind of a diagram of what is needed for BCS classification as far as information flow. Typically within a company, my colleagues in preclinical, there is very good information usually coming to me in the clinic. Chemistry provides decent information with their formulation

scientists. What is actually needed for the BCS is something like this, there has to be a lot more talk across these inter-departments because we are relying on information generated elsewhere. If I am using preclinical data to help classify a compound as highly permeable, chemical characterization is the one that usually does the full dissolution profile. So, we need to figure out how to have better information flow.

The next thing I am doing is bringing across dollar amounts. The size of the dollar sign represents the change in costs for a department. Red means that the costs for a department go up when they decided to classify something this way. For instance, chemical characterization has to do more characterization on a compound than they are used to. Green means where it saves. So, as you can see, I am in clinical pharmacokinetics, I look good and I can claim that we saved our company a million dollars, but other parts of the company are actually spending more. So, this is another barrier that one has to overcome within industry and is why it hasn't been used so much.

[Slide]

I am going to talk about that a little bit

when I talk about blue sky, how will industry benefit from the proposals.

[Slide]

Change within a company is kind of like a chemical reaction. To orient you on the slide, on the Y axis is kind or resources, and going from the old, on the left-hand side, to the new, on the right, you can see that overall if I use the old way, the in vivo bioequivalence, I actually have to spend more resources than the new. But I have to overcome this barrier of activation energy. I have to change how data flows within a company. I have to overcome some mind sets.

I submit that if there is benefit and it is only slightly better than the activation energy, that change is going to be slow in a company. They are going to fail to see that for that little good we have to change all these ways that we do things within a company. On the other hand, if through expanding the BCS we can provide a lot broader application of it, those systems will change a lot faster and we will see actually a far greater use of BCS within industry.

[Slide]

In that same survey I looked at how many

drugs are potentially future candidates for BCS if we were to include all highly soluble compounds. From that survey we come with something like 45 percent of all candidates would be considered highly soluble, with another 25 percent unknown. So, given that some will fall out of that 45 percent, they may be replaced by the 25 percent and I submit that that is probably not too unreasonable. So, there is a great potential for the number of candidates that the expansions proposed today would cover.

[Slide]

I would like to leave you with a few thoughts. First, we feel that the current guidance is useful. Pfizer has saved over a million dollars with it. The barriers right now within company on changing paradigms result in the low rate of use they have so far with the guidance. To overcome that, one thing that will help is expanding the BCS where more candidates will equal a greater savings, and that will be very useful for companies and, as I say, you will see it used a lot more. With that, I will turn it back over to Lawrence.

DR. HUSSAIN: Vince, can I make a comment?

DR. LEE: Yes.

DR. HUSSAIN: I think one of the benefits that I think needs to be on the table is the concept of quality by design and I just want to bring a formulator's perspective here. When the work of a formulation development group starts, for initial screening everything is based on in vitro dissolution and we pick a dissolution that we think might work. Actually, we have seen cases where companies may go down the path and actually optimize their formulation before they do the first bio study and in that study the dissolution test was all wrong to start with.

So, focusing on the dissolution, relevant dissolution, helps us to do the right thing the first time and I think that is one of the scientific benefits that is not always clear. So, bringing more science to formulation development and linking biopharmaceutics to formulation development is another big benefit here.

Also, when I was working on the BCS I saw 18 bioequivalent studies in one NDA, and I am not so concerned with the cost at this point. I am more concerned that this is a new drug entity for which the safety and efficacy has not been fully evaluated and you are exposing normal, healthy

volunteers to a test which may not be adding all the value. I think that is the motivation that sort of drives us here.

DR. JUSKO: Could I ask Jack to clarify one thing here?

DR. LEE: Certainly.

DR. JUSKO: The test compound that you described, I presume you already had oral and IV data for that compound.

DR. COOK: Actually, the way we classified it as highly permeable is that this drug is excreted virtually unchanged in the urine. So, just by measuring urinary excretion we were able to show that the bioavailability was above 90 percent.

DR. JUSKO: So it was a Class I compound?

DR. COOK: Oh, yes. This is a Class I because that is the only way currently that you can get a waiver for in vivo bioavailability. What we are proposing today is to expand that further.

DR. JUSKO: Thank you.

DR. YU: Thanks, Dr. Amidon for the excellent presentation for an overview and applications of the biopharmaceutics classification system, and Dr. Cook for an excellent presentation on the industrial experience of the BCS.

I want to emphasize that the driving force for us to have this current guidance and for future extension is the science, the science behind the philosophy driving this change. In the next twenty minutes or so I will talk about two aspects. One is regulatory implementations, and the second is basically potential extensions of the BCS.

[Slide]

As you can see, this guidance was issued in August, 2000. It is now about 18 months. This guidance basically allows for biowaiver for highly soluble, highly permeable and rapidly dissolving and wide therapeutic window index drugs. There are also characteristics of the drugs to ensure that the solution is not the limiting step in terms of oral drug substance process. Again, the permeability is also not the rate-limiting step.

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So, those characteristics allow them to say that the gastrointestinal emptying is basically the limiting step for these solid oral dose form for BCS Class I drugs.

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In terms of applications, basically this guidance allows applications for BCS for

investigational drug applications for Phase I to Phase II post-approval changes certainly as ANDA, abbreviated new drug applications.

[Slide]

So far, we basically have received strong scientific support. As Prof. Gordon Amidon pointed out, there is very little resistance. Some concerns expressed in the public workshops are that we are too conservative or overly conservative with respect to solubility class boundary with respect to BCS Class III drugs, highly soluble and low permeability drugs. Again, the submission activity is relatively low. So far we have received a total of about five NDAs, ANDAs and post-approval changes.

[Slide]

I want to discuss with you some of the experience we have had with this current BCS guidance. This slide shows you basically the experience with the solubility . The pH range for solubility studies is 1.2, or sometimes we say 1.0 HCL to 7.5. Temperature is 37 degrees. The solubility is basically the highest strength divided by 250 at all relevant pH's. For example, for diazepam what you are really looking for is

lowest solubility, in this case a pH of 7.4, to determine whether this drug belongs to Class I or belongs to another class, Class II or IV. So, there are solubility studies, relevant pH, relevant temperature, and determined by the lowest solubility at all relevant pH's from 1.2 to 7.5.

[Slide]

I want to discuss with you the experience with permeability. So far, the applications we have received classify permeability based on the following methods: pharmacokinetic studies in humans. For example, bioavailability is basically 90 percent or above. To ensure the permeability of this drug, that it is highly permeable.

We also received applications using an in vitro cell culture model. We sometimes receive inquiry about the literature method or literature data. I have to point out that the agency has little experience to accept literature data as the sole evidence to support or to classify permeability for the regulatory purpose.

[Slide]

In these four slides I took advantage of the new technology and I just added them this morning in the hope of addressing the concerns,

especially Dr. Marvin Meyer's concern about permeability classification. It is not in your handout. First I want to point out that the permeability classification, especially the extent of intestinal absorption, is not bioavailability. Just because bioavailability or extent of absorption includes the extent of drug input into the system added to circulation, so it includes everything, especially for example the solution, metabolism and so on.

However, for the purpose of the BCS, you use the extent of intestinal absorption which means extent of drug across the intestinal membrane is not considered a factor of solubility, for example, metabolism is subject to hepatic metabolism. So, we only consider one step here, the extent of drug across membrane. While the bioavailability considers many, many processes involved, including the solution, gastric emptying, GI motility, hepatic metabolism, and so on. So, there is a difference between extent of drug absorption and extent of intestinal absorption for the BCS biopharmaceutics permeability classification purpose, the extent of intestinal absorption.

