it's a moot point. To show clinical trials to prove safety and efficacy from these products, also unnecessary, because the two products are identical. It's just made by two manufacturers. So the drug and the excipients are identical.

And that's the presentation I was trying to make. I made it within the 10 minutes.

DR. MORRIS: Yes. Thank you, Dr. Alam. So are there clarification questions for our speaker? No? If not, we thank the speaker. So our next open public hearing speaker is Dr. Dale Gerding, associate chief of staff for research at Edward Hines Jr. Veterans Affairs Hospital; professor of medicine at Loyola University of Chicago, Stritch School of Medicine.

And he's -- oh, yes, and I should say he's representing himself. So thank you for participating, and please proceed.

DR. GERDING: Thank you very much,

Dr. Morris.

How do I advance, here? Oops, it went that way, huh? Thank you.

Just to introduce myself. I am a clinician, infectious disease specialist. I happen to be running the research program at the Edward Hines VA. I'm also professor of medicine at Loyola University in Chicago.

I have been studying infectious diseases in my research lab, and have specifically clustered in difficile disease, for almost 30 years. And I really wanted to make a presentation here because I think this disease has changed markedly just in the last few years, and I have great concern about its treatment.

I have disclosures. I am a consultant for a number of companies, including one company that is the current marketer of the innovator drug vancomycin, or vancocin, and that is ViroPharma. And I also have patents for non-toxigenic clostridium

difficile as a preventive for C. difficile disease. And that has been licensed to ViroPharma, so you should know that.

I work for the Department of Veterans Affairs. They never want me to represent them in any public discussion, and I want to be sure that I'm not representing them right now. Although they have been, clearly, the major supporter of my research, and I want to acknowledge them for that.

I want to make just four points in the presentation. First of all, the CDI or clostridium difficile infection is a diarrheal and colitis disease of the GI tract. It was first discovered in about 1978. Since the year 2000, the rates of this disease in the United States have been rising markedly, and that is of great concern.

There is a common epidemic, hypervirulent clostridium difficile strain that is being increasing reported from hospitals throughout the United States. I'll

show you data for that. And not only is the disease more frequent, the disease is also producing high mortality and higher rates of having to have the entire colon removed in order to treat this disease when medical management fails. And especially the elderly patients are the ones at highest risk right now.

Currently, non-absorbed oral agents that are locally active, such as vancomycin -- and Dr. Alam's presentation is a very good introduction to the treatment of this disease -- those are the most effective agents.

The recent data suggests that vancomycin is actually the most effective treatment for severe disease and it is the only FDA-approved treatment for this disease. And new investigational drugs, the ones that look most promising, are also orally administered, non-absorbed or poorly absorbed agents. So this seems to be the trend in

terms of how the disease is being treated.

Here are the data from CDC on the rising incidence of CDI, or clostridium difficile infection, in US hospitals. It's based on ICD-9 (?) coding. The disease is primarily acquired in hospitals. And patients come into the hospital, take antibiotics, their GI tract then has the flora disrupted. They ingest spores of this organism while in hospital, end up getting diarrheal illnesses. And you can see, most of the disease is diagnosed as any listed that is -- occurs not as the primary reason for hospitalization, but as an unintended consequence of hospitalization.

This is the map of the United States. It has nothing to do with the current election. The states in red are those states for which CDC and our laboratory have documented the presence of this new epidemic strain in the United States. In 2004, when we first became aware of this

problem, there were six states involved. We currently have 37, plus the District of Columbia. And I think, for the most part, the states that are not represented are those that we have not received specimens from hospitals.

Just wanted to point out the data from Canada. This is from Vivian Loo in Montreal, where hospitals there have a marked epidemic -- or had a marked epidemic with this current hypervirulent strain. What is important, I think, is that patients in their 60s, 70s, and 80s, as shown in the left column, have very high frequency of disease.

And you can see the rate in the second column, per 1,000 admissions. Probably we can just make that simpler by saying, in the 60s, 2.5 percent of patients get C. diff. In the 70s, in these hospitals, it was nearly 4 percent. And the patients in their 80s, it was over 5 percent. And if you were over 90, the risk of getting this

disease was 7.5 percent.

On the right side is the 30-day directly attributable mortality from C. diff. And you can see it going up with age, by decade. Again, with 5 percent in the 60s, 6 percent in the 70s, 10 percent in the 80s, and 14 percent mortality in patients in the 90s. So this is a severe disease, very serious, and increasing in frequency.

I'll show you an example of a patient that I saw in 2005, because I'd never seen a case like this prior to that time, although it had been reported in the literature. This is the abdominal X-ray of the patient, showing dilated loops of bowel.

This is the history. He was a relatively young man, 51 years old. Came into the hospital with a pneumonia, was treated with multiple antibiotics. Was determined that he needed a coronary artery bypass surgery. He underwent this open heart surgery. Was successfully managed. About

four days after his surgery, developed diarrhea on a Monday. Then, suddenly, went into shock. Demonstrated a very rapidly rising white blood cell count, up to 65,000. And died on Thursday. And we were unable to bail him out of this disease.

This kind of fulminant severe, rapidly fatal disease is what we are seeing more frequently with the current epidemic strain that is circulating.

The abdominal CT scan shown here probably doesn't make a lot of sense to most of you, but -- not being clinicians -- shows typical findings of that very thickened colonic wall with this disease and the presence of fluid, here labeled ascites, in the peritoneal cavity. This is a markedly disrupted gastrointestinal tract with C. diff disease. You see the normal colon on the left, as seen at colonoscopy; and on the right side, you see the marked yellowish, heaped-up pseudomembranes of pseudomembranous

colitis, which is the advanced form of this disease and the most severe.

When you look at these pseudomembranes under the microscope, you see the pseudomembrane comprised of inflammatory cells and proteinatious (?) debris, and you also see marked mucosal destruction and damage with this inflammatory response.

If the patient dies, we frequently find that there is a confluent pseudomembrane, shown here by this greenish-yellow membrane that covers the entire colon in this particular patient.

This inflammatory response to C. difficile toxins alters the GI tract physiology. For example, these patients obviously have marked fluid loss with Toxin A, which is the enterotoxin of this organism, produces increased fluid loss. Toxin B is a potent cell cytotoxin; it actually kills the cells in the GI tract. And the patients commonly demonstrate a very

markedly elevated white blood cell count, as the patient did that I presented.

In addition, there are other inflammatory mediators that are markedly increased, lactoferrin, interleukin-1 beta, interleukin-8, and then, in addition, the cyclooxygenase and prostaglandins system is also elevated in response to this infection.

In summary, clostridium difficile infection is a severe inflammatory colonic disease, with a high mortality and morbidity, particularly in elderly patients. Both C. difficile Toxins A and B, and the associated inflammation produced, cause structural, functional, and biochemical changes in the GI tract of patients, that really are poorly understood.

Currently, there is no in vitro model that has been developed that mimics C. difficile infection in the GI tract. And I don't think we know the best in vitro model to demonstrate bioequivalence in C. difficile

infection right now.

And given that vancomycin is currently the preferred treatment for severe C. difficile infection, and the drug that we really rely on for medical management if we are going to avoid having to remove the colon, I think we have to have some clinical evidence of efficacy for a generic agent or new formulation before we expose patients, with a life threatening infection, to a drug that has never been given to a human previously.

I suggest that the FDA openly discuss both the uncertainties inherent in the bioequivalence discussions, especially for a disease like this with a disrupted GI tract, as well as the risk and benefits to patients associated with approving a bioinequivalent formulation.

Thank you.

DR. MORRIS: Thank you, Doctor. And we have some follow-up questions, keeping in

mind that, again, we're talking about the general prospects of the locally acting drugs and no specific compound -- as an example and (inaudible). Marv? Marv, first.

DR. MEYER: If we take a Drug X and we find that we have two products, two formulations, whichever, we want to try to determine if they're equivalent. And let's presume for a minute that they're 25 percent different in bioavailability in the gut at the site of action. And, I presume, to do that clinical trial, you would have to do a parallel study rather than a crossover of some type.

Can you estimate how many patients you would need to detect this 25 percent difference in the clinical study?

