FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY

ADVISORY COMMITTEE MEETING

DAY 2

Rockville, Maryland

Wednesday, July 23, 2008

PARTICIPANTS:

Committee Members (Voting):

KENNETH R. MORRIS, Ph.D., Chair
College of Pharmacy
University of Hawaii at Hilo
JESSIE L-S. AU, Pharm.D., Ph.D.
The Ohio State University

JOHN F. CARPENTER, Ph.D.
School of Pharmacy
University of Colorado Health Sciences Center

CAROL A. GLOFF, Ph.D.
Carol Gloff & Associates
MERRILL GOOZNER
Consumer Representative
Center for Science in the Public Interest
MARILYN E. MORRIS, Ph.D.
School of Pharmacy
State University of New York
ANNE S. ROBINSON, Ph.D.
Department of Chemical Engineering
University of Delaware
ELIZABETH M. TOPP, Ph.D.
Department of Pharmaceutical Chemistry
The University of Kansas

Temporary Members (Voting):

JERRY M. COLLINS, Ph.D.
National Cancer Institute
National Institutes of Health
ARTHUR H. KIBBE, Ph.D.
Nesbitt School of Pharmacy
Wilkes University

PARTICIPANTS (CONT'D):

Temporary Members (Voting) (Cont'd):

MELVIN V. KOCH, Ph.D.
University of Washington

MARVIN C. MEYER, Ph.D.
College of Pharmacy
The University of Tennessee

HARRIET B. NEMBHARD, Ph.D.
Pennsylvania State University

Committee Members (Non-Voting):

MUKUL A. AGRAWAL, Ph.D.
Industry Representative
Roxane Laboratories, Inc.

PHILIP R. MAYER, Ph.D.
Industry Representative
Wyeth Research

RICHARD J. STEC, JR., Ph.D.
Industry Representative
Hospira, Inc.

PATRICIA C. TWAY, Ph.D.
Industry Representative
Merck Manufacturing Division

Designated Federal Official:

LCDR. DIEM KIEU H. NGO, Pharm.D.
BCPS

Guest Speakers:

ABU ALAM, Ph.D.

PAUL DORINSKY, M.D.

PARTICIPANTS (CONT'D):

Guest Speakers (Cont'd):

DALE GERDING, M.D.

JAMES POLLI, Ph.D.
School of Pharmacy
University of Maryland

GUY ROUSSEAU

FDA (Non-Voting):

HELEN WINKLE
Director
Office of Pharmaceutical Science

NORMAL SCHMUFF, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment II

KEITH WEBBER, Ph.D.
Deputy Director
Office of Pharmaceutical Science

WALLACE P. ADAMS, Ph.D.
Office of Pharmaceutical Science

GARY BUEHLER, R.Ph.
Director
Office of Generic Drugs

BADRUL A. CHOWDHURY, M.D., Ph.D.
Office of Drug Evaluation II

SUSAN CUMMINS, M.D., M.Ph.
Pediatric and Maternal Health Staff
Office of New Drugs

PARTICIPANTS (CONT'D):

FDA (Non-Voting) (Cont'd):

FRANK HOLCOMBE, JR., Ph.D.
Office of Pharmaceutical Science

MICHAEL E. KASHTOCK, Ph.D.
Office of Food Safety
Center for Food Safety and Applied Nutrition

JOHN KAUFFMAN, Ph.D.
Division of Pharmaceutical Analysis
Office of Testing and Research

ROBERT LIONBERGER, Ph.D.
OGD, OS

LAWRENCE YU, Ph.D.
Director for Science
Office of Generic Drugs

* * * * *

P R O C E E D I N G S

(8:36 a.m.)

DR. MORRIS: Good morning, everyone. Let's call this to order. I'd like to first welcome everybody, and just make a couple of comments that have to do with the sort of general nature of our discussion. There's of course no specific products being discussed; this is a general discussion.

And let me read the prepared statement. For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held, as we saw yesterday -- that's off the script.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder -- oh, sorry. If I had better glasses I could -- thus, as a gentle reminder, individuals -- do I have to

start over?

LCDR NGO: No.

DR. MORRIS: Oh, good. I didn't want to get shot.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee Members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the Committee is reminded to please refrain from discussing the meeting topic during breaks or at lunch.

Thank you.

And so before we start, if we could go around the table and do introductions; and as with yesterday, we can start with Keith.

DR. WEBBER: Keith Webber, deputy director of OPS, Pharmaceutical Science, FDA.

DR. WINKLE: Helen Winkle, director of --

DR. MORRIS: Your mic's not on, Helen.

DR. WINKLE: There we go. I'm sorry. Helen Winkle, director of Office of Pharmaceutical Science, CDER.

DR. BUEHLER: Gary Buehler, director, Office of Generic Drugs.

DR. YU: Lawrence Yu, director for Science, Office of Generic Drugs.

DR. AU: Jessie Au, distinguished university professor at Ohio State.

LCDR NGO: Lieutenant Commander Diem-Kieu Ngo, designated federal official.

DR. MORRIS: Ken Morris, professor of Pharmaceutics, University of Hawaii, Hilo.

DR. ROBINSON: Anne Robinson, professor of Chemical Engineering, University of Delaware.

DR. MORRIS: Marilyn Morris, professor of Pharmaceutical Sciences, University of Buffalo.

DR. TOPP: Liz Topp, professor of Pharmaceutical Chemistry, University of Kansas.

DR. NEMBHARD: Harriet Nembhard, professor of Industrial Engineering, Penn State University.

DR. KOCH: Mel Koch, director of the Center for Process Analytical Chemistry, University of Washington.

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

DR. KIBBE: Art Kibbe, chair and professor of Pharmaceutical Sciences, Wilkes University.

DR. GOOZNER: Merrill Goozner, I'm with the Center for Science in the Public

Interest. I'm the consumer representative on the Committee.

DR. COLLINS: Jerry Collins, National Cancer Institute at NIH.

DR. GLOFF: Carol Gloff, Boston University, and the independent consultant.

DR. TWAY: Pat Tway, Merck & Company, representing pharma.

DR. STEC: Rich Stec, Hospira, Inc., industry representative.

DR. MORRIS: Thanks, everyone. Now, Diem will read our statement.

LCDR NGO: Good morning, everyone. Before I re-read the statement, can I just remind everyone to silence your phones and pagers, or put on vibrate mode.

And if Sandy Walsh or Rita Chappelle is in the room from the press office, please stand up. Okay, I guess they're not here yet.

The Food and Drug Administration is convening today's meeting of the Advisory

Committee for Pharmaceutical Science and Clinical Pharmacology of the Center for Drug Evaluation and Research under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representatives, the members and the temporary voting members of the Committee are special government employees, SGEs, or are regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information, the status of this Committee's compliance with the federal ethics and the conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act, are being provided to participants in today's meeting and to the public.

FDA has determined that the members

and temporary voting members of the Committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial interests when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this Committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to

them, including those of their spouses or minor children, and for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

For today's agenda, the Committee will receive and discuss presentations from the Office of Generic Drugs, OGD, on one, "The Bioequivalence Methods of Locally Acting Drugs that Treat Gastrointestinal Conditions;" two, "The Use of Inhaled Corticosteriods Dose Response as a Means to Establish Bioequivalence of Inhalation Drug Products;" and three, "The Drug Classification of Orally Disintegrating Tablets (ODT) as a Separate Dosage Form, and the Need for Subsequent Guidance on the Expectations and Recommendations That Would Be Required for Applications Proposing the

Dosage Form."

This is a particular matters meeting, during which general issues will be discussed.

Based on the agenda and all financial interests reported by the Committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 USC Section 208(b)(3) and Section 712 of the FD&C Act to Dr. Marvin Meyer for his stock ownership in two health care sector mutual funds. The waivers allow this individual to participate fully in today's deliberations.

FDA's reasons for issuing the waivers are described in the waiver documents which are posted on FDA's website at www.fda.gov/ohrms/dockets/default.htm. Copies of the waivers may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of the Parklawn Building.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Additionally, we would disclose that Dr. Carol Gloff is excluded from participating in today's discussions on "The Use of Inhaled Corticosteriods Dose Response as a Means to Establish Bioequivalence of Inhalation Drug Products," due to her involved with an affected firm.