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In the guidance we basically specify a number of methods. You can use any method you would like to classify the drug in terms of permeability class boundary in terms of permeability class membership. So, there is a list of a number of methods availability specified in the guidance, including in vivo intestinal perfusion in humans; including pharmacokinetic studies for example in humans; including in vivo and in situ intestinal perfusion in animals and, certainly, we also include the in vitro cell culture model.

[Slide]

I just want to elaborate to give you an idea, if you use an in vitro method or an in situ method, in order for this method to qualify to pass the permeability of drugs for the regulatory purpose, the sponsor is required to demonstrate that he has established the so-called system suitability, so basically to show the link or relationship between the permeability, for example, cell culture permeability, and extent of intestinal absorption for 20 representative drugs. For example, you have to have a drug, certainly for these 20 drugs you have to spread from low, medium

and high. So, you have a certain range from low to medium and high. You also have to show the in vitro method integrity, for example using mannitol or dextran as a marker. In the case of the cell culture models, you have to show that the cell culture model expresses the transporter for example, in this case Pgp, P-glycoprotein transporter.

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In order for this specific model to qualify for regulatory purposes with respect to the permeability classification, you need to establish the correlation between the extent of intestinal absorption and in vitro cell culture permeability in this case. This was done at the FDA lab, and Donna Volpe is the investigator and actually she is sitting in the audience.

As you can see here, for these 20 drugs we pretty much get very reasonable correlations between the extent of intestinal absorption and apparent CACO 2 cell permeability. With this establishment, this specific model in a specific sponsor's lab can be utilized for class permeability of drugs. Now, if you use the same principle in a different lab you have to requalify.

So, we put in relatively conservative criteria in place to make sure the data that come from sponsors does show that the permeability of a specific drug is highly permeable or poorly permeable.

[Slide]

Again, even with the permeability method, not only do you need to show that the cell culture establishes the system suitability to show that the drug is highly permeable, you are also required to do stability studies to make sure this drug which you are measuring in an in vitro system is stable. These are the recommendations in this slide based on the guidance. For example, you need to show that the drug is stable in simulated intestinal fluid. You need to show that the drug is stable in simulated gastric fluid. Certainly, for stability purposes you need to use stability indicating assay, validated assay. The guidance suggests at this point that the drug is stable if less than five percent is degraded in both small intestinal fluid and the gastric fluid.

[Slide]

Basically, this is our view in terms of regulatory implementation and some of the challenges and issues we have faced so far.

Next I want to discuss with you the revisions and extensions with respect to solubility class boundary and with respect to biowaiver extensions, especially for BCS Class III drugs. The objective here, again, is to have a science based in vitro solution to BE standards. Again, I want to emphasize here that the driving force for us to have extensions or to have the current guidance is science. It is the science.

Let's talk about the first proposal change, solubility class boundary. Currently, the pH range in defined solubility is 1.2 to 7.5. The potential future direction is for a pH range from 1.2 to 6.8 in defined solubility.

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Basically, this is the GI tract here. You have a pH in the stomach, pH in the small intestine; pH in the jejunum. The pH range in the stomach is 1.4 to 2.1 under fasting condition. The pH range for the duodenum is 4.9 to 6.4. The pH range in the jejunum is 4.4 to 6.6. Finally, the pH range in the ilium is 6.5 to 7.4.

Let's look at how long it takes for drug solid dosage forms to get into the ilium where the pH is relatively high, as you can see, at 7.5. On

average, in terms of residence time it is 85 minutes for a drug particles to go through the stomach, duodenum, jejunum and to the ilium. So, it takes 85 minutes for a drug solid dosage form or drug particles to get there.

Now let's look at what are our in vitro dissolution criteria. Our in vitro dissolution criteria is 85 percent dissolved in 30 minutes. So, by the time the drug gets to the ilium it is likely all the drug is dissolved. Intuitively we would think if all the drug is dissolved, why do we need this criteria? That is first.

Second, in our current dissolution testing for BCS, we have a dissolution test at pH 1.2 or 0.1 HCL, 4.5 and 6.8. So, in this regard to have consistency between solubility and dissolution class boundary it seems reasonable to reduce the pH requirement from 7.5 to 6.8.

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Now let's move on the next potential extension, which is BCS Class III drugs. Currently we have a biowaiver for BCS Class I, namely highly soluble and highly permeable. One proposal is a wavier to highly soluble and poorly permeable drugs.

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So, the question we ask is why do we choose Class III, why not Class II or Class IV? For Class III drugs it is highly soluble and poorly permeable drugs in rapid dissolving dosage forms which essentially behave like a solution if the dissolution of a solid oral dosage form dissolves rapidly. It essentially behaves like a solution.

Let's look at the solution requirements here. The FDA policy on oral solutions is basically if bioequivalence is self-evident biowaiver can be granted, and no in vivo demonstration is needed if the test solution contains no inactive ingredients or other changes in formulation from the reference product that may significantly affect the absorption of the active moiety or active ingredients. So, only if the excipients do not affect absorption.

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Now let's look further in terms of mechanistically. Again, you can dose oral dosage forms such as tablets or capsules. A solution is certainly a liquid dosage form. When the solid tablet comes to the stomach or the solution comes to the stomach, what happens for the solution is

basically gastric emptying, the emptying from the stomach to the small intestine. However, for solid products there is one process which is the dissolution. So, there is a difference in terms of the process in the stomach. But when it comes to the small intestine there is not much difference there. The drugs in solution get absorbed. So, basically in the small intestine or in the colon there is basically a process in terms of mechanistic absorption which is the same for oral solutions or for solid dosage forms.

[Slide]

Now let's look at the next assumption here. We say if the test product equals a simple solution, if we can show it, and if we have reference products which equal a simple solution then automatically you say the test product equals the reference product if there are two criteria here, they are rapidly dissolving and the second criterion is no excipient effect on oral drug absorption. No excipient effect.

[Slide]

This is basically a list of potential BCS Class II drugs. I say potential because there is no concrete information to support yes or no and so

I say potential. This is a list of BCS Class III drugs.

[Slide]

So the hypothesis here is if two immediate release solid dosage forms dissolve rapidly at all physiologically relevant conditions and contain no excipients that may potentially affect the oral drug absorption of the BCS Class III drugs, then the bioequivalence of these two solid IR products is assured and biowaiver can be granted.

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This is basically the proposal for studies or data collection to test the hypothesis. Certainly we can collect data from human bioequivalence studies to compare a simple solution with two solid dosage forms of at least ten model BCS Class III drugs to show that those data may confirm the literature, the NDA or ANDA or FDA internal studies, maybe unpublished data. We are thinking about going through the PQRI to collect the unpublished data from the sponsors and, if necessary, to do relevant in vitro dissolution and cell culture studies.

There are two potential issues here. The first issue is transport which we touched on in the

morning. As you can see, there is much in vitro evidence to show that transport may affect the absorption of a certain number of drugs. On the other side, we though if dose proportionality is shown over the range from the lowest to the highest strengths, we can conclude that the effect of the transporter may not be significant with respect to the bioequivalence. It may be still significant in terms of drug-drug interaction but with respect to bioequivalence this may not be significant.

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The next question is the potential effect of excipients. Excipients of oral drug absorption can certainly affect GI motility. They can affect permeability. In order to minimize the risk of the bioinequivalence caused by the excipients, we basically have two options.