DR. GERDING: That's a -- I can't do that off the top of my head, because that's an exercise that we go through in constructing every kind of clinical trial. I can tell you that, for example, we tested, one of the earliest studies, metranitisol (?) versus

vancomycin, in this very kind of clinical trial. And we found with 50 patients in each group that there was no difference, but I don't think we had the power there to actually state that the two drugs were equivalent. My guess is, with a 25 percent difference, you -- you're saying 25 percent difference in, say, dissolution or --

DR. MEYER: In actual delivery of drug to the site of action.

DR. GERDING: To the site of action. Yes, well, that's an even more difficult question because delivery of drug to the site of action is harder --

DR. MEYER: No, I'm not asking you to measure that, per se --

DR. GERDING: Okay.

DR. MEYER: Rather, just the therapeutic outcome.

DR. GERDING: Yes. And I think, probably, you would need a minimum of, say, 100 patients in each group, if you were to do that. And even then, you'd have to do a power

calculation. And -- you know, FDA requires a delta 10 percent or 15 percent on clinical trials to show non-inferiority.

And you're actually, I think, asking that same question, basically. And those trials are generally running about 200 to 300 patients in each arm, right now.

DR. MEYER: Thank you.

DR. MORRIS: Other clarifying questions? If not, we'll thank the speaker. Again, thank you, Doctor.

DR. GERDING: Thank you.

DR. MORRIS: So our final speaker in the open public hearing is Dr. Guy Rousseau from Axcan -- whoops -- Axcan Pharma. Oh, I see. Oh, there it is. Sorry.

But welcome, and thank you for presenting, and please proceed.

DR. ROUSSEAU: Okay, good morning. My name is Guy Rousseau, I'm a vice president of regulatory affairs and quality assurance at the Axcan Pharma. So I'm pleased to present here

today on the session on locally acting GI products.

I'd like to begin with a reminder that the goal of bioequivalence is to assure therapeutic equivalence in patients. In essence, bioequivalence tests are surrogates for safety and effectiveness.

The goal of my presentation today is to share information on local acting rectal suppositories. To illustrate this, I will use mesalamine suppositories, which are indicated for the treatment of ulcerative proctitis.

In developing appropriate bioequivalence standards for locally acting GI drugs, it is important to stress that for different dosage forms and routes of administration, there are different solubility and release characteristics which can influence the type of bioequivalence testing that should be considered.

For example, rectally administered

suppositories have low solubility and non-immediate release characteristics. These non-immediate release characteristics are due to melting, post-melting dispersion, drug partitioning, and distribution equilibrium.

Because of the pharmaceutical and pharmacological characteristics of this product, we support the FDA "Draft Guidance on Mesalamine" for rectally administered suppositories. This Guidance recommends that in vivo bioequivalence be demonstrated with "Bioequivalence study with clinical endpoints" and "Bioequivalence studies with pharmacokinetic endpoints." Such guidance is needed because there's no scientifically agreed upon methodology to establish the bioequivalence of locally acting, rectally administered mesalamine suppositories.

No in vitro and in vitro standard test methods have been agreed upon, and there is no simulated rectal fluid of in vivo dissolution. In addition to a lack of

methodologies, there are physiological factors that contribute to the variability of systemic blood levels of rectally administered mesalamine suppositories. Remember, that systemic blood levels are downstream from the site of action, as was explained earlier by Dr. Yu.

Let me show some data that demonstrates this variability. These are the data from the NDA Biopharm Review, and show i coefficient of variability on both Cmax and AUC in healthy volunteers are shown on the red circles on this slide. And on the next slide, on this slide, similar i coefficient of variability are reported in patients.

In light of these data, if there's generally accepted that mesalamine suppositories produce highly variable systemic blood levels, both in patients and healthy volunteers.

And most importantly, because therapeutic efficacy of rectally administered

mesalamine is thought to result from a predominantly topical effect, standard pharmacokinetic parameters bear little relationship with clinical efficacy. Pharmacokinetic parameters are important to assure safety of any systemic exposure, which is downstream from the site of clinical effect.

As expected, the release of a drug from lipophilic suppositories are multifactorial. There is no in vivo-in vitro correlation for an in vitro dissolution test for a hard fat mesalamine suppository.

When the Committee discusses what role biorelevant dissolution and systemic pharmacokinetics should play in developing bioequivalence recommendations, it is important to take into account the scientific and regulatory considerations of rectally administered mesalamine suppositories that I have reviewed this morning and which are listed on this slide.

In conclusion, the currently available data support treating the bioequivalent testing required for locally acting GI products that use different release mechanisms or route of administration on a case-by-case basis.

Thank you for your attention.

DR. MORRIS: Thank you. And are there any follow-up questions for -- or clarification questions -- I should say, for our speaker?

Actually, I just had one, Dr. Rousseau. When you say there was no IVIVC correlation, does that mean that -- and don't reveal any confidences, of course. But, I mean, does that mean that there's no routine dissolution test done? Or it's just that it's not used in the correlative manner?

DR. ROUSSEAU: It's not used in the correlative manner.

DR. MORRIS: Thank you. Any other clarifications? Oh, yes. I'm sorry, Keith.

DR. WEBBER: As an example, is this

drug one that is considered to be significantly systemically absorbed, or not?

DR. ROUSSEAU: No.

DR. MORRIS: Anyone else? If not, thank you, again.

(Discussion off the record)

DR. MORRIS: So this concludes the open public hearing. And I have just a prepared statement to read.

So the open public hearing portion of this meeting is now concluded and we will no longer take comments from the audience. The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the Committee, as well as the public comments.

I'm sorry?

(Discussion off the record)

DR. MORRIS: Oh, yes. And just to make sure everybody knows, we have another open public hearing this afternoon. And with that, I think we're on break until when?

So we're now going to break, briefly. And at 10:45, we'll reconvene. And please refrain from discussing any of the meeting topics during break.

Thank you.

(Recess)

DR. MORRIS: If we could reconvene please? We were just rearranging some overflow guests.

We have just a brief announcement.

LCDR NGO: Please know that there's no standing in this room. If you need a seat, please look around. There's a few seats up here available.

And there's an overflow room that's being set up around the corner outside. Again, no standing in this room.

DR. MORRIS: Except to leave and come in, I think. Right?

So with that, our next speaker is Rob Lionberger from OGD to talk on continuing the material -- background material on our

discussion. A familiar face with Rob. So please, Rob. Proceed.

DR. LIONBERGER: All right. Thank you very much, Ken. And good morning to everyone on the committee.

Today I want to try to describe a little bit more concretely some of the challenges the Office of Generic Drugs faces with respect to bioequivalence of locally acting GI drugs.

And remember from our previous discussion sort of narrowed the scope of the discussion to immediate release products, low solubility drugs, but also drugs that need to be dissolved in order to be effective. So we're leaving out of the discussion drug products that are completely insoluble. And save that topic for another discussion.

So for these type of locally acting drugs, it's really the in vivo release from the drug product that determines the delivery of the drug to the site of action. So just

to give you first an overview of my talk, first I want to explain what we mean by low solubility drugs, and then I'll talk a little bit about how we view PK studies. And then I'll follow that up with two examples trying to make our discussion less abstract and more specific. And finally, I want to conclude with a discussion about what the next steps would be toward moving toward using a biorelevant media to aid in evaluating the dissolution of bioequivalence of locally acting products.

So first I'm going to talk about solubility. We have to say, well, why are we making this distinction between high solubility drugs and low solubility drugs? And the reason is that we believe that for the high solubility drugs that equivalent in vitro dissolution over a range of pH conditions in aqueous buffers will ensure equivalence in in vivo dissolution for those products.

And -- I mean, part of the basis for this is the long experience FDA has with BCS-based biowaivers for systemically acting drugs. All of these are based -- all of these biowaivers are based on the same understanding that in vitro dissolution in the aqueous buffers covers the range of in vivo conditions for these high solubility drugs. And the focus of this meeting, and today's challenge, is that we don't yet have the same level of confidence in in vitro dissolution for the low solubility drugs.

So our definition of low solubility comes from the BCS guidance. And in this guidance, it describes -- primarily describes drugs -- it classifies a drug as low solubility when the highest strength will not dissolve in 125 ml of aqueous media at any pH between 1 and 7.5. So if there's any pH where the drug does not dissolve, then it will be considered as low solubility.

This is a very conservative

definition. I mean, part of that conservatism comes from the orientation of the BCS guidance toward granting waivers for the class 1 high solubility, high permeability drugs. So it tends to be cautious on the side of classifying drugs as high solubility in terms of that waiver.