We would also like to disclose that Dr. Richard Stec and Dr. Patricia Tway are serving as industry representatives acting on behalf of all regulated industry. Dr. Stec is an employee of Hospira, and Dr. Tway is an employee of Merck & Company.

We would like to remind the members and the temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or an imputed

financial interest, the participants need to exclude themselves from such involvement, and their exclusion would be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that they may have with any firms at issue.

Thank you.

DR. MORRIS: Thank you, Diem. First topic of the day is "Bioequivalence Methods for Locally Acting Drugs that Treat Gastrointestinal Conditions." And we're going to start with presentations, the "Bioequivalence of Locally Acting GI Drugs; and Lawrence Yu, the Director for Science at OGD, is going to introduce the topic.

DR. YU: Thank you. Good morning, Professor Ken Morris and FDA Advisory Committee Members, my FDA colleagues, and distinguished guests.

As Professor Ken introduced, I'm

Lawrence Yu, director for Science, Office of Generic Drugs. It gives me a great pleasure and privilege to introduce this morning's topic, "Bioequivalence of Locally Acting GI, or gastrointestinal, Drugs."

At the end of today's presentation, we will ask two questions, specifically: what role should biorelevant dissolution play in developing bioequivalence recommendations for low solubility locally acting drugs that treat GI conditions? What role should systemic pharmacokinetics play in developing bioequivalence recommendations for low solubility locally acting drugs that treat GI conditions?

I should emphasize, this morning's discussion on locally acting drugs will be focused on -- in general of bioequivalence -- general bioequivalence of locally acting GI drugs; will not focus on any specific drug or drug product. Again, this morning's discussion will focus on

bioequivalence of locally acting GI drugs in general; do not focus on any specific drug or drug product.

We will have three presentations. I will give an overview. Professor Jim Polli from the University of Maryland will discuss scientific principles and the scientific considerations. Dr. Rob Lionberger from Office of Generic Drugs will discuss with you the bioequivalence of poorly soluble locally acting GI drugs.

My presentation will discuss bioequivalence in general, locally acting GI drugs -- the discussion which have occurred by this Committee in October of 2004, and finally, update you of the progress we have made so far.

So what is bioequivalence? The bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredients or active moiety becomes available at the sites of drug

action. Now, this is for pharmaceutical equivalent or pharmaceutical alternatives. In short, the bioequivalence is defined as the absence of a significant difference in the rate and the extent of drug absorption.

So when we define the pharmaceutical alternative or pharmaceutical equivalence, what is the pharmaceutical equivalence? I know this terminology is not very commonly used in the scientific literature. The pharmaceutical equivalence means the same active ingredients, the same dosage forms, the same route of administration, identical in strength or concentration; may differ in characteristics such as shape, excipients, or packaging.

Bioequivalence clearly (inaudible) in the approval of generic drugs, but also, widely used for the approval of new drugs. Bioequivalence is used to link clinical trial material to a to-be-marketed product for the changes in formulation, for the changes in

manufacturing process, for the changes in dosage form, such as from capsule to tablet, or table to solution.

The equally significance is to the approval of generic drugs. Bioequivalence, along with the pharmaceutical equivalents, ensure the therapy equivalents. The therapy equivalent product can be substituted each other -- therapeutic equivalent product include generics, can be substituted to innovative product, or we call it, reference listed product.

Bioequivalence, it's also utilized for the post-approval changes, regardless whether innovative product or generic product, or brand name product, for the significant major changes, such as the formulation and manufacturing process.

21 CFR defines approaches to determining bioequivalence. In vivo measurement of active moiety or moieties in biological fluid, which we usually call it,

pharmacokinetic method or pharmacokinetic study. In vivo pharmacodynamic comparisons, we call it, bioequivalence study with PD endpoints. In vivo limited clinical comparison, which we call bioequivalence study with clinical endpoints. And in vitro comparison, in vitro dissolution comparison. And finally, any other method deemed appropriate by the FDA.

Now in the recent years, in vitro method, or in vitro dissolution method, has become more and more widely used. Nevertheless, the pharmacokinetic study remains the most popular, most commonly used method -- preferred method. And the pharmacokinetic is usually conducted in healthy volunteer in single dose crossover.

(inaudible) individual product already given to patients, for example, or healthy volunteers, we will have that, we will have a plasma concentration profile, as it shown in this slide. We will have a Cmax.

We will have AUC.

As we define the bioequivalence as the absence of a significant difference in the rate and extent of drug absorption, here, the Cmax is a surrogate for the rate of drug absorption. AUC, or area under the curve, is a surrogate for the extent of drug absorption.

So therefore, we use, commonly use, pharmacokinetic study to demonstrate bioequivalence of -- especially, for (inaudible) systemic drugs. We use AUC and Cmax as a pharmacokinetic parameters or surrogates for determining whether product, test product, and difference product bioequivalent or not.

Well, yes, pharmacokinetic studies is very successful. Pharmacokinetic studies has allowed -- approved over 7- or 8,000 generic drugs, as used by almost majority or all American public; contributed significantly to the health care systems in

America.

However, this method may not be applied, as it may not apply to the locally acting GI drugs. Here are the reasons. For systemic drugs, the site of action is downstream. So therefore, the concentration in the plasma in the blood control the rate -- control the safety and efficacy. The same pharmacokinetics ensure the same safety, ensure the same effectiveness of drug.

However, for locally acting GI drugs, the site of action is upstream of the systemic circulation. In other words, the site of action, does the drug produce its effect before it gets absorbed, before it has reached the systemic circulation. So therefore, the concentration in the plasma may not totally reflect -- reflect the concentration in the bloodstream in terms of time and location. Time and location.

Let me explain to you further. If it supposedly has two sites of absorption.

For example, in the duodenum or ileum, if there's two sites of absorption, the pharmacokinetic curve may be very similar. However, site absorption could be different. Because a different of site absorption if this drug produced its effect in the duodenum or the ileum, in the jejunum, then if the drug is absorbed in the duodenum, certainly, it will not produce effectiveness as a jejunum.

However, the drug absorbed from ileum will produce effect in the jejunum, because the drug travels from stomach, duodenum, jejunum, and ileum, and the colon. Of course, if this drug produces effect in the colon, then, regardless of whether (inaudible) duodenum or jejunum, it doesn't matter, because the same drug concentration probably is reached in the colon.

So therefore, I said, the pharmacokinetic equivalents may not produce equivalents in terms of performance. Of

course, it depends on drug and drug classes, depends on site of actions in the GI intestinal tract, GI tract.

Then, what factors affect the performance of those locally acting GI drugs? Those factors very similar -- the factors impact the drug absorption dosage form factors, drug substance or excipient factor, or sometimes in the drug absorption, (inaudible) we call the formulation factors, and physiological factors. For example, immediate release dosage versus systemic release dosage for a modified release dosage form. Impacting solubility, excipient, the permeability, and GI motility, GI pHs.

Now, there was one significant difference when we compared the factors affect (inaudible) drug (inaudible) versus the factors impact the performance of a GI locally acting drugs: major impact is excipients. This is because for drug absorption, excipients mainly impact the

rate, extent of absorption. But for the locally acting GI drugs, excipients not only impact drug absorption, but also impact -- I should have said, may impact -- may impact the performance of those drugs in the GI tract. Because, for the simple reason, excipients are there when drug produces impact in the GI tract.

So, when we consider the bioequivalence method of -- for locally acting drugs, those factors, those performance factors, formulation factors, physiological factors, those factors will have to be considered.

For those locally acting drugs, include the GI -- locally acting GI drugs, inhalation product, and topical products, indeed presents tremendous challenge for us, for the Office of Generic Drugs. And four years ago, in October 19 to 20, 2004, this topic was discussed, was presented to you, to seeking advice of this Committee. I know the

many, many members, including Art, Marvin, and Mel and Carol, and Ken, were members of that 2004 FDA Advisory Committee for Pharmaceutical Science.

At this meeting, we asked you four questions. Number one: For locally acting GI drugs, is a pharmacokinetic an in vivo sensitive formulation performance as useful as a part of determination of bioequivalence?