Option number one, we basically identify and exclude excipients that may affect the absorption or pharmacokinetics. In other words, at this point we consider all excipients acceptable; we identify one, we basically exclude it. That is the first option.

The second option is we basically exclude every single excipient at this point. We basically

include them when we find specific excipients have no effect whatsoever on oral drug absorption in vitro and in vivo. So far we have tested a number of products and if they had no effect we included them. So, basically those are the two options we have.

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With that, I conclude my talk and with the following questions we want feasibility and input from you. Thank you very much. Thank you for your attention.

DR. LEE: Thank you, Lawrence. Ajaz?

Committee Discussion

DR. HUSSAIN: Just a perspective that I wanted to share with the committee before we start deliberations. When we put together the first guidance that was published in August of 2000, what were the reasons why we did not include Class III is sort of the one thing which I wanted to point out. The other thing which I wanted to point out which I will address first is our regulations currently allow waiver of in vivo studies when you have in vitro and in vivo correlations. For immediate release dosage forms we don't have that option because correlations are usually not present

or not apparent because dissolution in many cases tends to be not rate limiting.

So, in vitro and in vivo correlations have not actually been very useful for most immediate release dosage forms. There are a few exceptions. So for the BCS based biowaivers, when you think about it, we are making decisions on in vitro dissolution as a source of comparison in absence of such correlations. So the thought process and the justification is based on mechanistic underpinning of that.

If I look at Class III drugs, what sort of held us back for recommending waiver in the first instance when we looked at it was the issue of permeability being a mechanism by which you essentially have the same conditions in vivo. So, the volume differences for dissolution in vitro and in are sort of one reason behind that sort of holding back from that recommendation.

Also, keep in mind that solution bioequivalence has always been waived, or options have been available for solutions, and some of the work we did suggested that the way we evaluate excipients would have to be tightened up. So, if you look at the bioavailability, bioequivalence

guidance we actually use a higher standard for solubility forms whereby we limit it to highly permeable drugs because that is sort of protected against some of the excipient effects. In the new guidance that we issues on BA/BE it actually pointed out some of the issues with respect to sorbitol or osmotic ingredients for solution drugs because we have been seeing cases were a solution actually has lower bioavailability than a tablet, and you have one example in your handout. Those are sort of the motivations and thought processes that held us back at that point. So.

DR. LEE: Thank you. Are there any questions for the presenters? Yes?

DR. RODRIGUEZ-HORNEDO: Yes, maybe a point of clarification, how do you define or how do you classify a compound that is ionizable so that the pH determines its solubility? It is not clear to me from the reading material.

DR. YU: Solubility over the pH range is defined as 1.2 to 7.5. So, if it is ionizable, for example as a free base, the solubility will be much higher at the low pH; the solubility will be lower at the high pH. So, actually whether this drug is highly soluble or not is determined by the high pH.

On the contrary, for acid, for example, the solubility will be lower at the low pH and higher at the high pH so that basically determines whether this compound belong to high solubility or not by the low pH. Essentially in terms of ionizable, we basically ensure that it matches the solubility of all pH's to determine whether it is highly soluble or not.

DR. RODRIGUEZ-HORNEDO: So, it is determined by the minimum solubility of the compound at any pH?

DR. YU: Correct, absolutely, yes.

DR. RODRIGUEZ-HORNEDO: If I may ask a question that is related to something we are going to be discussing tomorrow, I guess then the classification is also dependent on the solid state of the material.

DR. YU: Absolutely.

DR. RODRIGUEZ-HORNEDO: So, if you have an amorphous compound versus a crystalline compound it will change the solubility. The classification may change depending on solid state structure.

DR. HUSSAIN: Well, I think this is sort of an equilibrium solubility.

DR. AMIDON: Solid state properties,

particularly if they can change when the dosage form is introduced into the gastrointestinal tract, are problematical. I think when we use solubility here we think of it as approximate equilibrium solubility. But, in reality, we are only interested if the drug stays in solution for over, you know, four to six, eight hours in the gastrointestinal tract. We don't need to wait days; in days the drug is out of the GI tract. So, in some ways we think of this as kind of a kinetic solubility, but to a physical chemist that is an oxymoron, right, because solubility is equilibrium by definition. So, we think of equilibrium solubility. So, amorphous compounds or compounds like carbamazepine which hydrate and change their physical form in contact with water have to be handled more carefully.

DR. LEE: Yes, Gloria?

DR. ANDERSON: On page three of your presentation you have solubility equal to greater than highest strength per 250 ml at all pH's. Is there a number that you associate with solubility that is highly soluble, not very soluble, or does this high strength refer to the dosage?

DR. AMIDON: That is a good question. We

are asked that frequently. We use the term high solubility of a drug to be one whose highest strength dissolves in a glass of water. That is not really solubility. That is what we are calling a high solubility drug. You know, if your drug dose is 250 mg and it has to dissolve in 250 ml, 1 mg/ml would be a high solubility drug. But if your dose is lower, then you could go to a lower solubility. So, the actual solubility changes with dose. The solubility limit changes with dose.

DR. ANDERSON: And from drug to drug.

DR. AMIDON: And from drug to drug, yes.

DR. LEE: Joe, you have a question?

DR. BLOOM: Basically when it is called high solubility it is depending on dose.

DR. COOK: It depends on the highest formulation strength one would make. So, it is drug specific and it is the highest strength, and whether that strength will dissolve in 250 ml or not at all relevant pH's. So, you can't think of it as a milligram/ml; it is just a yes or no.

DR. KIBBE: And that applies to the highest strength that is available whether or not there are multiple strengths. No one can get a waiver for a 5 mg tablet when a 50 mg won't meet

that criteria? Is that right?

DR. COOK: Currently.

DR. LESKO: I think it is important to be clear. The solubility is based on the highest approved strength. If you can imagine a bioequivalent situation where there is a reference product approved and somebody is looking at an abbreviated new drug application, the highest strength that is approved would be the reference for solubility determination. That is different than the highest dose that may be approved if, for example, somebody can administer two tablets or three tablets within the range of an approved dose. That is not what we are talking about. We are talking about the strength of the tablet. We are trying to mimic a bioequivalence study where you compare a tablet of drug that is a test to a tablet of a drug that is a reference, and that is what we want to compare at the highest strength.

DR. KIBBE: If four products are commercially available from the innovator, four dosage strengths, 2 mg, 5 mg, 10 mg and 20 mg, then your decision to allow people to get a waiver is going to be based on the highest one whether or not they want to market the highest one or not?

DR. LESKO: That is correct.

DR. KIBBE: Even though they want to market the 2 mg, they can't claim that the 2 mg would meet your criteria and, therefore, it should get a waiver.

DR. HUSSAIN: That is the way it is right now.

DR. LESKO: You didn't say what the highest approved strength was, but if 20 was the highest approved strength, then that would be the basis for the solubility determination.

DR. KIBBE: Regardless of what the company wants to market?

DR. LESKO: Well, if they want to market 10 mg and they don't market 20 mg, then 10 mg would be the reference.

DR. KIBBE: That is my point.

DR. LESKO: Yes.

DR. KIBBE: That just changed the answer, I think. If there is a company on the market that has four strengths and the highest strength is not a very popular strength but it is on the market as the innovator, and I want to only come in as a generic and market the bottom two strengths, which represent 80 percent of the market, I don't have to

have, to get a waiver, that the highest strength is soluble at 250 ml. I only have to have the highest strength I want to market that is soluble at 250.