And so because of this conservatism, there's a wide range of drugs that fall into the low solubility drug category. And I want to point out some of the key distinctions here. First categories would be weak acids and weak bases, which have pH dependent solubility's. So these might only -- because of this change in solubility with pH, they might only be low soluble at a particular pH in this range. And they might in fact be highly soluble at other pHs and perhaps even the pHs that are relevant to their in vivo performance.

Another category of low solubility drugs -- and this would be ones that in none

of the aqueous media are they highly soluble, but in the in vivo fluids where there's other things than just pH changes, there's bio acid surfactants. There -- there's a category of low solubility drugs -- this means low solubility in aqueous media -- which actually have reasonable solubility in the in vivo fluids.

And finally, there's sort of the leftover category of drugs that really are truly low solubility. Even in the in vivo media. And in these drugs, you might see -- if they were absorbed, you might see solubility limited absorption. That if you increase the dose of the drug, you might see a decrease in bioavailability -- and bioavailability might be a sign of this, because the contents of the GI tract reach a saturation solubility. And you might see in this category novel formulation technologies might be used to develop these products to actually get local availability of the

product.

So there's a range of drugs that fall into the category of low solubility, which may affect some of our bioequivalence recommendations.

Now, GI acting drugs may or may not have significant systemic absorption. As Jim Polli said, the drug doesn't know whether it's supposed to be locally acting drug. So we have examples where there could be 30 to 50 percent of the dose absorbed, or -- you know, less than 1 percent of the dose absorbed. And even potentially cases where there's absolutely none absorbed.

As we look at them, for actually most of the drugs that we've looked at, you can detect some drugs systemically. Especially with improved bioanalytical methods. So in many cases where the drug needs to dissolve in order to have pharmacological activity, because there's some dissolved drug there there's the

potential for some absorption through diffusion across the membrane. So often times, even if there's not a significant amount of absorption there still can be drug detected systemically with a sensitive bioanalytical method.

And as the committee discussed, I think it was four years ago, there's wide agreement that if there's concerns about demonstrating equivalent safety between test and reference products, pharmacokinetic studies certainly are requested and may be requested for that purpose.

But what I want to talk about here more specifically, since I don't think there's really any disagreement on this issue here, is how can we use the information you gain from observations of drug absorption to tell us something about what's going on in the in vivo environment. Remember, the challenge for the low solubility drugs that we don't have for the high solubility drugs

is that we're not as certain about the relationship between the in vitro testing and the in vivo dissolution that actually drives drug absorption.

And so we can I think generally say that the rate of absorption is related to the local GI concentration. For example, if I were able to de-convolute a PK profile to obtain an observed rate of absorption, this is generally going to be driven by the concentration gradients along the intestinal membrane. That's what drives the absorption. So if I double the amount of drug available in the GI tract, I ought to see a concomitant increase in the rate of absorption from that concentration gradient.

So it tells you, again, the rate of absorption is related to local GI concentrations, which we think is a key part of the bioequivalence evaluation.

One of the challenges with doing this is, there's many different sites in the

GI tract. And so -- you know, certainly for the modified release products, this is been the significant challenge in understanding how to interpret pharmacokinetic studies. But the problem is a little bit simpler when we limit our discussion to immediate release products. And the location of the drug after its release from immediate release dosage form generally is governed significantly by the GI transit. So there's sort of time dependence.

So if I look at sort of a drug transiting through a GI tract and dispersing over time, still if I can look at a -- if I look at absorption at a particular time, say before one hour, then I might know that that drug has actually been released in the upper part of the small intestine -- the duodenum and the jejunum. If I see absorption not occurring until later, after four or five hours, primarily then that drug hasn't been released from the formulation until it has

reached the colon.

So depending on -- because of the sort of time dependence of location due to the GI transit, we can make some inference about where the drug might be when absorption is observed.

And just again, to compare systemically acting drugs really, plasma concentration sort of occurs before and it's presumably determinate of the pharmacological effect of the product. For locally acting products, drug that we observed in plasma generally is -- you consider it as a side effect of the main thing that you want to have occur. But this side effect is actually related to the drug release from the product, which we think is the key place to focus our attention when we're trying to come up with methods that can demonstrate bioequivalence.

And so, in the examples that I'm going to present to you I want to point out some of the reasons why the low solubility

drugs are more challenging. And as we look at these examples, to prepare for our discussion, I hope that you'll consider how we might make our in vitro test more predictive of in vivo performance. Because I think that's the main goal that we're trying to achieve here.

And Jim Polli talked about -- you know, from his side, some of the specific reasons why low solubility drugs are more challenging. And these are related to the different categories of low solubility drugs.

So our first example -- and I think this is related to one question that Jerry Collins asked earlier about have we approved any products since the last advisory committee meeting. And this is one -- this first example is an actual example where there have been A and D approvals that have come from this approach.

And so in this example, the drug at issue is delivered as a prodrug, but there's

also an active ingredient. The prodrug is P, the active ingredient is A. The site of action of the active ingredient is in the colon. But for this product, drug A is rapidly absorbed from the small intestine.

So if I dose A orally in an immediate release product not very much will reach its site of action because it will be absorbed first. So one strategy to get around this is to deliver the drug A to the colon as a prodrug, P, and in the colon the bacteria in the colon metabolize the prodrug to release form A, the active ingredient.

And so for both of these, there's measurable absorption. There's a significant amount of A absorbed, but a very small amount of P. So the prodrug is -- there's limited absorption, but it's detectable so you can tell by looking at the absorption of the prodrug where it's actually been released from the formulation in vivo.

If we look at the solubility of

this example -- here specifically focusing on the prodrug, because that's the form that's dosed -- this is an example where over the pH range, the solubility changes. So at low pH, the drug is low solubility.

As you get to pHs more representative of the small intestine, you see higher solubility in that region where it's actually -- and then it's -- and the colon pH you'd expect the prodrug to be highly soluble. And the active drug also at intermediate pH might be considered low solubility based on the dose.

And the dissolution for the prodrug just follows what you'd expect from its solubility. If you try to do dissolution in acidic media, you don't see any dissolution because of the very low solubility. As the pH increases, either in un-buffered water or pH control buffers, you see rapid dissolution of the prodrug. Again, this is example -- it doesn't meet the definition of high

solubility because of the pH dependent solubility.

For this product and other related products using the same active ingredient, OG formed a multi-disciplinary working group including medical officers, pharmacologists, and other disciplines. We also had contributions from FDA's OTR lab to look at different potential bioequivalence methods for this product. And we considered dissolution, we considered PK studies both for safety and as surrogates for local delivery. We also considered whether clinical end point studies needed to be used, because we couldn't get enough information from other types of studies.

And we also undertook several investigations, FDA lab did dissolution studies on some of these products, we did simulations of GI transit drug release absorption and PK to look at their connections. And so this involved individual

review and discussion of each product.

For the particular example that I'm giving today, the determination of this working group was that bioequivalence should be determined by demonstrating equivalent dissolution of the prodrug between test and reference products. And that fed and fasting pharmacokinetic studies measuring both the prodrug and the active ingredient should also be used and required to meet a bioequivalence criteria to demonstrate equivalence.

And so for this drug, if we sort of follow it's process through the GI tract you can see where the bioequivalence recommendations come in. First, P is released from the formulation essentially once the pH reaches about -- you know, reaches a reasonable amount of solubility in the duodenum.

Dissolution is -- this is driven by dissolution. We compare dissolution in multiple pH media to ensure that that would

be equivalent. And sometimes you can think, like, this dissolution if this is the same, all right, everything else that follows ought to be the same as well.

As the parent drug transits through the small intestine, there's a small amount of the parent drug -- prodrug -- that's absorbed. And we think, obviously, since this absorption process is driven by the concentration gradient if there were more parent drug released from the formulation from one product and the other, then you'd see a concomitant increase in the systemic exposure versus the other. So it required the PK of the parent drug, which could be measured -- it's sort of like a measurement, a sampling -- to be the same.

The remaining P -- most of it, in fact, in this case -- transits through the small intestine. In the colon, this conversion of P to the active ingredient -- the active ingredient at its

site of action is also absorbed from that region. And so again we can verify that the active ingredient is actually released at its site of action by looking at the fact that it actually is absorbed. If it wasn't released, it wouldn't be absorbed.