Question number two: Are there any drug specific issue that aids FDA in interpreting results of a pharmacokinetic study on a GI acting drugs with respect to a conclusion about bioequivalence?

Question number three: When is it possible to use dissolution testing alone to demonstrate bioequivalence of locally acting GI drugs?

And question number four: What should a comparative clinical trial study be conducted to demonstrate bioequivalence.

All this is available on the FDA

website. The Committee, this provides us the following recommendations. This exactly was -- was copied, so it's very busy slides. But let me point out the some of the conclusion which you have reached have had significant impact on us.

Number one: The pharmacokinetic studies are useful to assure the safety of the test product. In other words, we should use pharmacokinetics to assure the safety of the test product.

Number two: The members stressed that dissolution tests are formulation tests, can be a surrogate for clinical tests.

Number three: The bioequivalence for locally acting drugs, such as nasal, GI, topical be part of a Critical Path Initiatives so that those method, or bioequivalence method, it can be acceleratedly developed so that they'd be available of the generic drugs to the American public.

The Committee concluded, finally, that in order to prove bioequivalence, in vitro dissolution, along with the pharmacokinetics, should be acceptable. So in vitro dissolution, along with the pharmacokinetics, should be acceptable.

Now, those in vitro dissolution can be easily conducted to -- for highly soluble drugs, but they may not be possible, or may be difficult to do, to -- for lower soluble, poorly soluble drugs for -- because for poorly soluble drugs, in order for the drug to dissolve, very often we have to put a (inaudible). That's why we want to seeking advice today. We're seeking advice today.

Now, based on your recommendation, in May of 2007, FDA Office of Generic Drugs issued the White Paper or document on Critical Path for Generic Drugs. In this document, we identify four areas, including quality by design for generic drugs; including bioequivalence of systemic drugs;

including bioequivalence for locally acting drugs; finally, characterization for complex drug substances or drug product.

So therefore, we pick -- we took your advice and put bioequivalence for locally acting drugs, including nasal, inhalation, topical product as a part of our Critical Path Initiative for generic drugs.

We also have made some progress. I recognize this progress is limited. I certainly wish it would be faster than this. That -- immediate release dosage forms. As I talked, when we look at a performance factor for locally acting drugs, we have a dosage form, we have a formulation, we have drug substance, and we have physiological factors. So therefore, in order for us to make a scientific, mechanism-based recommendation, we have to look at those factors.

The first fact is dosage form. What is immediate release, or modified release, or other dosage forms? So for

immediate release dosage form, if drug substance are highly soluble, for immediate release dosage forms, if the drug substance (inaudible), if the test and the reference list of drug product have the same formulation, qualitatively and quantitatively.

Now, if you look at the Orange Book FDA has documented many cases -- Q1 and Q2. Q1 means that formulation -- that qualitatively the same. Q2 means they are quantitatively the same. The bottom line is that when your Q1, Q2 the same, or they are the same formulation in terms excipients, in terms amount.

So if the drug is dosed in -- is a highly soluble, formulated in immediate risk dosage form, if the test (inaudible) generic product and the reference list product have the same formulation, and (inaudible) the bioequivalence may be demonstrated by in vitro dissolution tests covering

physiological relevant pHs. That's because when you have a same formulation, impact of a difference of excipients is diminished or, I can say, eliminated.

When you eliminated excipients' impact, what is major impact here. Its impact is (inaudible) dissolution. (inaudible) dissolution. Yet, we have (inaudible) the sameness or similarity of in vitro dissolution, to ensure the similarity or the sameness of dissolution in vivo. So that, therefore, when we have a same formulation for highly soluble drugs, formulated in immediate release dosage form, when you have a same or similar dissolution profiles, we can scientifically conclude that these two products are bioequivalent.

So what about highly soluble, formulating immediate risk dosage form, yet as a test and (inaudible) level could have a different formulation. Then, we may say that we made the study include in vitro, in vivo

PK and PD, as well as even clinical trial, maybe clinical trial studies may be recommended.

Let me give you an example to illustrate those points. Now, for this, Drug X surpassed the test product, and the reference product have the same formulation, qualitatively and quantitatively.

If they have a same formulation, we basically recommended the dissolution method alone. When we show the similarity in dissolution at the 0.1 HCL, pH 4.5 buffer, as well as pH 6.8 buffer.

Now, you may ask, for those highly soluble drugs, would they dissolve reasonably faster, probably within 30 minutes, are complete, why do we ask it for dissolution at the high pHs, pH 6.8 or pH 4.5? Because dissolution almost complete or they are complete in the stomach at low pHs. This because we want to make sure that we cover all the pHs happened in patient. I recognize

some are even healthy volunteers up here. The patient is they will have pHs in the stomach. They have a -- we have to have a lot of people have a stomach pHs 4.5 or higher. Certainly, majority of us have a pHs at 1.2 or 2. This part of reason why we ask three pHs so that almost in any (inaudible) scenario pHs in -- almost in any patient, they are covered. Therefore, we expect very, very low risk.

And here is a Drug Y of the test product and the innovative product, or reference list product. They use different formulation. What happened. As I said, if they use different formulation, even though they are highly soluble, even though they are formulated immediate release dosage form, yet, we recommend in vitro, in vivo, even clinical trial studies. In this case, the bioequivalence is demonstrated by a PD endpoint.

So we have a good idea with respect

to highly soluble, formulated immediate release dosage forms, what we should do, in terms of recommendation for bioequivalence method. The question is what about other dosage forms. What about the other drug products. So for poorly soluble drugs, is a topic for today. I know you recommended dissolution along with the pharmacokinetics should be acceptable, yet, in for poorly soluble drugs, it is a challenge to conduct dissolutions because we have added this effect into many cases. So we are seeking advice at today's meeting.

For modified release dosage forms, we are still recommending, at this point, with the clinical endpoints. Certainly, we are actively exploring in vitro and in vivo approaches. We recognize that bioequivalence with clinical trials is probably too expensive. But that's the way right now we goes, because we do not have a sufficient scientific evidence data recommend the other

simplified or simplified approaches. Certainly, we are exploring. So we're seeking advice, too, on this.

So finally, I give you the overview of bioequivalence for locally acting GI drugs. I discussed what the (inaudible) is. I explained why the locally acting GI drugs unique. I reviewed the Committee discussions or recommendations in four years ago. Finally, I update you on what progress in this arena.

With that, I conclude my talk. And any comments and questions are welcome.

Thank you.

DR. MORRIS: Thanks, Lawrence. At this time, can we have just clarification questions before our initial discussion. I think we'll start with Marvin.

DR. MEYER: Lawrence, I was particularly interested in the excipient effects.

DR. YU: Thank you.

DR. MEYER: Do you have an -- maybe you won't thank me. Do you have an example of a situation where the drug itself is reasonably soluble, has pretty rapid dissolution, at various pHs, it acts in the gastrointestinal tract, there's no systemic availability, so you can't do a PK study --

DR. YU: That's correct, yes.

DR. MEYER: Do you have an example of an excipient that would not be -- seem to have an effect in dissolution testing, but somehow, either before or after dissolution in the gastrointestinal tract, would cause a failure, a therapeutic failure?

DR. YU: Thank you, Marvin. When you talk about excipients -- you talk about how excipients impact dissolution, how excipients impact performance.

DR. MEYER: Right. Dissolution, I presume, you could pick up by doing dissolution testing.

DR. YU: Okay. Thank you. So

basically, excipients impact mainly on performance of product.

DR. MEYER: Correct.

DR. YU: In terms of the actions. And I'm not aware of any examples. And I have to say, for commonly used excipients like microcrystalline lactose, the impact probably is unlikely. However, we do not have solid evidence they do not impact it at all. That's a reason we are conservative; we recognize them.

Thank you.

DR. MORRIS: Go ahead. I'm sorry. Go ahead, Jerry.

DR. COLLINS: Jerry Collins. Good morning, Lawrence.

Just from your comments at the end, if you could clarify. So since the last Committee meeting four years ago, there have been no approvals based on any criteria other than clinical endpoints?

DR. YU: No, we do have approvals, because for highly soluble, formulated immediate

release dosage forms, if they can demonstrate a sameness of dissolutions -- bioequivalence is demonstrated by in vitro method, we do have approvals for those drugs.