DR. LESKO: That is correct.

DR. LEE: Has there been any thought about using dose numbers in all these kind of descriptives?

DR. AMIDON: Well, yes, actually if the dose number is less than one than you are a high solubility drug. So, really that is the way I think of it.

DR. LEE: Yes, Bill?

DR. JUSKO: This is a very illuminating set of presentations and I have learned a lot from it. My first, somewhat facetious, comment is, Gordon, I wonder why in your triple integral you didn't include the upper limits of the A variable?

[Laughter]

We will talk about that later.

DR. AMIDON: you are the only one that has ever asked that question. It is not really written right but no one has ever noticed. It really should be a vector integral, quite frankly. It should be a vector integral written over the surface of the intestine, yes.

DR. JUSKO: That makes everything clear!

[Laughter]

Speaking computationally, faculty members in our department teach students about Lapinsky's rule of five. I wondered if there is some role in all of what you are doing for a computational approach, structure activity kinds of calculations to address estimations of permeability values.

DR. AMIDON: Yes, I actually use them all the time. The question is what evidence would you want to bring to the FDA. I think within industry, if I don't have an experimental partition coefficient I would calculate one just using some software program. I mean, it is one of the first things I do to determine kind of what the permeability of this drug might be. So, I find it a very useful qualitative tool. I know that there has been some interest. Well, Lawrence has actually done some computational work when he was with Glaxo. I think the FDA is very concerned about making decisions based on some computational result, but I personally use them all the time, yes.

DR. COOK: As somebody who may work for a company who looks into this, we find it very useful

for candidate selection, realizing that compounds with the desirable absorption characteristics are ones that likely make to market. If you can have activity plus it is well absorbed, you have something that you should actually fast-track through the system. Our experience is that they have been very useful at that stage. The correlations haven't been precise enough to where we feel comfortable saying for sure it is a Class I compound, and to, you know, absolutely predict it is above 90 and, therefore, do other tests. But some day maybe.

DR. JUSKO: In the graphs that I saw showing the non-linear relationship between fraction absorbed and permeability, there was a lot of data on the high side and only three or four points, some complicated by metabolism issues, indicating small fraction absorbed when permeability was low. Plus, the relationship was very steep. So, that makes people wonder how reliable predictions are going to be if the critical information has such a steep profile.

DR. COOK: Well, thank goodness, the area of interest is actually the flat part of the curve because if you look at where metoprolol is, that is

kind of where it starts the flat part of the curve and you have to be there or greater to be considered a highly permeable compound. I think most people agree that that is really hard on that area of the curve where a little bit of insensitivity in your assay measurement could result in a big change. Here, we are on the flat part of the curve and are less susceptible to that.

DR. HUSSAIN: I think that is an excellent point.

When we were putting in the class boundary that actually came as a decision-making point. The reason we said 90 and above is because of that. Originally I think we thought of 80 and that is the steep part of the curve, and one of the criteria for 90 percent as the boundary was driven by that.

At the same time, I think for assessment of permeability one of the recommendations in our guidance is actually to use an internal standard, a known high permeability internal standard so that you can say it is better than that. That is how we addressed that.

DR. JUSKO: That is what I didn't quite understand from Dr. Yu's presentation, whether he was indicating that the companies needed to study

all 20 drugs and establish the profile or could just use the indicator drug as a cut-off.

DR. HUSSAIN: The recommendation is to actually establish your own system with all 20 drugs; demonstrate suitability, and once you have demonstrated suitability of the method, because lab to lab variability is significant in some of those things so we wanted every lab to define suitability and then, after that you could use one of the internal standards.

DR. JUSKO: In these recommendations you are going by cell culture systems. I wonder, is there no room for animal data? Win Chao has shown a very nice correlation between fraction absorbed of a large number of drugs in rats and man.

DR. HUSSAIN: I think with respect to extent of absorption, animal data is allowed with respect to perfusion experiments in direct methods of permeability. We stopped short of using extent of absorption in rat. I know we had that discussion with Prof. Win Chao and he had about 100 compounds. So, we stopped short of that in our recommendations in the guidance. But animal perfusion experiments truly are okay. They qualify. So.

DR. YU: In fact, I have a similar plot which is from rat instead of CACO 2, also 18 drugs.

DR. LEE: Jurgen?

DR. VENITZ: I am very supportive of the approach and I want to congratulate Gordon and the FDA for moving it along as far as you have. Very much like Marvin, I have some concern about the permeability assessment based on in vitro data. I guess I am wondering whether you have any experience with misclassification using the human in vivo as your gold standard. In other words, if you know you have bioavailability of 90 percent or above, you have a high permeability drug. How does that compare to the in vitro predictions based on CACO 2 cells lines?

DR. HUSSAIN: I don't have any experience where we have found that problem occur. We are actually in the process of publishing a validation study, our own data, on in vitro studies, and Donna will be here who has done that work. So, I don't have an example.

DR. VENITZ: I know of one that was supposed to be a poor permeability drug and it turned out to be a high permeability drug--

DR. HUSSAIN: Cimetidine would sort of

come to my mind as probably an example where I think extent of absorption in vivo in humans, the data would suggest it is either 100 percent or slightly less than that. But under CACO 2 and other perfusion studies, it comes out as low permeability. So, misclassification is on the lower side.

DR. COOK: Yes, I would echo that. I did an informal survey of some other companies and that is what their indication was, that more often than not the CACO 2 system was very conservative.

DR. VENITZ: With your proposal that wouldn't be a big deal because you are lumping one and three together. So, it doesn't make a difference in terms of the waiver. But as it currently exists, that would make a big difference in terms of with you are waiving or not.

DR. AMIDON: it would only make a difference in the dissolution standard you would have to meet.

DR. VENITZ: Right. The second question I have for you is about this Class III extension. Do you have any experimental evidence, other than the theoretical considerations that you went through, to suggest that for a Class III compound we can

safely waive it and still show in vivo bioequivalence.

DR. YU: This is basically for information. We are considering those extensions and we will come back with the data next time. We will come back next time to this same committee with data.

DR. LEE: So, Lawrence, you understand correctly that probably the high end of the Class III would be more like the low end of the Class I?

DR. YU: Yes.

DR. LEE: Therefore, you can waive it?

DR. YU: Yes.

DR. AMIDON: I think there are some drugs where there have bee intubation studies, you know, gastric, duodenal, jejunum. So some of those data sets are availability for at least one or maybe two Class III drugs in published literature. There is more data also in NDAs. I think, for example, that type of data showing site dependence would be one set of data.

DR. VENITZ: Since you are going to go out and come back, that would be the kind of data I would like to see to support it experimentally, not just theoretically saying we think Class III is

fine.

DR. YU: Absolutely. We are looking, for example, at the evidence which would show bioequivalence between solid oral dosage forms versus a solution. We have about seven or eight drugs right now. We intend to collect at least ten drugs to deny or confirm the hypothesis we discussed here today.

DR. LEE: Larry?

DR. LESKO: Yes, I wanted to answer that last question because when we were doing the research at the University of Maryland as part of the scientific basis for the SUPAC guidance we had two drugs from this class, the class that we are talking about today, Class III with the high solubility, low permeability, and Lawrence had them on one of his slides, cimetidine and ranitidine. Those were another two drugs which we tried, through various manufacturing method changes, to sort of ruin the formulations, create big differences in dissolution but in vitro they were very robust in terms of bioequivalence. So, I think that is some evidence that would support what Lawrence is talking about.