And so putting all of this information together, the dissolution, the pharmacokinetics of both active and the prodrug, would then allow us to conclude that the local deliver of this active ingredient would be the same between test and reference products that showed equivalence in all three of these bolded measures.

The simulations that we did showed that as we -- if you had a hypothetical test in reference products where you varied the ratio of the dissolution rates, we looked at which measurements -- either the AUC of the local delivery in the site of action, or the AUC observed or the active ingredient, or the AUC in Cmax observed of the prodrug, which

would be more sensitive to changes in formulation. And as might be expected, the measurement of the pharmacokinetics of the prodrug were the ones that would be most sensitive to changes in the formulation of the product. And the other measures would be very insensitive to formulation changes, generally in this case, because the drug has approximately, let's say, a three-hour transit time through the GI tract in order to dissolve. So if one product dissolves slightly slower than the others, it would still be completely dissolved by the time it reached the colon. So those measures weren't very sensitive to small differences in dissolution.

And if we reflect on this example, all right, I pointed out really everything that happens to this drug is driven by its initial dissolution. Once the drug is dissolved, any memory of the formulation and any difference between the test and the

reference product is erased. And so in this case, you can ask yourself, is there a dissolution test which would eliminate the need for the multiple PK studies in this case. And there's extensive amount of PK studies required in this case. The drug's somewhat variable to these, studies require large numbers of subjects. We required them to do fed and fasting studies and measuring two analytes.

So essentially, they had to pass four statistical tests for bioequivalence for -- to demonstrate this product.

One of the -- some of the discussion around this product raised questions about dissolution. One of the somewhat interesting questions raised about dissolution was the question of our dissolution requirement, testing individually in the three different media, was questioned because it lacked sequential exposure to pH. So some of the public data that was submitted

to this, or the demonstration between a reference product and a test product obtained, believe, from overseas. So this is not a U.S. product. Showing that if you did dissolution just to the pH 4.5, these products were equivalent. But if you exposed them to the acidic media first, then the test product was faster than the reference product. Perhaps because of some reprecipitation (?) or salt form chemistry involved, in that case.

For this product, the bioequivalence decision was supported by both the fact that in most cases, right, you're not exposing the drug to pH 4.5 for two hours. It's exposed for very short time to this pH, and then to a higher pH where it's much more soluble. As well as the fact that we had the supporting PK study data showing that the release of the parent drug, as measured by the PK study, was equivalent in the in vivo conditions.

But this raises some of the issues that come up when we look at the dissolution for potential complexities that come up when we look at dissolution methods for low solubility drugs.

In our second example, going to look at a drug where -- and this is one where we haven't made a final recommendation for this product. Look at a drug where the solubility of this drug is, there's no aqueous media where this drug actually reaches high solubility. But for this product, we know that approximately 33 percent of the dose is absorbed. And so we know that even though the drug is not soluble in in vitro media, that in vitro aqueous media there likely is solubility in the in vivo conditions.

And for this drug, we also noticed that the AUC increases with dose, it doesn't decrease with dose. So there's no evidence that the absorption of this drug is limited

in any way by solubility. Even when you do it -- have a significant increase from the normal dose. I think there was a fourfold -- study that showed a fourfold increase in drug didn't saturate the media in terms of the in vivo solubility.

This example is also illustrative because for this product, there are marketed tablet and suspension formulations. And there's been comparisons of these products in terms of both clinical endpoints, pharmacokinetic studies, and dissolution studies. So we can have some examples on how these different methods compare in terms of looking at products that would be different.

So if we look at a tablet and suspension formulation, the clinical endpoint studies that are available generally don't show significant difference. Generally, OGD for clinical endpoint study to show equivalence, the 90 percent confidence intervals in the success ratios have to be

within plus or minus 20 percent. So certainly the endpoint 2 would be equivalent, depending on the number of subjects and the power, probably clinical endpoint 1 would also be a study that would be consistent with showing equivalence in the clinical endpoints. For the tablet and suspension products, which clearly have differences in their performance.

And this just shows what -- I think most people believe that clinical endpoints aren't particularly sensitive to detecting differences in formulation.

But the tablet and suspension products, in this case, do show different systemic exposures as measured by the PK study with the tablet actually, for some reason, showing higher exposure than the suspension product. The suspension dissolve faster in similar type media. So certainly, the differences were more clearly detected between here.

But it's not clear what the relationship between all of these are.

In dissolution for this product, in order to get this product to dissolve significantly you had to raise the pH to super physiological levels and use very high amounts of surfactants to get rapid dissolution of both the suspension and the tablet formulations. And so this isn't really a biorelevant media, it's really a media chosen to get rapid dissolution for use as a quality control test or a release test.

This is just a graph of the PK comparison showing that in this case, by looking at when the drug is actually observed in plasma, you can tell that there is drug being released and available for absorption in the small intestine. Which is -- part of the site of action of this product is in the lower small intestine, and the ileum as well. But you can see that there's also a difference between the tablet and suspension.

But the fact that there is measurable significant absorption suggests the drug actually may be soluble in in vivo media and perhaps biorelevant media, even though in the aqueous buffers you need to go to very high surfactant concentrations in pH to observe it being soluble.

And so when we think about potential bioequivalence approaches for this product, we could consider PK studies are possible because the drug can be measured and quantified. But then if we say, well, we want to combine that with dissolution media, what approach should we take? One potential approach might be to look at, well, we'll look at different pH range trying to get in the physiological range, and we'll try to find surfactant concentrations that provide more sensitive comparisons of formulation.

I think the concern with the higher concentration of surfactant is that that might disguise potential differences in

formulation, say potential differences in particle size which may affect the bioavailability or local delivery of the low solubility drug.

Or, based on the -- focusing here on the topic for this product, we might want to investigate using biorelevant dissolution media, either the fed or fasted intestinal fluid, to demonstrate whether in fact there is significant -- since we suspect there is significant in vivo solubility for this product.

And again, here, the questions for reflection are, is dissolution in very high concentrations of surfactant useful for demonstrating bioequivalence as opposed to being used as a quality control test. Some of the other issues that this example raises are, potential role of inactive ingredients. At least in the suspension formulation.

You know, there's some difference between the pharmacokinetics of the

suspension and the tablet, we don't really understand why. But the suspension has many different excipients than the tablet formulation. And certainly, we don't have very many examples where excipients in tablet formulation have a big effect on the local delivery.

But for solution formulations, FDA has published some studies on Sorbitol, where definitely it's known that excipients in liquid formulations can have a big effect on GI transit and absorption. So that's the potential that might be related to things that are specific to the suspension formulation.

And the role of particle size. We know for this product that there's other data they didn't present that indicated that particle size can affect the product. And that raises the question of whether this dissolution media would be discriminatory in terms of formulations that had differences in

particle size.

And so, as we move on toward the next step, given one example where for a particular product, in vitro dissolution studies plus in vivo PK studies provided, I think, a lot of demonstration of evidence for the bioequivalence in terms of local delivery for a low solubility drug.

You know, there might be some very product-specific aspects of this, because it was a prodrug that allowed you to localize the two different -- the active and the prodrug -- to different regions that might be specific to this product. But where we'd like the committee's input is, how do we generalize this approach to other products. And specifically looking at the different categories of low solubility drugs.

First, ones that have -- like my first example, where there's high aqueous solubility in a particular pH range. Which might be relevant to its delivery. The

second example might be one where we might expect there's low solubility in typical aqueous in vitro media, but if you go to a biorelevant media, media with high surfactant concentrations, there might be high solubility, rapid release. And we also want to think about problems where there's in fact no high solubility in in vivo or biorelevant media, and what approach would you take with those products.

And so, here, just to spark discussion, for the high aqueous solubility and limited pH range, if we can use that dissolution then the aqueous buffers, like other high solubility drugs, dissolution in those aqueous buffers might be reflective of the in vivo product release.

Again, for all of these locally acting drugs, a lot of the discussion is always going to be contingent on the site of action for the particular drug. If a drug acts in the colon, where there's a long GI

transit time that allows dissolution and it's highly soluble in the intestinal media, that can be different for a drug whose site of action might be earlier in the small intestine.

So that all of these recommendations always I think have to be contingent in some way on the site of -- on the site of action of the drug. And also, if we're going to involve PK studies or other methods to look at in vivo release, also contingent on the relationship between the site of absorption and the site of action.