DR. COLLINS: Okay, so --

DR. YU: We do also have approvals for top -- for locally acting GI drugs with a PD endpoints.

DR. COLLINS: Okay.

DR. YU: And certainly, we also have approvals with clinical endpoints. That's why we have so many approvals, and the leadership of Gary Buehler, I guess, and Helen Winkle.

Thank you.

DR. COLLINS: And is it consistent in the Office of New Drugs, in the Division of Gastrointestinal Drugs, the criteria that they use for manufacturing changes or formulation changes? Is there harmonization between OGD and OND in those regards?

DR. YU: I would say yes. In fact, we don't have the options. Reason is that, Jerry,

you probably know, when you were in the FDA, we received a lot of (inaudible). The (inaudible) when we're respond to those (inaudible), will be consistent response from FDA from New Drug side, from Generic side.

DR. COLLINS: Great.

DR. YU: Thank you. So therefore, in fact, any complex dosage forms in drugs, for example, these drugs, we will have to discuss with New Drugs' side; get their concurrence or agreement, or sometimes we co-develop the method for those locally acting GI drugs. We collaborate with them very actively and I truly appreciate the input and the contribution by the Office of New Drugs, by the other side of FDA, in supporting us. Thank you your question.

DR. MORRIS: Other clarification? Questions?

I, actually, have one. Ken Morris. Lawrence, just digging a little bit into what Marv was asking about. Have -- I don't want to start a discussion, but just to see. Have

you looked at any excipients that have known membrane activity?

DR. YU: We do recognize that excipients could impact transporters. I think, you know, the Morris is a -- it's in her area, in transporters.

We do have a scientific investigation report, excipients impact absorption, excipients inhibit, or if sometimes introduce absorption with respect to inhibit (inaudible) transporters, uptake transporters. I have to say, those report, it pretty much are concentrating in vivo, and the -- we are, so far, as far as I know, there's only one scientific publication, publishing pharm research last year, discuss excipients' impact on Tylenol, I believe, the drug. So we're not -- besides that, we have not seen any significance in impact excipients in vivo, in vivo.

DR. MORRIS: Thank you.

DR. YU: Thank you.

DR. MORRIS: If there are no other questions, I think we can move on to Professor Polli?

DR. YU: Jim.

DR. MORRIS: Jim.

DR. POLLI: Dr. Morris, Committee members, appreciate the opportunity to be invited here. For those of you visiting from outside Maryland, hope you're enjoying your stay in Maryland. Okay.

I've been asked to speak about bioequivalence of locally acting drugs, in particular, the two questions with regard to what role should bioequivalent dissolution play in developing BE recommendations for lowly soluble locally acting drugs that treat GI conditions, and then what role should systemic PK play in this regard? Okay.

And in thinking about this, most of my experience is actually in -- as probably with many people's, with these systemically acting drugs -- and here's something that

actually just came out, just about a month ago, that talks about the relative benefits of in vitro testing versus in vivo testing, so I figured I would just at least share this perspective with you, as it relates to systemically acting oral products.

In vitro tests can have some benefits. Certainly, in terms of reduced cost or benefits, especially in situations where we expect bioequivalence. And there is a fair number of such products where we can actually expect that.

Another reason is that, you know, in vitro tests sometimes more directly assess product performance. As we'll discuss, bioequivalence is really not necessarily focused on safety and efficacy, rather product performance, as we'll discuss.

Also, by virtue of being a more direct assessment of product performance, it avoids some of the complications like indirect assessment, which sometimes

pharmacokinetics gets involved with. Some drugs, as this Committee has talked about, many times in the past are highly variable, and by relying on plasma as an indirect assessment of product performance, that actually just complicates the picture more than anything, in some circumstances.

And then a third reason is, really, ethically reasons. For example, the FDA, several years ago, implemented the biopharmaceutics classification. One question might be: for a systemically acting drug, let's say, if the drug is a Class 1 drug and it's rapidly dissolving, is it ethical to an in vivo study? Okay.

So there are differences between bioequivalence and safety and efficacy testing. This is the same definition that we just saw Lawrence present. And in bioequivalence, it doesn't specifically mention it's the same as safety and efficacy. And by virtue of that, there's different

types of tests that can be employed. And I think the reason for this difference is that formulation performance evaluation is at least as discriminating as clinical safety and efficacy evaluation.

So this Committee is certainly, I would expect, be confident that bioequivalence assures clinical safety and efficacy. And that could be illustrated here in this type of diagram. So if we divide products in terms of, say, those that are safe and effective versus those that are not safe and effective, and where does bioequivalence fit into this, we would certainly hope that it fits into this area, here, where bioequivalence is really assuring safety and efficacy. And we even see that there's space outside this circle, where there's still blue color. So there is still safety and efficacy, but it just doesn't necessarily meet the bioequivalence standard.

So bioequivalence assures safety

and efficacy, clinical safety and efficacy. And by virtue of being sort of a more conservative test, it's at least as accurate and precise as comparative clinical studies, at least, certainly, that's the intent. Because it's really not the same thing as safety and efficacy, in terms of it as a test. Okay.

Let's also look at, you know, clinical testing, how good is that as a test for bioequivalence? Here's some perspectives on mesalamine. Some comments about mesalamine safety and/or tolerability of test and placebo are sometimes close. This is a -- mesalamine is used to treat situations which just sometimes actually improve over time anyway. So considering rates of improvement and underlying variability, it's not always easy to tell whether it's really a test that's being very sensitive.

There's certainly lots of variables in doing clinical studies. For example, in

this particular situation, there's different severities of disease, instruments to measure efficacy, and what is the definition -- what particular is being used for the primary endpoint.

And there's also dose response type issues. Here's a quotation from this particular article: "Despite numerous studies investigating the effect of mesalamine dose on clinical efficacy, it remains unclear whether a dose response of mesalamine exists. Other larger studies have not consistently shown a dose response for mesalamine above doses of more than 1.5 grams per day."

So in terms of the clinical study, if one were to argue, well, that's the gold standard; well, really, how good is the clinical study in terms of being very discriminating. If the dose response is not particularly good, does it -- is that really a positive attribute? I think the answer

would be, well, that's not great.

So in thinking about locally acting drugs, here's actually an illustration from a book that came out, maybe, about 10, 15 years ago, "How Does Aspirin Find a Headache?" And if I remember, Dr. Topp actually studied aspirin as a graduate student, so maybe she knows the answer to this. But it gets us thinking about, well, do locally acting drugs know they are not supposed to be systemically active? So it sort of gets at the question, well, what's so different about locally acting drugs, anyway? And Lawrence, in his presentation, did emphasize certain features. Okay.

In terms of systemically acting drugs, certainly, conventional human PK studies are the norm. And for these types of products, as Dr. Yu indicated, the site of action is systemic tissue beyond the plasma. In this regard, there's an engagement of an extrapolation type assumption, extrapolating

forward from the plasma. And if the plasma's the same, we would conclude whether the absorption is the same. And if absorption is the same, then by virtue of pharmacokinetics, ADME's the same absorption distribution, metabolism excretion, and hence, they are therapeutically equivalent. Okay.

So this is illustrated here. And the questions that are being posed is how can dissolution testing be used for poorly soluble locally acting drugs, and how can plasma data be used?

So for systemically acting drugs, we have this scenario here. We have drug dissolution, drugs in plasma, and then drugs in tissue. Again, we're engaging in this sort of extrapolation type of thinking. It's a little bit different conceptually, in terms of locally acting GI drugs, where it's more of an interpolation type of process that we might have to consider. Where there's drug dissolution, and some types of tests can be

done in vitro, and the drug may wind up in the plasma, and that could be quantified. And the target tissue is between dissolution and plasma.

So in some regards, there is a difference, even though the drug may not know it's not supposed to be not -- even though the drug may not know it's locally acting, there certainly is a difference in the site of action. Okay.

So in terms of the question of plasma concentration, does that reflect formulation performance? Do plasma concentration -- is that indicative of formulation performance? I guess the particular question is do similar plasma profiles assure similar concentration at the site of action?

And when one speaks with clinicians, a common question is, well, how do you know where the drug is released? Well, in terms of what could be relied on, in

terms of pharmacokinetics, as this Committee knows, there's issues -- there's metrics such as total exposure, peak exposure, and early exposure.