DR. VENITZ: So, you showed that the two

different solubility forms were bioequivalent in vivo?

DR. LESKO: Yes.

DR. VENITZ: What about comparing the solution to a solid dosage form?

DR. HUSSAIN: Well, I think that is what Lawrence is proposing now but we don't have prospective data on that now. We have some in-house data but I think Lawrence is proposing to do some studies comparing solution to tablet, and so forth. So, that is one of the sets of experiments that we probably will bring back to this committee.

The other experiment that is ongoing right now, we have completed the manufacturing and so forth, and actually the studies have begun at Tennessee, the biostudies. That is to create formulations of a low permeability drug. We took a low solubility, low permeability drug, furosemide, and created dissolution profiles which are very different and actually induced a pH sensitivity in that. I don't know when those studies will be completed but they have already begun. So.

The solution as a standard I think is also important because when we were doing the BCS

guidance we looked at excipients. I think excipients come back as an issue, and we were collecting data with solution, simple solution that was established, and I think from that we identified about 50 excipients which are commonly used which don't seem to have an effect. So, we could build a basis for that and I think that was one of the questions Lawrence posed, should we identify excipients which may be potential problems. That is what we tried to do in the first guidance. I think that is the easier route because for solid dosage forms there are only about 50 common excipients and you can make all sorts of dosage forms with those 50 excipients. Of those, the potential problems were surfactants, sodium laurel sulfate, and so forth. And, we have supportive data to say it may not really be an issue in vivo. So, that database also could be brought back.

DR. JUSKO: Do you think you can ever really be conclusive about the excipients? Because there could be a very specific interaction between a particular excipient and a drug based on their distinct chemical features.

DR. HUSSAIN: We that interaction be a

chemical or physical interaction, or an interaction at a transport or absorption level? I think our focus is more on the absorption because that is where the concern is. If it is a physical interaction or a chemical interaction, it sort of comes out as a stability issue rather than a bio issue in some cases. So, there would be different ways of addressing chemical interactions.

DR. JUSKO: Might one manufacturer use a particular excipient in their product and someone use a different one, and then there would be a potential difference?

DR. HUSSAIN: That is possible. For oral products you could have different excipients.

DR. LEE: Particularly with the Class IV drugs. Well, shall we keep this conversation going? Marv has a question.

DR. MEYER: Yes, one question perhaps to Lawrence. Is there a greater potential for an error to be made for the Class III than Class I? I am asking from the standpoint of your table. If you take a drug, Class I by definition is 90 percent fraction absorbed, the most we can go up to is 100 percent. If you take glycinopril, it is 30 percent fraction absorbed, and that goes up to 40

percent. Now, you have a third increase in the available drug. As you get down in FA you have bigger orders of change if you do something to cause a change.

DR. YU: That is why the effect of the excipients is kind of critical.

DR. MEYER: Whatever. The formulation, whatever you didn't see because you didn't do the biostudy causes it to go from 30 percent to 40 percent or 30 percent to 20 percent. That is a bigger change than 90 to 100 or 90 to 80.

DR. COOK: If I could jump in, you could have a change the other way and have a drug that is 100 percent and all of a sudden it goes down to 10 percent. So, it is just depending on whether you are looking at increased chance of adverse events or a loss of therapeutic benefit. But I think the risk is there--

DR. HUSSAIN: Jack, sort of a different perspective on that, I think with the rapid dissolution the likelihood is minimized the other way around. I think the excipients with sodium laurel sulfate, and so forth, I think the concern that Marv raised was one of the reasons for holding it back to highly permeable drugs. If you have an

excipient like sodium laurel sulfate that can enhance permeability what will happen with highly permeable drugs? Very little. But for low permeability drugs the margin of error is high.

DR. AMIDON: I just want to caution or advise the committee to not think of excipient effects as yes/no but to think of them as dose-response curves and it is a matter of at what dose and what level they are having an effect. We know that sodium laurel sulfate at a very low concentration has no effect and at a very high concentration dissolves the intestine. So, it is a dose-response curve issue. So, having thought a lot about this excipient issue and interactions with the gastrointestinal track, if we get into the excipient issues we should proceed carefully and mechanistically in evaluating those potential implications.

DR. HUSSAIN: A different perspective that I think also is important with excipients is if excipients have significant interactions that alters bioavailability it actually is a much larger issue than bioequivalence. It becomes a label issue because if it is an interaction that changes bioavailability the potential for that interaction

will be there in the marketplace and I think we try to avoid that, and I think the excipients that are available generally, with a few exceptions, are essentially from that perspective. The famous example is sorbitol.

DR. LEE: Then I will just propose that we take a 15-minute break so that we can maybe focus and discuss some of the issues more. Will you please come back at 3:15?

[Brief recess]

DR. LEE: Lawrence posed two questions to the committee. Actually, I should inform the audience that I began to form study groups in the committee to look at the issues. I have four individuals working this particular topic, Bill Jusko, Leon Shargel, Lemuel Moye and myself. Right after lunch I delegated my responsibilities to Bill and he is going to be the lead correspondent.

DR. JUSKO: Are you going to put the questions back up that we are to focus on? We have all heard from this morning's and this afternoon's discussion about the BCS classification system and the guidance that is in place for Class I drugs. It was interesting to learn this afternoon how few companies have actually taken advantage of this

classification system and proceeded to use it, with only five or six having been indicated.

The discussion this afternoon provided much more illumination of the basic scientific ideas and regulatory approaches to dealing with the BCS system, and we were asked to focus on two particular questions. Within the second question, it appears that there is plenty of room for recommendations as to how to proceed with the second question.

But let's go to the first one since it is the easier one to deal with. We were shown that there are discrepancies in the pH values used to determine solubility versus dissolution. So, the first question is should the agency consider revising the pH range of the solubility class boundary to be consistent with the dissolution pH range?

In my own view, the answer is quite obvious that one should seek consistency. Perhaps other members of the committee would like to provide their comments.

DR. MEYER: How about changing the other one to 7.5, have the same range but have 1 to 7.5 instead of 1 to 6.8?

DR. AMIDON: Can we comment?

DR. LEE: Sure.

DR. AMIDON: I think one element there, Marv, would be the harmonization also with Europe. At a workshop we had at the end of January with European representatives--6.8 is kind of an international standard, U.S., Europe, Japan for dissolution studies, simulated intestinal fluid. So, I think it is partly also that, harmonization to kind of the world standard. I think if we were to go from 6.8 to 7.5 we would have some problems.

DR. KIBBE: Yes, I remember when I was a young child my mother always telling me that you don't do things because everybody else did them. So, we have a harmonized number but the question really is, is it missing information or not? That is really the bottom line. Would we really miss out on something important if we left out going up to the physiological pH which exists at the terminal end of the GI tract? If w are clear that we are not going to lose anything, then it is okay. If we are worried that we are, then we should extend the other to 7.5 instead of cutting back to 6.8. That is the question I think.

DR. COOK: If I can comment on that, I

think the strongest evidence was when Lawrence put up the slide about transit time, and it is 85 minutes to that terminal end but we are requiring dissolution to be essentially complete within 30 minutes. So, it will never see the higher pH before it is all dissolved.

DR. KIBBE: Your disease requirement is in vitro dissolution and it is predictive of in vivo dissolution, but in vivo dissolution of something in 15 minutes might be 15 minutes and it might be 45 minutes. Okay. So, that still isn't a guarantee. I am not saying that 7.5 is where we ought to be, but I think we ought to know whether we are losing any information.