As we step to more difficult cases for drugs that aren't demonstrate high solubility in any aqueous buffers, there I think it's the first step or looking at using biorelevant media to first evaluate the solubility of the drug and the biorelevant media that are available and discussed in the literature to see if that confirms that there's high solubility.

And then encourage sponsors to investigate and -- perhaps FDA research -- to investigate the biorelevant media for use in dissolution to move toward a dissolution method that's reflective of the in vivo conditions. And again, for this case -- you know, as we do have knowledge gaps about what's the best relationship between the in vivo and in vitro dissolution, the role of PK studies or other studies -- PD studies -- that are sensitive to the in vivo release of the product, I think would be part of sort of next step in bioequivalence methods, that we can't directly go to a dissolution based approach with these low solubility drugs.

When the drug is not soluble at all in biorelevant media, then I think really need to look in a very product-specific way of how this product is actually getting its appropriate local availability. Is there a special formulation mechanism, is it particle

size reduction, addition of surfactants or lipids to the formulation to make it available locally and look at relating the bioequivalent method there -- bioequivalence method for that product to better understanding of the mechanism of that product. If we think a little -- so those are the next steps that we might want to take.

If we look a little bit further down, I think the longer term goal would be to move toward a case where biorelevant dissolution media can eliminate the need for additional in vivo studies. This is really focusing on where we think the critical aspect is.

The thing that determines the local availability is the in vivo dissolution. If we can move toward methods that are predictive of that, that determine local GI concentration, we think that that's the best way to cover physiological range, can share

bioequivalence over patient population for these low solubility drugs. And certainly, as we discussed here, depending on the different excipients, this may lead to additional studies, either if there is any question about whether those excipients affect the local delivery or systemic exposure, efficacy, or safety of the product.

And so, if the committee can offer insight into this question, it will be very useful. If we want to say we want to get to a state where the biorelevant media will be predictive, what will be some of the signs? What evidence would the committee like to see from a scientific point of view to reach that point?

And here are some suggestions from here. For me, personally, that if the biorelevant dissolution can predict in vivo dissolution, this is the goal, and how do we assess this, we could asses it by looking at drug absorption. Perhaps an in vitro in vivo

correlation where you looked at fast -- slow formulations over a wide variety of drugs. Also, in an investigational sense, looking at imaging studies where you would label a drug and you can directly observe its in vivo release. That might be the type of scientific studies. The imaging studies really aren't suitable for bioequivalent studies because we're really not able to label the test product in an appropriate way. But for investigating and demonstrating that a method's appropriate, that might be an appropriate scientific approach.

And also, as we start to see biorelevant dissolution used more in quality by design type approaches to the development of formulations of low solubility drugs, that's another sign that it's ready for use in bioequivalence type methods. And I think this links together the bioequivalence and quality by design. You really can't do effective quality by design, either for

formulation or process, unless you have an appropriate way to measure the success of your formulation changes, your design changes. And so that the biorelevant dissolution media -- you know, is not just limited to bioequivalence but will also have an impact on quality by design and formulation development.

So I'd like to thank the committee for your attention and here just present the questions for discussion focusing on your advice on what the role of biorelevant dissolution media should play and role systemic pharmacokinetic should play in developing bioequivalence recommendations for low solubility drugs.

So thank you very much.

DR. MORRIS: Thanks, Rob.

So before -- I'm sorry?

So before we start the general discussion, we just want to open the floor for clarifying questions first. I'd like to

kick that off myself and then go to Mel -- and I guess to Mel right now, unless we raise other ones.

On slide 5, when you're talking about the -- I don't know if you -- well, you don't necessarily have to put it up. But when you're talking about the considerations in classifying the categories of low solubility drugs, the one thing when you get to the truly poor solubility -- I'm wondering -- and if I've asked you this in years past and you've answered it, excuse me. But I'm wondering if you've included the criterion in of the difference between the lattice energy contribution versus the activity coefficient as a further sub categorization.

In other words, if -- you know, my activity coefficient is limiting, then I can beat the hell out of the crystal and I just get to my crappy solubility faster. Right? Whereas if it's really -- if you're really

seeing a significant -- of course we're talking about -- you know, pseudo-equilibrium in a sense. But -- you know, whereas if you're really talking about something where the lattice is providing the resistance, then -- you know, you'd see the other -- the opposite effect.

DR. LIONBERGER: Yeah. I think that's a good point to sort of really -- for these truly poor solubility drugs to try to understand -- you know, what the actual -- you know, mechanism is. If a sponsor is able to use polymorphic for with much higher -- you know, pseudo solubility to get that, that's important to know in focusing on whether bioequivalence tests are sensitive to detecting differences relevant to that.

DR. MORRIS: Yeah, okay. And actually I was thinking more in terms of -- you know, particle size and particle size reduction techniques that might alter the order of the system a little bit just in that. But -- you

know, that's just my question.

And Mel? Yeah?

DR. KOCH: Yeah, mine's more of a point of clarification. And it may not be relevant to the subject, but you mentioned at one point that a product being studied -- I believe on slide 16 -- was a non-U.S. product. And I don't know the relevance there, because I probably need to know what is a U.S. product? Is it API from the U.S.? Is it excipients all from the U.S.? But I think when you make the comment that it's non-U.S., I think --

DR. LIONBERGER: Yes. I mean, I think I'm just making that comment to clarify that that wasn't an approved generic product in the U.S. This is just information submitted through some of the public processes that we have around drug approval.

So I mean, obviously, since we're not really discussing specific drugs or what they are, we can't really go into much more detail about that. But that was just an

example of some of the concerns that have been raised for this.

But it's hard to -- you know, it's hard even for us to evaluate --

DR. KOCH: Okay.

DR. LIONBERGER: The origin of that without more specific information.

DR. MORRIS: Basically, that you wouldn't have seen the package that was behind those data --

DR. LIONBERGER: Right, so we have no -- you know, we just have -- that's -- you know -- it's through the public process. We don't have any control over what's submitted.

DR. MORRIS: I think Marilyn, you --

DR. M. MORRIS: Marilyn Morris. In your discussion, you assumed that absorption was always diffusion limited. And certainly uptake into tissues, even in the colon, or absorption can be limited by transporters. And I was just wondering if you considered this in your evaluation.

DR. LIONBERGER: So I mean, for -- and sort of -- I don't know that OGD sort of -- when I think about this, I generally think when you want to use the PK study to infer something about the local concentration, you want to have some evidence that the response that you're measuring is linearly related to the local concentrations. And one aspect of this might be, is as you increase the dose, does the pharmacokinetic measurement increase linearly as well? And that would rule out a lot of, see, nonlinear mechanisms for uptake transporters or efflux transporters as well.

So I think that's sort of how I've thought of that issue is, you'd want to -- before you'd use the PK data to make that back inference about local concentrations, you'd want to have some idea that there's a linear relationship, even if you didn't know exactly the mechanism where there was paracellular or transcellular absorption, or whether transporters were

involved or not.

But if you knew that the response was linear in, say, an increase in dose, then I think that would be -- seems like to me that that would be evidence that you have a valid sort of measurement technique.

DR. M. MORRIS: So but in the PK studies -- if I could follow up -- these are generally done in healthy individuals --

DR. LIONBERGER: Yes.

DR. M. MORRIS: Where you're doing your comparisons. And my concern is that it's been shown that certain transporters -- for example, in the colon -- can be induced with disease. For example, with ulcerative colitis, it's been shown that the peptide transporter pep-T1 (?) and also monocarboxylate acid transporter MCT-1 can be induced. Therefore, there would be differences in tissue uptake, and potentially in absorption.

So I mean, it just leads -- I know it's certainly another complication. I was

just wondering if this has been considered.

DR. LIONBERGER: Generally, we do get this question a lot in terms of doing bioequivalence studies. Even for systemically -- you know, more simpler products, the question of whether you should do the bioequivalence studies in patience or healthy subjects. And I think our general approach is -- you know, since we think of be bioequivalence study as focusing on comparing formulation performance, all right? So you're using the healthy subjects to evaluate similarities in formulation performance -- you know, we generally think that that's appropriate thing to do.

And -- you know, we try to develop methods that are sensitive to differences in formulation so that if there aren't differences in formulation in healthy subjects, you wouldn't see those differences in the different environment in patients.

You know, I think for the GI acting

drugs, we also try to include the dissolution methods over range of conditions to also help address that issue as well. To look at if you see similar dissolution in different pH environments. If you have patients where, let's say something simple like the pH is very different, then part of -- showing equivalent performance comes from the dissolution data as well as the in vivo studies, whether they're done in patients or healthy subjects.