And just in thinking about this, I think at least there's one thing that would need to be considered, is that to use plasma only as a surrogate -- as a measure of bioequivalence, one would certainly need to probably have some sort of minimal level of systemic exposure. And I'm saying that because the goal is to have this test be a formulation performance type of test. And plasma, alone, would not differentiate between two scenarios.

One scenario where there's a product which performs where there's, say, minimal or no systemic exposure, and, meanwhile, a second product which, say, completely fails to release, would have, maybe, similar plasma exposure; i.e., very low plasma exposure. So in that regard, I

think, you know, one can certainly come up with situations where plasma, only, would not be acceptable. Okay.

Other considerations with regard to the extent that plasma concentration may or may not be indicative of formulation performance. One question they're after -- Dr. Yu's talk had to do with excipients. I don't know of any excipients that modulate. Permeability, if that was the nature of that question. And then, of course, there's metabolite issues, which I believe this Committee has discussed in the past, also. Okay.

With regard to in vitro dissolution in formulation performance, for poorly soluble drugs, we certainly anticipate in vivo dissolution being a really key determinant in terms of tissue exposure to drug. Such that any in vitro test, for the purposes of being a surrogate, must reflect relevant in vivo parameters. Now, what are

those things? Well, for poorly soluble drugs, that's extremely difficult. I mean, it's not possible to rely on in vitro dissolution testing, only, to assure bioequivalence for poorly soluble drugs, including locally acting drugs. Lowly soluble drugs are certainly more complex. Okay.

In terms of the question, clinical studies in formulation performance, are clinical studies indicative? The thing that comes to mind is, quite often, clinical studies, almost by definition, compared to the formulation performance issues that we discussed earlier, they're not as sensitive. I mean, arguably, bioequivalence is a very high standard. And comparative clinical studies can fail to be sensitive to formulation differences, even those that are otherwise bioinequivalent.

So in terms of establishing biomarkers for local delivery to the GI

tract, potential biomarkers that we're discussing here include in vitro dissolution and plasma concentration. In terms of, you know, what are we trying to target, our evidence for using such biomarkers, things that come to mind are in vivo dissolution, local tissue levels, plasma concentration, and formulation design. Of course, formulation design is, of course, very important in -- when one contemplates product similarity.

So as we've already discussed, in terms of in vitro dissolution in plasma, there's these issues of, you know, interpolating. To accept in vitro dissolution, alone, as a BE method for poorly soluble drugs, one would need to compare in vitro dissolution to either in vivo dissolution or local tissue levels.

So as an academic, I tried to do some literature searching on this. And there are just a couple of examples where one was

measuring luminal concentrations of drug. The technique was in intestinal luminal microdialysis, and it was done in pigs. I don't know of any situations where it was done in humans. Okay. So that's clearly more of a research topic, shall we say.

In terms of local tissue level, I don't think there's any examples that I was able to find.

As an academic, I'll use that and say, well, people, of course, working on this. There's imaging, for example. Positron emission tomography is one particular example. It's well suited for drugs, at least theoretically. But as you may know, one major limitation to this is, really, their very, very short half-life radionuclides, on the order of minutes, such that to evaluate formulations would practically be impossible, at least today.

However, you know, in vitro dissolution can be used as a surrogate for BE

under some circumstances. For example, the FDA has IVIVC (?) guidance. Presumably, that applies to such products. But, of course, one limitation of that guidance is that it's formulation specific, it's not portable across, say, different manufacturers.

Let's talk a little bit about dissolution testing. There's a variety of different roles of dissolution testing, spanning from formulation development, biomimetic test, quality control test, and bioequivalence surrogates. One term that's often used in the literature, in fact, it was in the two questions that were posed, this issue of biorelevant media. It's my opinion what that term means is that it intends to mimic the gastrointestinal luminal conditions, based on things like composition, physical chemical properties, things of that sort.

And one example that I'll give you is maybe something you've never heard of, is

FaSSIF-V2, and I'll elaborate more on that. And of course, there's a variety of quality control tests for the reference listed drug for regulatory purposes. And, as has already been alluded to in the first talk, dissolution is used as a bioequivalence surrogate. For example, for BCS-type panel tests and, as I mentioned previously, for IVIVC-type of situations.

Of course, this is -- it's much more challenging for poorly soluble drugs. Drugs have different properties. I mean, I think at first blush, one would need to characterize them as either -- well, there's acids, there's bases, and the neutrals. Their physical chemical properties are very different in the context of dissolution.

Obviously, their solubilities typically increased in micellar solutions. And that can be very large under in vivo type of circumstances.

In terms of possible biorelevant

dissolution media, here's some examples. And this is a bit of an older slide. And when I mean older, I mean only a couple of months old. So there's examples for preprandial stomach, postprandial stomach, fasted jejunum and fed jejunum.

And in this slide, this is information from a particular article that came out just a couple months ago in Pharmaceutical Research. And the message that I'm trying to give with this particular slide is that there is no universal dissolution medium. For example, here, in this slide, these authors have been very active in the area of dissolution testing, including coming up with new media. And, actually read this, the aim of the study was to update the compositions of biorelevant media to represent the composition of physical chemical characteristics of GI fluids as closely as possible, while providing physical stability during

dissolution runs and short-term storage.

It's an excellent article; they do excellent work. They are suggesting, at this time, a new -- a fasted stomach-type of media from a recent publication. They're proposing a new fed stomach-type of media. And they're updating things that they previously have published.

One thing that they didn't do was they didn't do any dissolution testing. So the point that I'm trying to make is I think it's fair to say that for poorly soluble drugs, it's certainly a research area, but there's certainly not a, shall we say, a magic bullet in terms of solving (inaudible) type problems.

And here's an example, just to give you an idea of just the profound effect that surfactants can have on product dissolution. We see it at the, you know, at the bottom, here, in water, is very little dissolved. And then it's enhanced several fold more, but

still well below 100 percent in these biorelevant-type media.

Of course, people are obviously working -- now, these biorelevant media are actually relatively expensive. People, of course, are working on cheaper alternatives that do the same thing. Do they accomplish that? The short answer is, well, no, not globally.

Here's some text from an article from a couple -- from about six months or so ago, "Validation of the correspondence of results in media containing synthetic surfactants and those containing bile acid components is necessary on a case-by-case basis." In other words, it doesn't work broadly, at least in their experience.

And then, I noticed the composition has some engineers on the panel, so I put this in just for, I think, there's several engineers on the Committee. I think a lot of progress has been made in the last 40 or so

years since dissolution testing took on a regulatory component, formally. And, but to what extent is it well-understood, the mechanisms underpinning surfactant mediated dissolution?

And I think it's fair to say that more could be done. And here's just showing some of our work. And the point here is to show that, in general, you can get a lot of solubilization by using surfactants, as shown by these open bars, here. But dissolution tends to be much, much attenuated. And that relates to not so much solubility, but because of surfactants are very big and they diffuse very slowly. So there's a diffusion penalty here, shall we say.

I guess one suggestion I would have would be to get more data. I think there's a huge amount of data in the literature. There's a lot of academic research labs working on this throughout the world. I'm also under the -- it's also my impression

that there's a lot of dissolution test method reports. There's a -- I mean, a lot of firms go through great efforts in studying the dissolution of their product, to make the best possible product.

The question is, well, how portable is that information? And in my experience, it's not very portable. So the thing I would actually encourage would be to collect data. If there's a question about the relevance of dissolution for a particular type of drug class or something like that, that's very challenging. My guess is it would be some advantage to actually collecting data. For example, the BCS media in different surfactant concentrations like SLS. Otherwise, it would seem to be very difficult going forward, because it is a difficult problem.

So some summary, with regard to low solubility IR locally acting drugs. I'm going to be an optimist and say that in vivo

studies have potential to sometimes serve as a BE test, perhaps even under some circumstances compared to in vivo testing. You know, in the future. Low solubility drugs are very difficult, though. There is no dissolution test for poorly soluble drugs that will automatically solve all your problems. I often hear people saying, well, there's biorelevant tests, right. Well those, I'd say, that's more of an academic term emphasizing composition more than, at this point, performance. And data is really needed.