DR. RODRIGUEZ-HORNEDO: I was going to comment on that same point, and I struggled with the way that the question is worded until I saw Lawrence's slide with the pH in the different regions of the GI tract. Maybe the question needs to be reworded because it is not really a matter of consistency with the dissolution range which should specify that it is maybe the physiologically relevant dissolution range. It wasn't clear if this was an in vitro dissolution test that you were trying to be consistent with, but what is more

important is that it is physiologically relevant. So, with that in mind, my reaction is more positive to the recommendation. However, my question still relies on what about acids? Maybe you have weak acids that are very poorly soluble at pH 7. Maybe it is not relevant physiologically but I would like you to address that. Are there any drugs or any properties of drugs that are going to be of concern?

DR. AMIDON: For borderline drugs? There are a few NSAIDs. There may be. I think that is a good example. What might this impact? I think it is only a few drugs that it might actually impact. I think that is a good point. I think our goal here is to get the general view. We will come back with the evidence in the future, and we are interested in the type of evidence that the committee thinks would be supportive of a positive answer to this question one. For what types of drugs would this have an impact?

I think I would agree. Harmonization is a secondary issue. The question is reflecting the physiological process and having a valid BE type dissolution. So, I agree completely. On the other hand, other things being equal, we would want to

harmonize rather than disharmonize--other things being equal.

Ultimately, it is dissolution that counts, not solubility. Our dissolution standard is based currently on 6.8. So, dissolution is what counts. Solubility is one of the factors determining the dissolution rate but the dissolution rate is what counts.

DR. HUSSAIN: One point that I think needs to be kept in mind is the initial introduction of BCS was in SUPAC which covered all drugs. The BCS guidance, though focused on methods for classifying, focused on waivers of highly soluble, highly permeable. So, I think that is the disconnect that we tend to see, that is, the range of 1.2 to 7.5 is because it comes from the SUPAC guidance and the rapid dissolution criteria that we developed were for the BCS waiver guidance only. So, that is how we will have to resolve that.

DR. LEE: Okay, so we have answered the first question.

DR. JUSKO: I think we have resolved the first question reasonably well. To summarize, I think the answer to that is the inclination is to have them both be determined at pH 6.8 but look

into the possibility that there may be unusual circumstances where pH 7.4 would be particularly relevant.

The second question is should the agency expand the application of BCS-based biowaivers to rapidly dissolving, immediate release products of BCS Class III drugs? That question is a more profound one and appears to be connected directly to the list of proposed studies and data collection efforts to test the hypothesis that this is achievable, and it would be good to look again at one of the slides from Dr. Yu. That one.

[Slide]

Clearly, it is premature that anyone go directly to implementing this type of policy, and I think we are at a stage where the committee is probably recommending that a number of studies be done to investigate and confirm that this is a reasonable thing to do. This list of studies was proposed and I would welcome comments from other people on the committee.

DR. SHARGEL: One, it does strike me as being a reasonable approach. I think, if I understand this correctly, the premise is that these drugs would rapidly dissolve and would be

very similar to giving it as a solution almost for the time spent in the gastrointestinal tract. So, the issue then becomes if you have a solution of the drug would the excipients in a solid dosage form make any difference in the permeability realm. That is the issue I think as to make this a universal kind of approach.

DR. YU: That is correct.

DR. HUSSAIN: I just want to make sure that you are not committing to do those studies with our money. We will take this recommendation to PQRI and have industry do those studies.

[Laughter]

DR. JUSKO: With all the money that Pfizer has saved, I am sure they are going to be the ones to fund it.

[Laughter]

DR. COOK: That is how I got my salary all the way up to $20,000 a year!

DR. LEE: Well, I think it is a serious question and I think underlying this is the meaning of permeability. I think I have heard repeatedly throughout the day that while we are very comfortable with dissolution solubilities being unambiguous, when it comes to permeability that is

not so. Since someone else is going to pay for it, we may as well address this issue more seriously. What do we mean by permeability?

DR. YU: Yes, for BCS Class III drugs we will collect a number of drugs and cover a wider span of permeability. From there we will answer some of the questions and some of the concerns with respect to BCS biowaiver for Class III drugs. For example, with internal studies we are proposing intermediate permeability. Once we have the data, I think the data will tell us which direction we should go in. Thank you.

DR. HUSSAIN: I think one sort of point that we would consider, I think is Hans Lennernas has published on water, a glass of water. Water has a permeability value which is fairly close to metoprolol. It so happens that the permeability of water itself is at the boundary. So, that has an implication that when you give a glass of water and a solid drug after an all-night fast, the glass of water might get absorbed more quickly than the drug has time to dissolve. I think we can bring that as a sort of research question and address some of that; some of the work that Gordon has done with perfusion studies, and so forth, and what

implication that has.

DR. LEE: Yes, Larry?

DR. LESKO: If we look at that slide as a way forward in anticipation of bringing results back to the committee in the future, to get back to the specific question about biowaivers, I wonder if the committee members would have any thoughts on what they would expect to see from these studies. In other words, let's say I go out and I do a comparative study of a solution versus these dosage forms, would it be important to demonstrate strict bioequivalence based on the 90 percent CI of 80 to 125? Would it be satisfactory to deal with the point estimate? These are important considerations in terms of designing and powering these studies to address the question that we have. So, I wonder if anyone has any thought on that.

The other part of this question is how we select the solid dosage forms. Is there any advice that committee members could give on the identification of particular excipients that would come to the forefront of people's mind that would be worthwhile considering as part of the selection process for the dosage forms. So, let's say that we do come back in a year or something like that

and have data, we don't miss something that may be particularly important in terms of potential excipient effects.

DR. SHARGEL: Somehow, Larry, I am compelled to talk about 90 confidence intervals and bioequivalence. So, if you do the study I would expect the same criteria would be held up.

MR. VENITZ: I would second that.

DR. BOEHLERT: I don't have a list of excipients that you should be looking for, but I certainly think that should be one thing you should consider in doing these studies because, you know, you keep repeating that excipients can have an effect on oral absorption and I would like to understand that better, where and how, so we could begin to identify which excipients might be problematic.

DR. LEE: Lawrence, have you shown us those ten mono drugs? Did you provide a list?

DR. YU: Well, this is just the 12 potential BCS class drugs. We will come back with some other drugs which are potentially Class III drugs. That doesn't necessarily mean we will study all ten. Maybe some data is already available from NDAs and ANDAs.

DR. HUSSAIN: I think we have done two studies, cimetidine and ranitidine, as Larry pointed out. So, we have a good database on that with manufacturing changes and dissolution changes on two of those already. So, one could look at a range of permeability values that could be selected to account for that. At the end of the experiments I think one aspect might be that you might need an intermediate class of permeability because right now you are going from 0-90, and I think when you start going down to 20 and 30 percent, that is where you start having problems. So, a range of permeability values will help us maybe define and intermediate permeability class.

DR. KIBBE: Is there less concern for a company who decides to change the site of manufacture from point A to point B and saying, okay, it is a Class III and I am just going to show you that I have the same dissolution characteristics because I have just transferred my process than with a second company who has a new formulation and wants to do a biostudy? Would that delineation help us move Class III's where we could waive it in one case and not necessarily in another?

DR. HUSSAIN: Well, I think SUPAC scale-up and post-approval change actually did that. It brought a risk-based approach or three-tier approach for that. For example, for site changes alone with no other changes, for a immediate release dosage form it is qualification based on dissolution alone. If you have other types of changes, BCS comes in when there are excipient changes, and so forth.