DR. M. MORRIS: I think generally that would be true. Except with the problem of excipients. If excipients in fact can affect transport, that's when you'll run into differences.

And so, again, if there's differences in excipients and they're shown to affect transport, then that's where you may not see equivalent results doing this.

Otherwise, I wouldn't expect any differences.

DR. LIONBERGER: Okay, thanks.

DR. MORRIS: Can I just follow up? This is Ken Morris, on Marilyn's point. So -- I hadn't thought of this before -- but so what you're saying is that unlike, say, a systemic absorption for disease state that's sort of elsewhere but except locally, that there may be an amplification of the impact of the disease on the transport across the local. So maybe something that's more sensitive locally than it would be were it systemic.

DR. M. MORRIS: It's true, because you'll see tissue effects but -- you know, you should see it for the same compound. You'll see -- you know, changes in transport in with disease for both products. It's just, if there's any effect on that transporter, such as by excipients, that that can lead to differences.

DR. MORRIS: Sorry. Go ahead, Jess?

DR. AU: Jessie Au. My question is to both you, Bob, and to Jim. Both of you referred

to Jennifer Dressman's work. His is more recent, 2008 -- yours -- but the imaging is 2003. And since the same group, I wonder if either one of you know if her group has started to look at relating, correlating, the imaging study with what she's doing with in vitro release media study?

DR. LIONBERGER: Yeah, I'm not aware of what they're doing in that area.

DR. YU: I don't think that we have contacted the imaging. What they usually do is --

DR. MORRIS: Don't forget your name, Lawrence.

DR. YU: I'm sorry. Lawrence Yu from FDA. And I'm not aware of any that study correlating the biorelevant media to image study conducting. And I think it is two separate groups. Jennifer Drescal from Frankfurt, Germany tends to focus on dissolution. And whether dissolution particularly will not tend to correlate to in vivo dissolutioning and the

pharmacokinetics. And I don't know where this imaging come from and I think there's another group in the profile -- pharmaceutical profile, they conduct those imaging studies. So it's kind of two separate groups.

DR. LIONBERGER: Yeah, I think that imaging one -- I presented there. They were measuring gastrointestinal transit times. So not using a marker for that. So it really wasn't looking at drug release in any way.

DR. MORRIS: Mel -- Marv? You've got to move Mel's sign. I'm reading the sign when I look at you.

DR. MEYER: Lawrence always calls me Art, so I'm a confused guy here.

Marvin Meyer. First of all, when I -- it bothers me a little bit when some of the methodology -- I'm not really being critical here, but -- some of the methodology like imaging is put down as a solution to some problems. And I would question, who's going to do that? The generic folks

certainly aren't going to invest the kind of money it would take to correlate their in vivo with imaging, because once they had their in vivo, they were done anyway.

And the brand name, I would think, might be a little hesitant to prove that a simpler way works because then the generics would use it. So I wonder if that's a practical consideration.

And I'm also bothered a little bit by the term "biorelevance," which I think is a -- it's in the eye of the beholder. For example, there used to be -- maybe still is -- a USP dissolution test that had 10 percent -- I think it was 10 percent methanol in it. I don't remember what the drug was. And I used to tell my students, well that's biorelevant only for people that are homeless and like to drink aftershave.

So I think we have to be real careful when we try to improve dissolution through some "biorelevant" means in order to

have enough dissolution to say we can now measure something meaningful.

I thought that Jim Polli's slide 22 with some possible biorelevant dissolution media, some of that looked pretty physiological and might be a good idea, but it still has to be correlated. I think when we get too far away from the pH 1 through 8, then we start to wonder, are we being relevant with our surfactant added, with our biosalt added, how are you going to prove that?So I'm a little cautious about using the term biorelevant.

DR. LIONBERGER: Yeah. I mean, I think in terms of the first question, sort of who should pay for this, right? I think that's a very good question. I think in our generic drugs sort of critical path opportunities, right -- you know, sort of try to identify some of these types of challenges in hopes of encouraging the people who benefit from the lower cost and availability of generic drugs to

fund some of the scientific research that's needed to support their availability. But whether that will ever happen, don't really know.

And but I think also, that when you talk about innovator companies -- you know, certainly they have at least some interest in -- you know, better biorelevant media for -- you know, formulation of better, more efficient product development and quality by design. That is -- you know, that also affects sort of demonstrating bioequivalence.

DR. MORRIS: Ken Morris -- if I can just see if I can bounce this off. So I sort of took the imaging comment that Rob made, Marv, in terms of the promise of imaging and the idea that imaging could be used to establish the correlation and then once established not use as a test. But -- you know, just for like a biorelevant dissolution medium. But I'm not --

DR. LIONBERGER: Yeah, that's fine --

DR. MORRIS: I'm not sure if that's

what you were speaking to.

DR. MEYER: I'm not sure I was speaking to it, either. But I just thought one of the comment -- many years ago, we did this study looking at chlorothiazide tablets. And a 500 milligram dose of chlorothiazide doesn't dissolve anywhere close to totally over any period of time in a 900ml beaker. And yet, we had a correlation for dissolution over -- I forget what it was now -- the first 30 minutes? Sampling every 10? Something like that. And we published it, but it's been years ago.

So I'm saying maybe we don't need to have dissolution for a soluble drug all the way up to 85 percent or 100 percent. Maybe we can get reasonable correlations with a shorter period of time until saturation is reached.

DR. LIONBERGER: Yeah. I mean, I think one of the examples that in Jim Polli's presentation showed that when they went to the

simulated intestinal fluid, right, they went from 0 percent dissolved -- you know, didn't get complete dissolution but showed -- you know, 10 percent, 15 percent in fed and fasted states. You know, and that may be actually what's actually happening in terms of saturation. And might be relevant to comparing products as well.

So I don't think you would generally need to have the biorelevant media show complete dissolution. You know, I mean, although these are questions about synch conditions and whether drugs clear -- you know, absorbed and removed as well. That sort of complicate this -- you know, in terms of -- not just having a biorelevant media, but also having a biorelevant dissolution process where -- you know -- in vivo, right, if drugs absorbed it can be removed and then there's more capacity -- you know, even though you don't have 900 mls of material and having to go to the synch conditions.

But synch conditions might not be

biorelevant. So another way to think about it.

DR. MORRIS: Any other clarification questions for Rob before we start the discussion?

If not, thanks much, Rob. Excellent. So can we have the questions? So we have two questions, logically divided into question dealing with bio -- dissolution, rather, versus PK.

So the first one is, what roles should biorelevant dissolution play in developing BE recommendations for low solubility locally acting drugs that treat GI conditions. And with that, I'll open the discussion.

Lawrence?

DR. YU: Can I make comments before the discussion regarding the transporter, regarding the biorelevant media, even by pH -- imaging technologies?

DR. MORRIS: Okay, that can actually

can be part of the discussion. That's okay.

DR. YU: That's why I'm waiting here. Number one, the transporter. Merrill, you probably know that actually that this is a research where I'm personally excited about. That we do a lot of bioequivalent studies in healthy subjects, we certainly pay attention to similarity between patient and the healthy subject. And transporter, how much they're going to impact it. We just published a paper about remical (?) pharmaceutics like two years ago on transporter impact on absorption.

I think excipients impact the transporters and the absorption is always very interesting topic.

In early '90s, the late '90s, might be 2000, there's a lot of transporter were discovered where the uptake transporter or efflux transporter. And also in individual cell culture, we've -- many academic research scientists found some excipients may impact the uptake or efflux transporters.

One of the things which we're still confident, with respect to (inaudible) healthy subject is, how those excipients utilized in those in vitro cell culture study usually is not very oftenly (?) utilized in actually coming all of dosing forms such as a tablet and capsules. For example, Tween 80, stuff like that. They -- sometimes they're used. They are very interesting to see how those exhibits impact in vivo. I'm very pay attention to that.

As I mentioned in my talk, so far I only see one report from Germany on this etalanumal (?) approach it published the last year in pharm research. Even with this case, I'm not quite sure the excipient's impact on those are real.

So there's a lot of things in scientific literature regarding excipient's impact on absorption in vitro, in cell cultures. Probably don't have a lot of evidence in terms of absorption.