So in terms of some of the questions here, what role should biorelevant dissolution play in developing BE recommendations for lowly soluble locally acting drugs that treat GI conditions? Well, I think in general, in vitro dissolution testing, alone, cannot -- is not enough -- there's not confidence there, at least at this point, for this to serve as the

sole type of test.

What role should systemic pharmacokinetics play? Well, given current options beyond clinical testing, it would seem to be a necessary requirement if one is thinking at least going to do a clinical study. My own opinion is that on a drug-by-drug basis, there is potential for it to be as reliable as pharmacokinetic studies used for systemically acting drugs. I don't think locally acting drugs know they're locally active.

What role should combined dissolution and PK play? I think there's, you know, really good, strong potential here, because these types of tests do get at product performance type of issues, which is a relatively high -- which is a high standard. However, relying on dissolution and PK certainly requires an interpolation assumption, that we described previously, and justification of the proposed dissolution

test across different formulations. That's probably being a particularly challenging type of assumption, though.

Thank you very much.

DR. MORRIS: Thanks, James. Nice presentation and thanks for coming.

Do we have questions or clarifications for Dr. Polli?

Okay, Marilyn, and then Harriet.

DR. M. MORRIS: Hi, Jim. Very nice presentation. I just --

DR. MORRIS: Don't forget to state your name, Marilyn.

DR. M. MORRIS: Oh, Marilyn Morris. I had a question regarding dissolution testing, and I don't really know very much about it. But I assume that the media is the same for general testing, whether it's a high solubility or low solubility drug. Correct?

DR. POLLI: I don't think so. I think when one goes about designing a dissolution test, I think one of the first things they

consider is solubility. And by most definitions of low solubility, it wouldn't be sufficient for an in vitro test. I don't know that this is the best thing in the world, but I think most people approach in vitro dissolution testing as a situation where you need complete dissolution under synch conditions. And that would mean the solubility would be many -- could be much higher than the solubility of the drug itself. So I think there's many situations where surfactants are used and -- but if the drug is highly soluble, I think in general, surfactants are not used. So I think --

DR. M. MORRIS: So the media could be different, and it's maybe not defined. I know you had a suggestion in one of your slides for a change in media.

DR. POLLI: Yes, the suggestion I was trying to make was really just one of data. I think poorly soluble drugs, because of what we were just talking about, everyone does things differently, I'd have to say, particularly with

regard to poorly soluble drugs. So to even contemplate, shall we say, a universal test which might be a panel of media, I think you would need to collect data using proposed media. And I think, in general, that doesn't happen. I think if one laboratory, they do things a certain way, they might like sodium lauryl sulfate -- another lab might like Tween 80. So I think there's a lot of information on dissolution test as, for example, represented by some of those study reports that I referred to.

But there's usually no interconnectivity between them, particularly across, say, different laboratories. So there's a lot of different practices that are -- have nothing in common with one another.

DR. M. MORRIS: I had a second question. What is the -- from reviewing the literature, the possibility of actually sampling intestinal fluids, such is done in other types of studies.

DR. POLLI: Yes, there are some, I think, at least academic labs that have done that. I think it's difficult. When I -- I have some GI clinician colleagues. When I talk to them about this they -- even though they do intubations every day, the clinicians, to think that you can sample, say, across the GI tract, just the tube that would be needed with the multiple ports. One person, I forget exactly how he put it, but, you know, extremely difficult, something on that order.

DR. M. MORRIS: You know, I know sampling's been done for duodenal fluid.

DR. POLLI: Yes, yes. So I think it's possible to do one site, but if -- let's say, if there's more than one site that might be of interest, like lower bowel, it's even more challenging.

DR. M. MORRIS: Thank you.

DR. MORRIS: Harriet.

DR. NEMBHARD: Thank you for providing this background for me. I have one specific

question and one general question. I'll start with the general background question first.

And that is, in your concluding slide, you said that dissolution has the potential to be as reliable as PK studies, on a drug-by-drug basis. So does this mean that establishing this relationship or this correlation between the studies is something that would be used for ongoing quality control as opposed to any initial validation of drugs?

DR. POLLI: Yes. I think what the question had to with the use of PK sampling as a bioequivalence test. Yes. I mean, so, what I was trying to say there is even though locally acting drugs may not know they're locally acting, as Dr. Yu, kind of, already indicated, there are issues about, maybe, locations within the GI tract that are being treated. So they probably do merit a drug-by-drug consideration. Now, what are the factors? I guess we'd have to talk about certain drugs. I haven't really

thought about it, I guess, for any particular drug.

DR. NEMBHARD:

DR. MORRIS: Can I -- I think, actually, Jessie, and then Liz. But I'm not -- let me put words in your mouth, Harriet. But I think you were asking more about the use of the test. In other words, would you use it in lieu of PK during development as opposed to just ongoing --

DR. NEMBHARD: Right, because it indicates a drug-by-drug basis, so that makes me think it's something for ongoing quality control, or am I off base here? I don't want to put words in your mouth, either. I'm just trying to understand the --

DR. MORRIS: You're talking about more where in the development path it occurs, I think, James.

DR. POLLI: Oh, so, in the context of development? Actually, I actually just don't know.

I don't know what the routine is in terms of reliance on in vitro tests for locally acting drugs.

DR. NEMBHARD: Okay.

DR. POLLI: I don't know what the answer is.

DR. MORRIS: And I think --

DR. POLLI: I think that was the same question that Dr. Collins was asking, in essence.

DR. MORRIS: Do you want to address that, Lawrence?

I mean, I can tell you -- I mean, basically, you wouldn't be doing -- you know, PK studies after -- you know, once you were approved, necessarily, unless there were changes. But during the initial drug development or if you were, depending on where you are in the generic process, what class you were in. But for low solubility drugs, you would do it prior to approval.

DR. NEMBHARD: Prior to approval.

DR. MORRIS: Right.

DR. NEMBHARD: Okay.

DR. MORRIS: And/or after the -- please.

DR. YU: I can comment on it. Actually, I can comment on back to Marilyn's question, too.

Well, it's a -- whether it's innovator or generic drug development, dissolution is pretty much very commonly used as surrogate. We recognize dissolution may not be (inaudible) in vivo, but quite commonly used because so easy to do it. Test it cost the -- you know, the couple month and very expensive. So the -- for drug development, whether it's generic or innovator, they always use dissolution as a surrogate, and dissolution is a predictive in vivo.

For highly soluble drugs, dissolution (inaudible) pretty much have very good indicative of in vivo, because it's very

easy to do and, as I point out, that you can do dissolution cover pretty much a physical relevant pH, from pH 1 to pH 7. However, for poorly soluble drugs, it depend on scientists, as the scientist depend on company, the company depend on the sponsor. But nevertheless, a scientist, as formulation scientist myself, is you always do your best at trying to devise a dissolution method at first, before you develop a formulations, because, otherwise, you don't know what's your target. Thank you.

DR. MORRIS: Thank you. And just so -- you wouldn't be doing a PK study as a batch-by-batch quality control --

DR. NEMBHARD: I had a second question, too, if I may. Harriet Nembhard, continuing.

Let's see. While I appreciated the lovely slide with the equation on it, I would also like an explanation of the notation in that equation. I was not familiar with it.

DR. POLLI: So maybe -- I'll illustrate this, maybe the data first.

So quite often there's a difference between the extent to which -- the thing we are interested in is studying -- you know, surfactant effect on dissolution. And -- you know, and one thing we noticed over time was that surfactants enhance solubility to a great extent, but not so much for dissolution. So the white bars are higher than the dark bars. And usually the ratio's somewhere about a third difference. So why is that?

So this is the extent of dissolution enhancement, 5. So 1 means there's no enhancement.

But there is enhancement because this is something which is positively valued. And there's two components to the enhancement: one is a dissolution component, one is -- I'm sorry, solubilization component, as represented by the fraction of

drug in micelles versus fraction of drug that are free. So if things are being solubilized, this has a positive value greater than 1.

And this is the diffusivity of drug loaded micelles versus the diffusivity of drug. And this is -- this part is less than 1, because drug diffusivity is much larger than that of a large micelle.