DR. RODRIGUEZ-HORNEDO: My observation is that most of these compounds are weakly basic. Right? Almost all of them?

DR. LESKO: Hydrochlorothiazide is a weak acid, I believe.

DR. RODRIGUEZ-HORNEDO: Yes. Most of them are weakly basic, and I am coming back to that issue of pH dependence on solubility. I know it is not the main issue here with the permeability but maybe something that hasn't been addressed is the pH dependence of the permeability. Is that of concern?

DR. COOK: I don't know if this list was proposed to take the ten drugs from. I think we could take it back. We want to look at acids and bases, and we want to look at a range of

permeability that probably even exceeds what we have here to provide the best data. So, I don't think I would get too hung up in saying that these are the model compounds that one would use. It is better to use a broader range that encompasses more things so we will have more confidence in the results.

DR. AMIDON: That is a good question about pH dependence. The pH 6.5 with the perfusing system that we use in humans provides a reference permeability, kind of like a thermodynamic PK; it is not really what is going on in solution but it is what you use to move ahead. So, we measure this reference PK. We have done permeability studies in humans with alpha methyldopa a long time ago, and that is pH dependent. It parallels that in animals, and there is a variety of reasons for that pH dependence. From the point of view of predicting drug absorption and drug absorption variability, it would be very important. So, I would want to know that as a development scientist. I don't see how it would help in a regulatory classification or decision-making process. We take the mean pH of about 6.5 for the human intestine and say, okay, we are going to use that as our

reference value and stay with that. It gets to cumbersome otherwise.

But for some of these drugs, I know because we have studied hydrochlorothiazide, they are very pH dependent, and we have also done furosemide. So, the actual operative permeability of pH 6.5, the permeability decreases there greatly because it is ionizing. It is probably absorbed. It has a very sharp absorption window because it is the permeability, solubility procedure that counts. Solubility is going up, permeability is going down. I think that is why it is a highly variable drug. It is not bioequivalent to itself, at least in one study, because of the variability so we are getting into problem drugs here--I should say variable drugs. I am interested in the pH dependence, but I can't justify it on the basis of regulatory use.

DR. LEE: It seems to me that this is an ideal situation for forming a subcommittee to work with Lawrence to just design a study. Right? The choice of drugs, excipients, in vivo, in vitro, other kind of parameters.

DR. YU: That is an excellent suggestion, yes.

DR. JUSKO: I think it would also be good

to keep in mind making maximum use of complementary information, like structure activity types of predictions, as well as the data gathered from animal studies so that one has more than one measurement to base any anticipated results on.

DR. YU: This comes to my favorite topic, my true research interest is in the structure activity relationships. As long as my boss says okay, do it, we will do it. Definitely.

DR. LEE: I thought you were going to say you would do simulation studies.

DR. YU: Yes, we will do simulation studies.

DR. LEE: Maybe that is the place to start.

DR. LESKO: I want to get to the proposed research because it is such a key to moving forward. One of my concerns, and maybe I will ask Lawrence to comment on this, is what is the possibility or probability that you will be able to find two solid dosage forms of these Class III drugs that meet the rapid dissolution characteristics that are being proposed for it? Is this a study that is sort of Jack Cook's blue sky, or is this a study where you can actually go into

the marketplace and find these things, or is it a set of studies where you would actually have to formulate the products to meet the rapid dissolution criteria, or all of the above?

DR. COOK: Larry, would you consider a solution versus tablet sufficient? That way, I only need to compare those two rather than two solid formulations?

DR. LESKO: Well, let's say we are doing two tablets, but as I understand this research, if you are going to go into the marketplace to find those solid dosage forms, tablets, whatever, they aren't necessarily formulated to be rapid dissolution.

DR. COOK: That is why I was suggesting a solution which is, for a highly soluble compound, a lot easier to formulate and compare that to a tablet. So, you have one that is extremely rapidly dissolving, the solution, and then the tablet and you can probably look at the excipients in that as well.

DR. LESKO: So the tablet would be rapid dissolution as well, 15 minutes?

DR. COOK: Well, it would have to be 15 or 30 minutes, whatever we propose. So, you would

have to make one formulation, is what I am saying, rather than two.

DR. LESKO: I think actually that would be a good idea because you are talking about ten drugs with a comparative study, which is no less than what we have for the original fasting study, bioequivalence studies. In fact, it would exceed it I think in terms of the total in vivo data to support a biowaiver. But, again, that question about what is the drug and what is the formulation, and whether they are commercially available or not, would be a limiting factor.

DR. YU: Certainly, I think we need to be flexible, and we have limited research dollars. If it is available on the market we will supply them for the studies. That is the value of having a subcommittee under the ACPS to get advice from the members to see how best to utilize the money to get the information we can get.

Secondly, we certainly want to utilize what is out there in the literature and what is out there in the NDAs and ANDAs. From there, we would design--we only can conduct what is necessary to address issues from those studies in NDAs or ANDAs which we are not able to address.

DR. KIBBE: Larry, why can't you go to the data the FDA already has and get the dissolution profiles of all these products to start with? I think it might be a little bit better if there were two products out there that would give you relative rapid dissolution. I think you would be better off looking at them, and using as a fall-back a procedure that isn't on the market, a solution.

DR. LESKO: Yes, I think the missing link there is the dissolution studies that would not necessarily be available in an application--

DR. KIBBE: Why not?

DR. LESKO: Well, because we are talking about a very specific set of dissolution test conditions to test a hypothesis of Class III. Those dissolution conditions may not have been studied as part of the normal drug development. So, you can't just go back to the applications and pull that information out. In almost all cases you have to go to a laboratory and redo that to the specifications that you would like to support the hypothesis. But that is doable. I mean, that is just reality; you just have to do it.

DR. YU: Absolutely. We actually conducted a food effect study which was presented

this morning. When we selected a drug we purchased the products and we did a lot of in vitro testing before we selected these two specific products for in vivo studies. It is doable and we have the facility to do that within the agency.

DR. MEYER: It seems to me though that one of the pieces of rationale I heard was that Class I and Class III act like solutions. So, if we did studies for low permeability drugs, solution versus a marketed or experimental tablet, what-have-you, just that two-way crossover, you would in a sense prove whether the low permeability--while we know it dissolves rapidly--also is sufficiently permeable or permeability isn't a factor. So, that seems to be a rational way of approaching it given your initial hypothesis, solution versus tablet.

DR. YU: You are right. You are absolutely correct, yes.

DR. MEYER: Can I raise one other question? Just to kind of support the concept of I think we still need to look at low permeability, and that is that study that Ajaz had in his handout from UT, ranitidine, sorbitol sucrose and metoprolol, sorbitol sucrose, both solutions. And, the metoprolol, which is highly permeable or

borderline high, had a confidence interval, sucrose solution sorbitol 86-100 for AUC so it was essentially bioequivalent, unchanged by sorbitol. Whereas, ranitidine, which is low permeability, dropped to 62 percent. So, the effect of sorbitol was much greater on the low permeability ranitidine than it was on the high permeability metoprolol. So, we do have to worry about excipient effects. Maybe this is the worst excipient known to man and that is biasing our information, but maybe it isn't so I think we still need to look closely at that.