I'm not talking about dry dry (?) interaction. Dry dry interaction for sure, a lot. So we're still confident that with the (inaudible) method in healthy volunteers.

Number two, with respect to biorelevant media. I do recognize this term is -- it's not probably very accurately utilized. And biorelevant media certainly is not referred to, you just put a surfactant, for example, or you just put a little bio acid. We refer to biorelevant media.

I think there's a number of research group internationally that did develop what we call the fed fasted -- those biorelevant media. What they developed is basically actually a sample, the fluid from human subject. And they analyzed the composition. And they conducted dissolution. You sometimes -- in vivo, in human, real subject. And then they tried to compare the visual to correlating view. So those methods developed -- those media developed -- is not

from simply, for example, theolitical (?). In fact this was, indeed, practical and experimental.

I know yesterday's talk we have more than 40 percent drugs are poly soluble, and many, many research scientists. At Pfizer, almost every scientist utilize those media to see how soluble they are to as indicative about potential absorption.

Because many cases, those basically -- there's nothing. No absorbable -- solubility in aqueous media. Yet many of them (inaudible) reasonable soluble in those -- the biorelevant media. So that way, scientists use those information as a predictor for other in vivo absorption. And there's a reasonable number of publication out there, there's a reasonable good correlation. And I think this time that science advanced -- that's why we asked you, should we consider those or not?

Finally, for PET imaging. And Jim

showed the slides and Rob showed the slides. I have to say, this certainly is not -- it's a highly unlikely, let's put it that way -- monochromatic that we will use as a recommendation for biochem studies. But certainly as a research tool to evaluate the method at which we can recommend would be reasonable or scientifically zoned or not. Thank you.

DR. MORRIS: I think first Marilyn, then Liz.

DR. M. MORRIS: Yeah, Marilyn Morris. I just wanted to quickly respond to Lawrence's response.

Some of the transporters that -- you know, I'm aware of -- the excipients -- I just wanted to bring that up. But some of the transporters -- I mean, it's very interesting. These are OPI (?) regulated in certain GI diseases, such as inflammatory diseases. And some of these haven't been well characterized, like the

monocovicylic acid transporters. So I think it's an area that needs to be looked at, because we don't have the data for those types of transporters, and they may be very relevant for some of the drugs that are used to treat GI diseases and important for the gastrointestinal uptake. So that was just the point I wanted to make.

DR. YU: Well, it makes sense. Thank you.

DR. TOPP: Hi, this is Liz Topp speaking. I want to make some general comments towards this question. And I'm going to do my little academic thing, so this may take longer than 10 seconds. So I beg your indulgence. It will not take the academic 50 minutes.

So I think when we consider this question about the role of biorelevant dissolution and then the role of PK measurements, I want to try to compare this locally acting drug issue with the issue of other drugs with other sites of action.

So suppose I have an orally administered drug that's intended to act on a tumor. If the drug is intended to act on the tumor, what I would really like to know is not the plasma concentration as a function of time, because that really isn't what I care about. What I'd really like to know is the tumor concentration as a function of time. I'd like to know the cumulative exposure of the tumor as a function of time, I'd like to know when the peak concentrations in the tumor are reached, and all those kinds of things relevant to the tissue that I'm trying to treat.

I generally can't know that. So generally I can't just be going in there and snipping tumor samples -- you know, as I do my dosing.

So I can't know that. So what I have to settle for instead is a measure of plasma concentration as a function of time. And that's where pharmacokinetics comes from,

right? That's why we do this.

So this isn't what we really want to know. CP versus time is not what we want to know. Cmax, CPmax, is not what we want to know. It's a surrogate for the things that we really do want to know, which are the concentrations at the site of action.

That same kind of thinking I would like to apply to this business of locally acting drugs that act in the GI tract. What is it that I really would like to know? Well, what I would really like to know is I would like to know the drug concentration as a function of time at the site of action in the GI tract. I can't know that, for the same reason that I can't know the drug concentration of the tumor. Same kind of argument.

In this case, plasma concentration versus time is probably not a good surrogate for what I really want to know, because in a sense as some of the compartmental models

that were shown this morning indicate, the plasma compartment in an essentially absorbed drug is essentially a side effect site for these locally acting GI drugs. So we've left the site of action, we've gone someplace else, anything that happens in a CP versus T sense is sort of off the table. You know, we're off the playing field, things -- we're downstream, as somebody said earlier.

So what I would really like to know -- so, okay, maybe I'd back up and say, okay, well what I really would like to know then is, how about CP versus T in the intestine, in the GI tract. I'd like to know CP versus T there. Well, actually, I wouldn't even really like to know that as a surrogate. What I'd like to know is CP versus T and, if you will, L. Longitudinal position down the GI tract. That would be really good to know. So I'd like to know plasma concentration as a function of time, and position in the GI tract.

Now, I can't know that, either. So I can't get the equivalent, the sort of the compartmental equivalent of plasma concentration as a function of time in the GI tract. Those local concentrations are quite difficult to measure. So then, what am I willing to settle for, particularly with regard to the question of how do I evaluate a generic, a drug, for its activity in the GI tract. How do I evaluate whether a generic drug is likely to be equivalent to the innovator product in this case? So I can't even know the CP versus T profiling in the area that's relevant.

So I think these types of biorelevant dissolution experiments can be particularly important in this case, but there is the question about what does -- what do we mean by biorelevant? And I have -- and I don't know what the FDA means by biorelevant, and maybe Lawrence you can jump in and beat up on me in a second for not

knowing that.

But I think today -- especially when we consider the alternative -- you know, and alternative approaches to conduct PK studies which are expensive and time consuming, that suggesting biorelevant dissolution from a panel of dissolution media -- none of which may be perfectly representative of the GI environment, because the GI environment is variable -- inter and intra subject-wise. So it may be reasonable for the FDA to suggest a panel of dissolution media that are -- that together represent the biorelevant environment.

So that if a generic product now is comparable to the innovator product in its dissolution profiles across this panel, then we can begin to say that these two products have a high probability of displaying equivalent effects in the local GI environment.

DR. MORRIS: I had one comment and

then I think we go to Mel and then Art.

Just -- I was actually going to frame a little bit of what you said to kick us off. But let me just stick it in now. Is that, in one sense the problem at hand is actually the same problem we deal with with absorption all the time, or site of action. Except we've taken some compartments out. Or, at least one or more compartments out.

On the other hand, we have this uncertainty as to the temporal displacement. So that is in a sense the framework that we're looking at. So the safety part aside, when we're talking about the actual -- so I think that's a very nice way of framing it. That's relevant on several levels.

Anyway, so let's continue.

I think it was Mel and then Art next.

DR. KOCH: Mel Koch. I guess I had a question as we started talking about some of the transport excipients, et cetera.

Do we take into account, at some level in the studies, the fact that the surfactant or other things that are added could actually reverse the activity such that not only increasing absorption but increasing backward sequestration, or something where it increases a physiological metabolite or something in a reverse direction that actually has an ultimate physiological effect?

DR. MORRIS: Could I just ask before we go ahead -- so you're saying, in other words, sort of like if you're partitioning into some other phase that exists because of the excipient that keeps it from going to the site of action? Is that?

DR. KOCH: Actually, what I'm thinking is, can the excipient or sometimes even the medicinal agent actually pull things out in a reverse fashion?

DR. MORRIS: Pull things from the site of action, you're talking about?

DR. KOCH: Right. It's having a physiological effect because it's trying to increase the transport across the mechanism -- or, membrane.

You're actually increasing the ability of things to be lost from the normal system.

DR. MORRIS: Lawrence?

DR. YU: I can make comments, certainly. But I'm no U.S. expert in transporter use, so you can correct me.

There's all kinds going out, there's all kinds of transporter. What the uptake transporter or efflux transporter going out. So real impact is really difficult to predict, I would say. I don't know what you think.

DR. M. MORRIS: Yeah. I -- you know, I agree. You know, my comments really addressed some of the transporters that are actually induced with disease, which I think are very significant in dealing with any GI diseases.

But certainly, we know that there's both in flux and efflux possible in tissue. And it's the tissue, probably -- the concentrations in the GI tract that we're -- that are important. And so certainly there could be changes in both directions.

DR. MORRIS: And Art? You had?

DR. KIBBE: First, I'd like to thank my colleagues for laying it all out for us. I think she really hit the nail on the head, and listening to her it just -- all the things that I've been thinking of really came to fruition. I agree with you, 100 percent.