So it's a battle between solubilization phenomena, which favors dissolution, surfactant media dissolution, versus diffusion where a micelle is hindered, shall we say. So this term negates, in part, this term, and using pharmaceutical surfactants, typically by a factor of three. So if you know the solubilization, you can at least get an idea of how the dissolution might be enhanced. So you'll always be disappointed. Yes.

So the point I was trying to make is -- now, these are academic-type studies.

I think in vivo, it's a lot more difficult, such that there's not a universal dissolution test, at least not yet, but we'll be optimistic.

DR. NEMBHARD: Thank you.

DR. MORRIS: Although, actually, there's a -- the non-academic -- Ken Morris -- non-academic component in that it's -- we're always -- dissolution testing is always this -- usually assuming a homogeneous phase, and this is a heterogeneous system, so.

Next, Jessie.

DR. AU: Jessie Au. Good job, Jim. I really learned a lot here.

I have a question, though. Thinking this is a real difficult problem, you mentioned duodenum, jejunum, ileum, and each one is going to be different. The stomach's also different. So you really have four compartments with different composition of the release media. And your site of action could be (inaudible) to your release

site. So and all the tests I'm listening to, the in vitro test is the beginning of the whole thing. And then we listened to the very endpoint, which is this systemic PK.

But what is really missing is, what is not absorbed. I mean, if you look at mass balance, the question must be asked, not just what's released and then what got in, but what is coming out. So I wonder if you can get some clues from looking at what is not absorbed.

So I now come to my question, and that is, if you know of any literature that tell us of the different media used for release, which one give us the best indicator of what's not absorbed? Is -- did I do okay with the question?

DR. POLLI: Yes, I think so.

DR. AU: You know what I -- yes, okay.

DR. POLLI: I think so. I'm going to summarize your question. Is there a universal dissolution media that will solve all of our

problems?

Whether you're talking about extent of absorption or extent not absorbed, or anything like that, I think for poorly soluble drugs, the answer is no. I think if you were to go through the USP, USP has monographs for dissolution. They're public monographs. You know, I think for poorly soluble drugs, you might see many, many different official tests. I think, in part, because, as Lawrence was describing, I mean, everyone kind of does things a little bit differently. They might check the reference listed drug test, but -- you know, there could be -- you know, could be real reasons why that doesn't apply to this, say, new formulation. I just don't think it's worked out, poorly soluble drugs.

DR. MORRIS: Liz, and --

DR. TOPP: Yes, I have a very simple question for clarification. Jim, thanks for your presentation. It's not often that I hear

my name mentioned in the middle of something like this, so that's kind of strange; and work that I did a long, long time ago, before many people in this room were born.

So I just have a very simple question for clarification, as I said. Are your comments primarily directed toward orally administered tablets that are intended to be acting in the GI tract? Are they primarily directed towards suppositories that are administered rectally to be acting in the GI tract? Or do you consider your comments to be equally applicable to both routes?

DR. POLLI: I must admit I was largely thinking about orally active drug -- orally administered drug. That's the area that I work in.

Yes.

DR. TOPP: That's helpful. Thanks.

DR. MORRIS: Actually, I screwed up the order, Marv. It's Anne, and then you, so.

DR. ROBINSON: Anne Robinson. I guess

I'm also, as a point of clarification, when we're talking about poorly soluble drugs, what's the mechanism of transport that's believed? Is it that it must be dissolved into the aqueous solution in the gut before it's absorbed?

DR. POLLI: Yes, I think the question had to do with the mechanism of absorption of poorly soluble drugs. I think, in general, there has to be a -- has to be released. And, I'd say people are doing studies now. If you do a search on the lipolysis model, that gives you an example of what people are thinking, where the product dissolves, but it's certainly being facilitated by a surfactant. Maybe not, necessarily, immediately adjacent to where the solid is, but then that surfactant is solubilizing.

So it's able to get the drug, at least, out of the dosage form. And then there's very rapid equilibrium between free drug and solubilized drug, so it forms sort of a depot for drug, not in the dosage form,

but otherwise cannot be dissolved. And the complicating factor is -- you know, it's more like a digestive process where there's a -- it's very dynamic, maybe, where the composition of the mixed micelle changes over time, that sort of thing, especially in the fed state.

DR. MORRIS: Marv.

DR. MEYER: Jim, the title of the morning session is, "Bioequivalence of Locally Acting Drugs," and yet it looks like all three speakers are focusing on low solubility locally acting drugs.

Is the implication that the issue of highly soluble drugs which meet the other criteria of not systemically available and acting locally, that's been pretty much solved by dissolution? Or is that for another day?

DR. POLLI: I mean, there's a BCS guidance which -- I don't recall, I think it might exclude highly soluble locally acting

drugs. I don't -- I mean, I don't know that locally acting drugs know they're locally acting. So in my mind, I -- it's hard for me to, at least, physiochemically, pharmaceutically just draw a big difference between locally acting drugs and drugs that are not intended to be locally acting.

DR. MEYER: But I guess my point is, clearly, if a drug does dissolve, you have a shot at doing dissolution. If it doesn't dissolve, you don't have a shot at doing dissolution. And that seems to be the focus today. So my question was, have we solved the does dissolve part by in vitro testing of locally acting drugs without systemic bioavailability?

DR. POLLI: For drugs that are poorly soluble or highly soluble?

DR. MEYER: Highly soluble.

DR. POLLI: I mean, I don't know of any examples where, basically, BCS Class 1 was -- fails.

There was a workshop last year where that question was posed and -- by both people from agencies in the U.S. and in Europe, and there was no examples of failures of that test.

DR. MORRIS: Yes, there's actually, the scientific and the regulatory component to Marv's point of clarification, which is a good one. Lawrence, would you care to?

DR. YU: Well, for highly soluble drugs, if formulating immediate release dosage forms, we do confident that in vitro dissolution pretty much ensure the similarity in vivo dissolution. So the question is what about the difference excipients which you (inaudible) the questions. And, certainly, we want -- you're welcome to comment on this issues.

And you're asking for any scientific evidence whether excipients is strongly impact the performance, my answer is we have not aware of any strong scientific evidence. But we also have not aware that

there's strong evidence that those excipients have no impact, whatsoever, because the one of the challenges is that there's so many excipients out there, how do we gonna conclusively the make a statement that those excipients will -- will not impact the performance. So this is, indeed, is a challenge. Thank you.

DR. MORRIS: Other clarifying questions? Actually, I have one. Ken Morris. I know you know that, but this is for the records.

DR. POLLI: Any relation to the other Morris?

DR. MORRIS: Yes, actually, yes. We're brother and sister. She's my little sister.

So my question, Jim, is on your last slide, where you commented when, under the part where it says, "What role should systemic pharmacokinetics play in BE recommendation for low solubility locally

acting drugs." And you were saying, given the current options beyond clinical study and apparent necessity.

And my question is, is in the case that somebody posed -- I can't remember if it was Marv -- we have no absorption, why would the PK data tell you anything? Do you -- I mean, did I miss something? I don't know. I'm not trying to put you on the spot, again, but --

DR. POLLI: Let's see, what was the question? I didn't get it.

DR. MORRIS: So the question is, you have that given current options beyond the clinical study and apparent necessity is the PK, the systemic PK --

DR. POLLI: Mm-hmm.

DR. MORRIS: And my question is, is if there's -- if it's not an absorbed drug -- I'm not talking about safety. I'm saying, let's say that you got the safety part in hand. But in terms of the equivalence, why -- I'm not sure

why we'd do systemic PK if it were -- there was no absorption.

DR. POLLI: I guess it maybe just reflects my perception that -- you know, as far as being a conservative test, in general, and being a discriminating test, that pharmacokinetics is more discriminating than a clinical study or a PD study.

I made one reference to a drug with a poor dose response curve. I mean --

DR. MORRIS: Yes.

DR. POLLI: People make big deals out of a percent difference in Cmax. But if -- you know, if the drug has a poor dose response curve -- you know, aren't we being pretty conservative.

DR. MORRIS: Yes.

DR. POLLI: So I think, in general, that if one excludes a clinical study, in terms of a sensitive test, pharmacokinetics has a very strong track record.

DR. MORRIS: So you'd just be looking

at elimination -- I mean, just excretion, essentially?

I mean, if it's not absorbed?