DR. HUSSAIN: I think we would need to but I think I would go back to what Gordon suggested in a sense, for a solid oral dosage form it is the dose of the excipient that is important. When you think of a syrup you are looking at a tablespoonful or two tablespoonfuls so sorbitol in a solution is a much larger dose and a tablet is a much smaller dose. So, that also I think is an issue that should be considered. So. But I think Ian Wilding has done the work with chewable tablets with cimetidine. So. So, two grams of sorbitol with mannitol had a dramatic effect on cimetidine. So.

DR. AMIDON: It may relate to the water reabsorption and the absorbable versus not

absorbable excipients, and it would inhibit water absorption which would slow down cimetidine's absorption and if the transit is also speeded up you can come up with a good rationale for the mechanistic reasons, which suggests that maybe you should classify excipients in some way. I mean, if the excipient is absorbed, it is gone at some point. So, maybe it is low permeability or non-absorbable excipients that may have a problem so you can perhaps reduce the problem that way. I don't know.

DR. HUSSAIN: I think we talked about that and actually low permeability, highly soluble excipients are the ones which gave problems. If I go back to Ian's work, and Ian could comment on that, he actually did an experiment--Ian, correct me if I am wrong--where he started with equal osmotic pressure between sucrose, pyrophosphate and sorbitol and mannitol, and showed that initial osmotic pressure essentially.

DR. WILDING: We were trying to produce osmotically equivalent concentrations of sodium acid pyrophosphate, mannitol, the intention being to try to work out what the mechanism was. As Gordon indicates, I am sure there are mixed

mechanisms going on in terms of how the excipients have their effect, but I am sure it is the non-absorbable excipients that will have the key issue in this regard.

I was just wondering as you were talking, the choice of excipients that you use in the context of these studies is obviously going to be important. I wonder how much of the work, as Vince indicated, could be done by modeling in advance to create the matrix which is then tested by the human biostudies. So, in looking at drugs for different fraction absorbed in terms of Class III, given the excipients' different release rates, trying to build some form of modeling for that which then forms the basis on which the human biostudies are done. Because what you might find, if you are not careful, is that human biostudies might not provide the answer to the questions, which would be a waste of time, money and effort.

DR. HUSSAIN: To that effect in the sense of we worked with Jim Pauley last two years to look at CACO 2 in vitro permeability experiments as a screen to try to identify, hopefully, excipients which might be affecting the permeability of the membrane itself. I think from the literature and

from what Ian and we have done, we know the osmotics. So, we are essentially looking at several mechanisms by which these excipients can exert an effect. So the studies we do and the models we select, if they are mechanistically based and based so we can actually get a hypothesis and test that, would be far more meaningful than randomly selecting those excipients.

DR. YU: Actually, we have done some mathematical modeling work to simulate Ajaz' study done at the University of Tennessee, to look at how excipients in this particular case, sorbitol five grams that one tablet will have, to look at how the sorbitol affects oral drug absorption of ranitidine. We have really nice results. Certainly, we also want to evaluate it in the low dose. I think those study results will all be valuable in the future for how to address some of the concerns expressed here. Thank you.

DR. HUSSAIN: One example that you have in your handout is from my presentation. The drug is atenolol, the tablet with a solution, and the tablet has twice the bioavailability than the solution. There is about 750 mg of sorbitol in that. So, you know that even 750 mg in a solution

can reduce bioavailability by 50 percent compared to a solid tablet. So, I think the thing which is exciting to me is the major mechanisms by which excipients exert their effect. As that happens, we actually happen a means of doing hypothesis-based testing underpinned by mechanistic basis for this.

DR. LEE: In other words, the excipients can no longer be considered as inert.

DR. HUSSAIN: I don't want to alarm people with that. I think we have to be very pragmatic. I think some excipients have effect but I think overall in a solid dosage form I don't think there is a major concern. So.

DR. YU: The majority are inactive and some of them, like sorbitol, may have some concerns, yes.

DR. ANDERSON: Aren't you talking about molecular interactions which are pH dependent, particularly with those things that have all those OH groups on them?

DR. YU: For solubility or permeability? What aspect?

DR. ANDERSON: Well, if the solubility of the drug is pH dependent, that is, if it has the nitrogen or carboxylic acid group in it, and you

have all the OH's on the other things, whatever you call them, you are talking about molecular interactions which are pH dependent. The pH really affects even those things with the OH groups on them because the OH groups are basic as well.

DR. COOK: I guess that is another way of looking at how you are classifying how the active adjuvants, to steal somebody else's classification, interact because not only are we worried about that but things that change the physiology, whether it be something that changes the osmolarity or something that interacts with the membrane itself. I guess the investigation of excipients is even broader than just the molecular interaction.

DR. LEE: Bill?

DR. JUSKO: It sounds like there has been considerable and very fruitful discussion about the issues relating to these proposed studies. My view, and I believe the committee believes that there is good possible potential for future biowaiver for the Class III agents, but before that is done a very careful assessment of many of these basic questions needs to be done. It appears that an ample data set needs to be collected, and many questions related to the role of excipients remain

to be resolved. So, there is great encouragement from the committee to continue along this line.

DR. LEE: Well put. Maybe a future committee will hear these results. Are there other issues to be brought forth before this group? We have had a very fruitful day.

DR. HUSSAIN: One issue, and I don't want to be caught again like with the highly soluble, highly permeable drugs, is the food effect. If we go with a waiver for Class III, I think the logic we be that we have to consider the food effect alongside because otherwise it doesn't make sense. So.

DR. LEE: That is for the record.

DR. HUSSAIN: So, this should also expand to the food effect too at the same time.

DR. YU: You are absolutely right. We will probably begin to collect the coefficient of valence for a number of drugs compared under fasting conditions and under fed conditions to see if the valence becomes bigger or smaller, and how to address this concern that we had this morning. Thank you.

DR. LEE: We began the day talking about subcommittees and I think this is an excellent idea

for clinical pharmacology, and not put a spotlight on clinical pharmacology but also may serve as a catalyst for other changes in the committee. Then we went on to talk about a very interesting issue about food effect on Class I drugs. I think the committee is not that comfortable. Well, the answer seems to be obvious but we don't have enough evidence to support our gut feeling.

This afternoon I think we got a very good understanding about the BCS Class I, Class III. I don't want to repeat what Bill Jusko just talked about. He put it very succinctly what needs to be done. I think that we are going to hear about the results of this work in a few years time, but the committee, or at least I would like to see the use of computation as a way to guide the experimental design, and also to think about this permeability more carefully, especially when we are encountering more drugs that require transporters for absorption.

DR. HUSSAIN: Let me go back to the issue of the food effect waiver because that is an important issue and I think I want to stress the logic of the situation being such that it doesn't make sense not to give waiver for fed studies for

Class I rapidly dissolving when we give the waiver for fasting studies. I just want to stress that fact because I heard from Marv that he is in agreement with that. I really would like to have a position of the committee on that one. So.

DR. LEE: That is the position.

DR. HUSSAIN: What is the position?

DR. LEE: What you just said.

[Laughter]

DR. HUSSAIN: So, the committee agrees with Marv and the logic prevails?

DR. LEE: Right. What I have seen today, shall we revise the guidance, reminded me very much about curriculum revision. Tomorrow we can forget about biology more or less, and we will focus on some physical chemical issues. So, we begin tomorrow at 8:30. Please plan on staying the entire day because we have a full agenda, I mean the committee members. You can leave the stuff here because it is safe.

[Whereupon, at 4:00 p.m., the proceedings were recessed, to reconvene at 8:30 a.m., Wednesday, May 8, 2002.]

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