I think the transporter issue might be a red herring. Because what are we really looking at here is whether the dosage form gives up its drug at the right time at the right place in the same way. And then whatever has happened to the patient, whatever has changed in that patient from being a healthy patient to a person with a

disease to a person with different transporters, that all acts on that molecule. And so if' we've got the same number of molecules at the same spot, regardless of who made the product, we're going to get the same result in that patient. Even if the transporters are different.

A quick thing for Mel. Many, many years ago -- and I'm old enough that I studied with Pythagoras -- but we did the effects of surfactants on sustained release products thinking that the presence of surfactants in the GI tract, along with the sustained release products, would promote absorption. And found out that in some cases it did, and in some cases the sequestering nature of my cells kept the stuff from getting in and we didn't see the effect.

So you know, that's a whole other game. It's -- we need to keep track of what we're trying to adjudicate. And that is, are the two products the same? And if we can

come up with decent dissolution studies that differentiate changes in product formulation -- if we can depend on Q1 and Q2 to get us as close to the same product regardless of the manufacturer, then a lot of the data we get, we don't need to go for extremely complex.

The only value to me for a drug that is intended to work locally in the GI tract, for taking PK data, is to make sure that the two formulations if they're different -- one isn't promoting absorption more than the other. And assuming that we can look at -- and there's no reason to think that we need three different pHs for dissolution. We can do pH dissolution at 6, at 6-1/2, at 7.

We can go through whatever sequence we want to segment the GI tract into segments to see where dissolution is happening with each product. We can, I think, with sophisticated dissolution, answer most of the

questions.

DR. MORRIS: I think Jess.

DR. AU: Jessie Au. I want to expand more on what Liz has said, and I was the one that said this is a downstream part. So I've been thinking a lot about that.

I look around the room-- I think for research, myself done a lot of work in regional therapy. So in some way there's some analogy to yours. I've done work in bladder cancer. And Jerry Collins sitting here has been doing peritoneal cavity therapy. So we have dealt with some of this issue before, from a scientific standpoint.

What we have learned in -- and I'm trying -- this is going to be academic. I'm sorry. It's not as practical as, what's the easiest test? But I do want to throw this out. Because I look at question 1 and question 2 and say neither one of them will get us where we want to be.

Where you want to be is two

questions. You ask, product performance. And another word you said was "site of action." And neither one of those will get you there. Those two questions.

So how do you get there? I think there are ways. Because when we did our bladder work -- I'm sorry I keep going back to my bladder, because I think there's relevance here. Is -- we're able to come up with ways to just measure the urine concentration, but find out what concentration would be in the tumor, which I cannot sample.

And I see this GI can be -- it's a little bit more complicated, because you don't have one cavity. You have a moving compartments. So if you look at an engineering standpoint, it's constantly a transfer function from one part to another. And your media will change, because your pH is changing, your content is changing. Your microbes -- you know, bacterial content, is

changing. But I think there are ways -- you know, academically you can go at it.

You're coming from here, dissolution, and you're going to systemic. Neither one is right. But in the middle, you can model. And you -- yesterday we listened to Monte Carlo Simulation. That's a great tool for you to see what kind of margin of errors will you have if you take some dissolution rate constant, plug it in, and say, if I make some assumption on the transfer function. And then look at my margin of error. How lightly is it, 25 percent difference or is it 50 percent difference? I think you get some guidance from there. And that is something that not necessarily push you to do in vivo study. But you do have to set up some modeling tools. And that's what we did.

And Jerry's done -- interperitoneal cavity therapy is really the first as far as I can see. So maybe Jerry can help us there

as well.

But a lot of those issues we have learned in the cancer field that can be --

DR. MORRIS: Let me just -- one point of clarification, I think though, for Art -- to your point before we follow up on Jessie's is that the one place where you might have a question -- because I -- during development -- you were talking about comparing manufacturer to manufacturer, but during drug development there are a lot of BE studies done within the -- you know, with the innovator. I know you know that, but just for clarification so that there may be the -- whether it's a panel or whatever, there may be a good rationale for doing that for the IND and first in human IND as well.

And then, I think we had Marilyn, then Jerry?

DR. M. MORRIS: I just wanted to clarify that one point again, going back to the transporters. You know, certainly, if there's

changes in transporters, the chemical would be affected in a similar manner. But the comment was really with regards to different excipients. And inhibition -- or, maybe, induction -- of transporters by different excipients that could potentially have effects. Especially on transporters that haven't been really characterized to the same extent as some of the -- say, the ABC transporters.

But I certainly agree with Jessie's comments with regard to modeling in order to try to address some of these problems.

One further comment with regards to PK studies. Certainly, doing PK studies will be important with regards to safety, and will provide one aspect of characterization. But I think in many cases you may see significant differences with poorly absorbed drugs. For example, a change from 2 percent absorbed to 4 percent absorbed you could have a doubling in your AUC. But is that really clinically relevant? Where you go from 98 to 96 percent

present in the GI tract.

So -- but for safety reasons -- you know, it gives you another measure. Thanks.

DR. MORRIS: Jerry, would you care to follow up on Jessie's question?

DR. COLLINS: Jerry Collins. Yeah, I think that if you combine what Dr. Au said with Art and Marv's comments, we're essentially trying to find a comfort zone of some observations that will mimic what happens in vivo. And at one level, we have some very good empiric tools. Dissolution has limits, but as an empiric tool it's clearly served a number of purposes.

On the other hand, we know -- as Dr. Au said, what things we would really be measuring. But we also know that if we're pragmatic and measure something like circulating plasma concentrations, have a modeling overview of that combined with the empiric tradition in this approach, then we're just looking for a comfort zone in

terms of what observations will predict in vivo behavior.

So there's -- going around the table it's interesting. This is a collection of people from a lot of different areas of expertise. And they're all coming at the comfort zone in slightly different ways. But among everyone, I think there's support for the idea that we're getting close to what we want but probably never have.

DR. MORRIS: Which order it was? But I think -- yeah, okay. So Anne and then Liz.

DR. ROBINSON: Yes. Just a follow up to what Jerry was mentioning. Anne Robinson. I think from the earlier presentation from Lawrence -- and from some of the background information -- it appears clear that for highly soluble drugs, the issue -- the measurement of dissolution very well gives an indication of transport. Because really what we're trying to capture with the dissolution is whether dissolution on its own, solubility, can capture

both the solubility and transport into the site of action.

And I think that's really what this question is getting to, is for those drugs that are poorly soluble, can we come up with a method of dissolution that will give us the same amount of information. And I think if that is the case, if we feel that the dissolution alone should represent both despite the concerns about different sites of action throughout the GI tract and the impact of link, then coming up with good biorelevant solutions is really the critical aspect.

DR. MORRIS: Liz?

DR. TOPP: I am very much intrigued by the idea of having biorelevant dissolution, as we've been talking about, combined with simulation. And I'm a big fan of simulation. I like that stuff a lot.

But I've done enough of it to know that I can make the answers be whatever I want them to be.

You don't have to be very good at it to do that. I mean, I can -- you -- any graduate student can tell you -- you know, I can make the answers be what you want, boss. Especially when there are models with a number of adjustable parameters.

So I guess one of the questions that I had that was sort of a follow on to that is that if we were going to recommend or if it were going to be possible to have biorelevant dissolution perhaps combined with simulation, then the simulation itself would have to be a standardized kind of thing, don't you think? That FDA would have to say -- you know, this is the simulation that we're going to do. And you're going to do it like this.

And I don't -- I think we've come a long way in simulating what happens in the GI tract over the last 20 years. But I would like to ask Lawrence, I guess, whether that's a direction that FDA is able, interested,

willing to go.

DR. YU: I'm not sure, Liz. This is Lawrence Yu. And -- how do I say -- usually I do not talk about modeling simulation, because I do not want to promote myself -- the research from myself -- you know. And we're talking modeling, certainly there's many, many parameters. I agree with you, Liz.

But none of you use my model. Sorry. Just because --

DR. ROBINSON: That's the way everyone feels, sir.

DR. YU: I particularly feel confidence. The reason because there are a lot of parameters in the model. For example, transit time, the volumes, they're all fixed. So your graduate student cannot change it anymore.

DR. ROBINSON: But they are very -- I'm sorry I'm interrupting him, I'm a little out of turn. But they are variable. Both within subjects and between subjects. And