DR. POLLI: Oh, for a drug which is not absorbed?

DR. MORRIS: Yes.

DR. POLLI: Actually, if a drug is not absorbed, I'm not sure pharmacokinetics could easily discriminate between --

DR. MORRIS: Right.

DR. POLLI: Shall we say, a performing product and non-performing product.

DR. MORRIS: I just -- I thought that, so I just wanted to make sure because it sounded like that's --

DR. POLLI: Okay.

DR. MORRIS: Yes.

DR. KIBBE: Just a comment on -- Art Kibbe. I'm sorry, am I out of order?

DR. MORRIS: No, no. You're in order.

DR. KIBBE: I'm in order?

DR. MORRIS: Well, you're always a

little out of order.

DR. KIBBE: I like to be a little out of order, just so you know. Wonderful to be here.

Just a point that you raised about drugs that are not known to be absorbed at all. And the only reason I would even consider doing any blood level study, and not even a full PK study, was to just assure myself that this particular dosage form hasn't got anything in it that might promote absorption when it wouldn't happen normally.

And just to comment on Lawrence's. I think we also should consider the possibility that if the monarch butterflies die, and they're not flapping their wings in California, the drugs might be absorbed. I think we shouldn't go looking for problems that are so unrealistically -- you know, possible that they create issues that we don't want to deal with. So you know, I'm not worried about lactose affecting

permeability of non-absorbed drugs and things like that. And I think we don't need to look for more problems than we deal with.

DR. MORRIS: Liz, I think you had a -- no? Is that it? Well, if that's it, thanks again, Jim.

DR. POLLI: Thank you.

DR. MORRIS: Nice job. So this brings us to the open public hearing segment of the meeting. And today, we have several speakers. And I'll start by reading the prepared statement.

So both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker -- we already have one

up there -- at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationship.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this Committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this Committee in

their consideration of the issues before them. That said, in many instances, and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair, and thank you for your cooperation.

And our first speaker today is Abu Alam, and he's the senior vice president of new business development at Akorn, Incorporated.

So thank you, Dr. Alam.

And please continue.

DR. ALAM: I think you guys heard about -- some of the speakers before me. So I'll pass some of the slides that I already have.

I'd like to thank the FDA Advisory Committee to give me a 10-minute slot to come

and speak before you. I'd like to also thank the audience for participating in this meeting.

The first slide just talks about this -- locally acting oral drugs is the topic that I chose.

And I think the previous speakers talked about the highly soluble drugs, which are not absorbed in the GI tract. And that's where I'm going to restrict my talk here. It's locally acting drugs that are highly soluble and that are competing in the generic space, so that we can have affordable medicine for the American public.

The -- I know the speakers didn't talk about some of the things that I would be including in my slides.

To characterize a drug substance, the purity and the impurity of the drug is very, very critical for the safety and efficacy of the drug, whether you give it as a GI not absorbed in the systemic or not.

Those two criteria are very important. And there are limits for these, and so that drug A from a generic company should match the RLD or the innovator's drug to the specifications and limits.

The molecular size of the drug is very critical for drug absorption, whether it's a polymorphic drug, which also affects solubility. The particle size distribution of a drug is very important for an oral drug formulation.

And the solubility of the drug, irrespective of pH, is very important, as one of the previous speakers talked about pH of the gastric to the intestinal fluids, pH 1 to 8.

The permeability of a drug is very important, because you can predict some of these by the (inaudible) equation, but the lipid water partition coefficient of a drug is very important. If the drug is very lipid soluble, it will be absorbed through the

passive transport.

The drugs usually have three different mechanisms of absorption. One is called epinocytosis (?), which is the size of the molecule. The other one is active transport. The other one is passive transport.

Degradation of the drug, both as a drug, as well as throughout the GI tract, is very important. Because if you have a degradation of a drug, you can have different impurities than degradants throughout the GI tract, which may affect the toxicity of a drug.

The analytical method that goes to support the drug substance is also very important. The specification and the stability of the drug, not only as a drug substance, but also throughout the GI tract, is very important.

You know, you cannot take the drug by itself, you have to put it in a dosage

form. The drug is formulated -- and the previous speaker talked about excipients. And usually, in the generic, we start -- we stay within a 5 plus, minus percent of the innovator's products. So for instance, if there are a bunch of excipients, they should all match the ethical product or the innovator's product. We go with the Q1, Q2 laws, which is plus/minus 5 percent, but in qualitative as well as quantitative, so that the behavior of the drug as it traverses through the GI tract will be very similar.

The manufacturing process of a drug formulation is important because there are various ways of manufacturing a finished dosage form. For instance, a tablet would have different -- design of a tablet, round tablet, oval tablet. In the case of a capsule, the capsules dictate the shape of the -- or the geometry of the dosage form. The specification of the finished dosage form also should match the RLD. And the stability

of the dosage form to -- not only for the expiration date, but also, as it goes through the GI tract, should match, very similar, to the RLD.

Now, how does the oral dosage form, after you swallow, goes through. And here's a slide that my -- the previous speaker also talked about. The GI, the first, it enters the stomach, where you have gastric fluid. The pH is about 1.2. There's also enzymes and other electrolytes present at that pH. Then it goes to the duodenum through the pyloric valve. Then it goes to jejunum, ileum, colon. And finally, it's eliminated in the feces. The drug is not absorbed, in this case. I'm talking about very highly soluble drug that is not absorbed.

Here I give some dissolution profile. Between subjects and within a given subject, there's usually a plus/minus 20 percent variability. And what I'm trying to say here is that the drug, test substance

A, and the RLD should match dissolution at pH 1.2, because that's where the first -- the drug first starts dissolving. This is a USP Method I or II. Back in '71 and '72, I published three papers on the rotating basket method which, eventually, in the '80s, became the USP dissolution method for Method I.

The next slide gives you the same profile that has to also match at the next segment, which is the duodenal pH 4.5. Very similar.

Now, these are just an ordinary profile. This is not a first-order plot or a log-probit (?) type plot. This is just a plain coordinate paper, looking at the whole profile.

At pH 6.8, again, the same profile. That means the drug, throughout the GI tract, is going to be dissolving in the same manner as the RLD.

Now, in quality control, sometimes we have specification for only one point.

For instance, you just go at 30 minutes or something, and you have an 85 percent drug dissolved. As a one technique, only one time point. And that's for a QC technique, not for a complete profile of a drug. In that case, you don't know the whole profile of the drug. How is it going to release? Is it going to release like a first-order or zero-order plot? Is it going to -- this is like a first-order plot or a log-probit, or a combination thereof.

This schema tells -- or I thought it depicts what does the drug product go through in the GI tract. It dissolves in the GI tract, whether it's all those three compartments I talked about, and then has a local action, in case of antibiotics in the lower tract, which is the colon -- colon or the horizontal or the descending colon, but it acts locally. And then it's eliminated in the feces.

Now, the pathway for systemic

absorption for these drugs are usually very low, less than 5 percent. Now, you cannot measure blood levels for these -- some of these drugs. So the systemic absorption is blocked.

For instance, this pathway is blocked, or very low. The drugs like Cipro and others, where this could be 70 percent bioavailable where it goes through this route. And it could be, again -- through the bile, and could be reintroduced into the GI tract. But a lot of drugs are not absorbed, at all, and goes through this way. Some of the drugs that act locally could go through here, and then re-eliminated in the GI tract. And those drugs would have systemic toxicity as well as the elimination through the kidneys.

The criteria I'm talking about, highly soluble drugs are not specifically absorbed. It's not a pro drug, where you have to break or cleave a bond to have the

parent molecule be available for absorption, or an action at the local action at the GI tract.

The dissolution is pH independent and is freely available at site of action. And there's no permeation. That means the drug does not have a transport mechanism to be absorbed into the systemic circulation. Just give an example, vancomycin works -- meets those criterion.

Conclusion. As I mentioned, both the drug purity, the drug characteristic, as well as the drug product should be comparable. And the dissolution profile in those compartments should be superimposable. The rate and extent of dissolution, that means the kinetic part, as well as the total amount dissolved, should be also similar. In that case, the in vivo bioequivalency is unnecessary.

First of all, you cannot measure blood levels. Secondly, it's not necessary;